



2016 ASPHO and PBMTC Abstracts

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DELAYED GRANULOCYTE-COLONY STIMULATING FACTOR (G-CSF) ADMINISTRATION FOR CHEMOTHERAPY INDUCED NEUTROPENIA REDUCES TOTAL G-CSF DOSES WITHOUT AFFECTING NEUTROPHIL RECOVERY IN A RANDOMIZED CLINICAL STUDY

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Background: The use of G-CSF after myelotoxic chemotherapy accelerates neutrophil recovery reducing the risk of febrile neutropenia. Current guidelines recommend initiating G-CSF 1-2 days after myelotoxic chemotherapy. However, the optimal timing of post-chemotherapy G-CSF administration has not been elucidated. Our previous work in murine models demonstrated that the reappearance of G-CSF sensitive myeloid progenitors does not occur in bone marrow until 3-4 days after completion of chemotherapy. This finding suggests that delayed G-CSF administration may be equally efficacious and significantly more cost effective compared to current practice.

Objectives: To determine if the absolute neutrophil count (ANC) recovery after myelotoxic chemotherapy would be equivalent in a delayed G-CSF administration schedule compared to a standard G-CSF administration schedule.

Design/Method: This study utilized a prospective, 2 treatment, 2 period crossover design. Children with solid tumors who received 2 identical cycles of myelotoxic chemotherapy were randomized to receive G-CSF in both a standard and a delayed schedule. In the standard schedule, patients received G-CSF 24-48 hours after completion of chemotherapy. In the delayed schedule, patients received G-CSF beginning the day that their ANC dropped below 1,000/ μ L. In both schedules, G-CSF was administered at a dose of 5 μ g/kg/day until the ANC was greater than 1,000/ μ L. 14 patients were analyzed in this study.

Results: There was no significant difference in the time to neutrophil recovery (number of days from the start of chemotherapy to an ANC > 1,000/ μ L post nadir) between the two G-CSF administration schedules: 15.0 \pm 0.5 days in the standard group compared to 15.6 \pm 0.4 days in the delayed group (p=0.22). The total number of G-CSF doses given, however, was significantly less in the delayed group: 6.5 \pm 0.6 compared to 10.5 \pm 0.3 doses in the standard group (p=0.0002).

Conclusion: Our preliminary data show that a delayed administration of post chemotherapy G-CSF resulted in a significant reduction in the number of G-CSF injections without compromising the G-CSF effects on neutropenic recovery after myelotoxic chemotherapy in children with solid tumors.

FINAL PHASE I RESULTS OF MITOXANTRONE IN COMBINATION WITH CLOFARABINE IN CHILDREN WITH REFRACTORY/RELAPSED ACUTE LEUKEMIA

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Background: Despite excellent outcomes in pediatric ALL, multiply relapsed patients have response rates ~40%, with <10% OS in CR3.¹ The prognosis for relapsed or refractory AML is ~20% OS.² Clofarabine and Mitoxantrone have proven efficacy in children with leukemia and offer possible synergistic activity in vivo.³

Objectives: To determine the maximal tolerated dose and overall response rate of clofarabine in combination with mitoxantrone as reinduction therapy for refractory/relapsed acute leukemia.

Design/Method: Prospective, open label Phase I/II study. Patients 0-30.99yr old with ALL, AML or NHL in 1st, 2nd or 3rd relapse OR induction failure were given 1 to 3 cycles of clofarabine (escalating doses 20, 30, 35 and 40mg/m²/day) Day 1-5, in combination with mitoxantrone 12mg/m²/day on Day 3-6. Dexrazoxane was given prior to Mitoxantrone. Dose escalation every 3 patients. CNS prophylaxis with intrathecal liposomal cytarabine. Patients allowed subsequent cycles pending response and anthracycline exposure.

Results: A total of 18 patients have been enrolled on the Phase I portion. Median Age is 13yrs (8months-23yrs); 11 ALL (3=IF, 6=Relapse1, 2=Relapse2), 6 AML (4=IF, 1=Relapse1, 1=Relapse2), 1 NHL (=Progressive Disease). There were 2 Grade III/IV toxicities at Dose Level 4 (Clofarabine 40mg/m²) (1 hepatic toxicity, 1 prolonged myelosuppression) hence 3 additional patients were enrolled at Dose Level 3 (Clofarabine 35mg/m²). Median time to neutrophil recovery was 24 days. Fourteen of 17 (82%) leukemia patients achieved a CR after 1 cycle of therapy. Of these, 93% achieved MRD negativity (<0.1%). Thirteen of 14 patients achieving CR went on to receive alloHSCT with continued remission at a median follow up time of 444 days (range 73-761).

Conclusion: The combination of clofarabine and mitoxantrone reinduction therapy for relapsed or refractory acute leukemia appears to be safe and well tolerated in children, adolescents and young adults with poor risk hematologic malignancies. The Phase I MTD of this combination has been established at 35mg/m² Clofarabine. Initial data from the Phase I portion is encouraging with an 82% CR rate and 93% negative MRD in acute leukemic patients. An extended multicenter Phase II Study is ongoing. ¹Gaynon, British Journal Hematology, 2005 ²Wells, Journal Clinical Oncology, 2003 ³Chow, Leukemia & Lymphoma, 2000

A PHASE II PREVENTION TRIAL OF DFMO IN PATIENTS WITH HIGH RISK NEUROBLASTOMA IN REMISSION PREVENTS RELAPSE AND INCREASES EVENT FREE AND OVERALL SURVIVAL

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Background: High Risk Neuroblastoma (HRNB) remains a challenge in pediatric oncology, accounting for 15% of all pediatric cancer deaths. While most patients are able to attain remission, the natural history of HRNB is well documented with approximately 70% event free survival (EFS) at 2 years and 50% EFS at 5 years after completion of immunotherapy.

Objectives: This study evaluated the effectiveness of the ODC inhibitor difluoromethylornithine (DFMO) as a maintenance therapy to increase 2 year EFS in HRNB patients that had achieved remission after standard therapy.

Design/Method: This study was an open label, single agent, multicenter, study through the Neuroblastoma and Medulloblastoma Translational Research Consortium (NMTRC). Enrollment began in June 2012 and ended in February 2016. Subjects received 27 cycles of oral DFMO at a dose of 500 to 1000 mg/m² on each day of a 28 day cycle. EFS and OS were determined on an intention-to-treat basis.

Results: A total of 90 eligible patients received DFMO. DFMO was well tolerated; with grade 3 transaminitis being the most common toxicity reported in 4 % of patients. The EFS and overall survival (OS) were 92% and 98% at 2 years. For the group of patients (n=73) whom were previously enrolled on the ANBL0032 study (Ch14:18), the 2 year EFS was 95% and OS 98%. The one patient who relapsed and died was only receiving half dose prior to relapse due to parental error.

Conclusion: The addition of DFMO for 2 years at the completion of upfront therapy results in improved EFS and OS for children with HRNB. The safety profile of DFMO showed minimal adverse events with excellent quality of life of children on study. These results will be confirmed in a prospective confirmatory clinical trial.

PATIENT/PARENT PERSPECTIVES ON GENOMIC TUMOR PROFILING OF PEDIATRIC SOLID TUMORS: THE INDIVIDUALIZED CANCER THERAPY (ICAT) EXPERIENCE

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Background: Genomic tumor profiling (GTP) is at the forefront of care in medical oncology. Its role in pediatric oncology is still evolving, with only a subset of patients currently expected to receive clinically significant results. Little is known about perspectives of pediatric oncology patients/parents on GTP.

Objectives: To describe perspectives of pediatric oncology patients/parents regarding GTP, including hopes/concerns about GTP, understanding of its purpose, and its impact on participants and their families.

Design/Method: We surveyed individuals who previously underwent GTP through the iCat pilot study of molecular profiling in children with solid tumors at Dana-Farber/Boston Children's, University of California San Francisco, Columbia University Medical Center, and Children's National Medical Center. Following return of profiling results, a cross-sectional survey of novel and validated measures was offered to the patient, if ≥ 18 y at enrollment, or parent, if < 18 y. Subjects were eligible if the patient was living; patient/parent spoke English and consented to further contact; and the oncologist gave permission to approach. Survey domains included hopes/concerns about GTP, understanding of its purpose, preferences for return of results, and impact of results.

Results: Of 100 patients who underwent GTP as part of the iCat study, 53 were eligible for this sub-study. Forty-five surveys were completed (85% response rate). 89% (39/44) reported hoping participation would help find cures for future patients, while 59% (26/44) hoped it would increase their/their child's chance of cure. Most had few concerns about GTP, but 12% (5/43) worried they would learn that their/their child's cancer was less treatable or more aggressive than previously thought. 64% (29/45) reported feeling their participation had helped others, and 44% (20/45) felt they had helped themselves/their own child, despite only one sub-study subject receiving targeted therapy matched to GTP findings. 44% of respondents (20/45) demonstrated some degree of misunderstanding of the purpose of GTP research. 54% (21/39) wished to receive all available profiling data.

Conclusion: Participants in pediatric GTP research perceive benefits of GTP to themselves and others, but expectations of personal benefits of GTP may exceed actual benefits. These issues, including a description of the nuanced purpose of GTP, warrant consideration during consent discussions about participation in GTP research.

GEMCITABINE AND NAB-PACLITAXEL FOR PEDIATRIC RELAPSED AND REFRACTORY SOLID TUMORS

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Background: Pediatric patients with relapsed/refractory solid tumors have poor outcomes. Therapies offering disease control but also preserving quality of life are needed. One such regimen that has been utilized is gemcitabine/docetaxel. Nab-paclitaxel (albumin-bound form of paclitaxel) is closely related to docetaxel and has shown anti-tumor effects alone and in combination with gemcitabine in preclinical models, including pediatric solid tumors. Gemcitabine/nab-paclitaxel has demonstrated efficacy in adults with pancreatic adenocarcinoma; however, there are no published data on the clinical use of gemcitabine/nab-paclitaxel in pediatrics.

Objectives: To determine the toxicity and efficacy of gemcitabine/nab-paclitaxel in patients with pediatric solid tumors.

Design/Method: We retrospectively reviewed the charts of 15 patients who received gemcitabine/nab-paclitaxel at our institution from 2010 to 2015. Gemcitabine 1000 mg/m² and nab-paclitaxel 125 mg/m² were administered intravenously once weekly for 3 out of 4 weeks OR once bi-weekly. Toxicities were graded using the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE; version 4.0). Best overall response was determined using the NCI Response Evaluation Criteria in Solid Tumors (RECIST criteria).

Results: Fourteen relapsed/refractory patients and 1 treatment-naïve patient received gemcitabine/nab-paclitaxel. The median age was 15.5 years. Diagnoses included osteosarcoma (n=5), rhabdomyosarcoma (n=3), germ cell tumor (n=2), non-rhabdomyosarcoma soft tissue sarcoma (NRSTS; n=3) and Ewing sarcoma (n=2). Of the 42 cycles administered, 22 cycles (52%) resulted in grade III/IV toxicity, and 13 patients experienced a grade III/IV toxicity). The most common grade III/IV toxicities were hematologic (n=19), AST/ALT elevation (n=3), infection (n=2), and myositis (n=2). Fourteen patients were evaluable for response by RECIST criteria. While there were no complete responses (CR), 1 patient had a partial response (PR) and 7 had stable disease, giving an objective response rate (CR + PR) of 7%. Median time to progression was 63 days. With a median follow-up of 430 days, 3/15 (20%) patients remain alive with disease.

Conclusion: Gemcitabine/nab-paclitaxel is a tolerable regimen with mainly hematologic toxicity. Gemcitabine/nab-paclitaxel is a reasonable palliative option with clinical benefit in a subset of patients, and should be studied in a prospective fashion.

DEVELOPMENT OF A NOVEL TUMOR TARGETING NANOMEDICINE FOR THE TREATMENT OF PEDIATRIC BRAIN TUMORS

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Background: Pediatric brain tumors represent the most common form of solid tumors among children, comprising approximately 15% of childhood cancers. An obstacle to successful treatment is the inability of effective chemotherapies to cross the blood brain barrier (BBB). Transferrin receptors (TFRs) are increased in brain tumors and have been shown to correlate with poor prognosis. Chemotherapies utilizing the transferrin receptor can successfully cross the BBB via transcytosis and target tumor cells. Carbon dots (C-dots) are a new class of fluorescent, non-toxic nanoparticles being developed for applications including bio-imaging and drug delivery.

Objectives: To determine the efficacy of chemotherapy conjugated to a novel transferrin and C-dot molecule for the treatment of pediatric brain tumors.

Design/Method: C-Dots were generated by hydrothermal heating of bread and subsequently conjugated to transferrin and doxorubicin (Trans-C-dot-DOX). Viability of pediatric brain tumor cell lines DAOY (Medulloblastoma), SJ-GBM2 (Glioblastoma), CHLA 200 (Glioblastoma), and CHLA 266 (Atypical Teratoid/Rhabdoid Tumor) treated with Trans-C-Dot-DOX or DOX was determined at 72hr using MTS assay. TFR levels of PBTs were evaluated by western blot analysis. Cellular DOX was imaged and quantitated using the ArrayScan VTI and C-dots were analyzed using Transmission electron microscopy (TEM).

Results: Western blot analysis indicated that all pediatric brain tumor cell lines expressed both TFR1 and TFR2. DOX and Trans-C-dot-DOX induced dose dependent cell death in all cell lines. Cytotoxicity of Trans-C-dot-DOX was greater or equal to DOX alone, indicating that the C-dots do not negatively affect DOX efficacy. Trans-C-Dot-DOX (10nM) treatment induced a 50-75% decrease in cell viability depending on the cell line. TEM confirmed the presence of C-Dots within treated cells. Furthermore, at 18hr of treatment nuclear DOX fluorescence was approximately 5-fold greater in the Trans-C-Dot-DOX (500nM) treated cells compared DOX alone (500nM).

Conclusion: These results indicate that C-dots can be successfully conjugated to transferrin and doxorubicin without affecting efficacy. The highly fluorescent C-dots will enable imaging of the transferrin-conjugated chemotherapy both in vitro and in vivo. Clinical trials using transferrin-conjugated therapies have demonstrated mixed results. The ability to image the transferrin-chemotherapy following treatment may provide information critical to improving the outcome of clinical trials using transferrin conjugated chemotherapy.

EVALUATION OF THE NEED FOR CHEST X-RAYS IN THE MANAGEMENT OF CENTRAL VENOUS LINE OCCLUSION IN CHILDHOOD CANCER

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Background: Central venous line (CVL) dysfunction from partial or complete lumen/vessel occlusion is a common complication during childhood cancer treatment. The management often involves intraluminal thrombolytic agents such as tissue plasminogen activator (tPA) if a thrombus is suspected. The current practice at many pediatric institutions is to assess CVL position with a chest x-ray (CXR) prior to every tPA administration.

Objectives: To describe our institution's experience with CVL occlusion in patients with childhood cancer and to determine whether a CXR is required before giving tPA.

Design/Method: A retrospective chart review of children (0 to 18 years) with newly diagnosed cancer with a CVL treated at the Hospital for Sick Children between 2010 and 2011 was performed. Episodes of line occlusion were identified both by reviewing patient CXRs for indication and identifying tPA doses dispensed. These episodes were reviewed and assessed for whether the x-ray findings resulted in management other than tPA. Cases where the x-ray resulted in a change in management were further reviewed to determine whether administration of tPA could have resulted in potential patient harm such as bleeding from systemic dosing of tPA from line misplacement or breakage.

Results: A total of 329 patients with newly diagnosed cancer with CVLs were identified. Eighty-five (25.8%) of the patients experienced a total of 124 episodes of CVL occlusion. There were 9 episodes of CVL occlusion (7.2%) where the CXR led to a change in management other than administering tPA. This occurred most commonly in cases of obstruction with PICC lines (11.4%; 5/44). The CXRs changed management less frequently in cases of occlusion in patients with PORTs (4.9%; 3/61) and external CVLs (5.3%; 1/19). In each case, multiple specialists deemed that the administration of tPA would have been unlikely to cause patient harm.

Conclusion: The routine use of CXR prior to thrombolytic therapy for CVL occlusion in children with PORTs should re-evaluated given the paucity of findings resulting in management other than tPA. Though there is a higher rate of management change in patients with PICCs, routine CXRs may also be omitted in these patients given the low harm of tPA administration.

DESIGNING CANCER CARE FOR KIDS BY KIDS: ENGAGING PATIENTS AND THEIR FAMILIES IN CREATING MORE EFFICIENT PATIENT-CENTERED CARE

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Background: Children receiving chemotherapy in clinic go through a complex process involving multiple steps, providers, and rooms. This complexity creates inefficiencies which consume time patients and families could spend doing what they want and need to do.

Objectives: The global aim is to improve the experience of children receiving chemotherapy utilizing a patient-centered approach in which patients take an active role in describing, evaluating and improving the care they receive.

Design/Method: Through an iterative process, we developed a child-friendly process map for chemotherapy administration and engaged patients, families, and clinicians to develop a "passport" data collection tool. Patients used the passport tool to collect data about their visit, including time stamps at the beginning and end of each activity, and qualitative descriptions of feelings at each step in the process. A discrete event simulation model was then created using passport, arrival and staffing data.

Results: Forty-eight oncology patients (ages 6 -16 years) documented their journeys with the passport tool. The mean visit duration was 169.7 minutes (range 45-438), and 49% of time was spent waiting. Idle time as a percentage of total visit time was incurred in registration (5%), triage (9%), and waiting for nurses (7%), providers (9%), and for medications in the exam (11%) and infusion rooms (8%). In the qualitative descriptions extended waits were frequently noted, particularly in the exam room. Negative emotions (scared, anxious or bored) were most commonly reported in the exam and infusion rooms where patients spent the most time waiting. Only positive emotions were reported in the "game" room (exam room waiting area). The infusion area also had more positive than negative emotions reported. Both of these areas have video games and other activities for patients.

Conclusion: This research demonstrates a methodology to actively engage and empower pediatric oncology patients to improve the care they receive. The information will be used in future PDSA cycles to identify and test opportunities to improve care by reducing the idle time spent during a chemotherapy visit by 20% in the next 6 months and improving the quality of idle time by targeting care points during which children are most unhappy or afraid.

PERCEPTION AND COMMUNICATION OF LIFE EXPECTANCY AND PROGNOSIS IN SICKLE CELL DISEASE: A MULTI-CENTER STUDY OF ADOLESCENTS WITH SICKLE CELL DISEASE, THEIR PARENTS AND PEDIATRIC HEMATOLOGISTS

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Background: Sickle cell disease (SCD) is a heterogenous condition causing substantial morbidity and early mortality, but life expectancy has improved in recent decades. Research shows that affected adolescents/young adults (AYAs) and their parents understand the effect of SCD on their future differently than physicians. How prognosis is addressed in clinical practice is unknown and important for shared, informed decision-making.

Objectives: To compare perceptions of SCD-related prognosis among AYAs, parents and pediatric hematologists.

Design/Method: We conducted surveys to English-speaking AYAs (ages 11 – 21) with SCD, their parents, and pediatric hematologists about prognosis in SCD. AYAs and parents were recruited from four centers during health-maintenance visits. Questions were grouped by theme and answers compared using Chi-square or Fisher's exact tests.

Results: 101 adolescents, 98 parents and 115 pediatric hematologists completed surveys. Adolescents were 51.5% female, 85% Black, with a mean age of 16.44 +/- 2.6 years; 72.3% had HbSS, 63.5% were taking hydroxyurea. Parents were 77.4% female, 84.4% Black; 73.5% of their children had HbSS, 56.1% were taking hydroxyurea. Parents (67.3%) and AYAs (53.4%) rated discussions of life expectancy as "very important", however 68% of parents and 57.3% of AYAs reported that their doctors did "not often" discuss how long patients with SCD live. Consistent with this, 37% of doctors reported discussing life expectancy with AYAs; 39% did with parents. Most doctors (77%) reported patients initiating prognostic discussions. AYAs (63%) and parents (50%) want doctors to discuss life expectancy. Most hematologists thought AYAs (98.2%) and parents (89.8%) were somewhat to very afraid of SCD. Parents reported more fear of SCD than adolescents (29.2% vs. 13% "very afraid", 39.8% vs. 36% "a little afraid", 30.2 vs. 51% "not afraid," p<.01). AYAs (50%) and parents (71%) did not believe that SCD would change life expectancy.

Conclusion: Prognostic discussions that include life expectancy are infrequent among AYAs with SCD; AYAs and their parents report wanting this information. Pediatric hematologists perceive that patients and families have more fear of SCD than patients and parents report. This study provides novel information to design interventions to guide conversations regarding disease prognosis and possibly treatment decisions with patients with SCD and their families.

**TOTALLY EXCITED ABOUT MOVING, MOBILITY, AND EXERCISE (TEAM Me):
MULTIDISCIPLINARY EFFORT TO HELP INCREASE MOBILITY FOR CHILDREN,
ADOLESCENTS AND YOUNG ADULTS DURING THEIR INPATIENT ADMISSION**

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Maetzold, Raymund Valderrama, Nicole Harman, Ion Cion, Quinn Franklin, Elsa Morse,
Debi Skillman, Cindy Schwartz**

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Background: Exercise and mobility can be beneficial to oncology patients. Pediatric, adolescent and young adult age patients are responsive to incentives and awards reinforcement. Few studies have shown effects of an inpatient mobility program in pediatric oncology.

Objectives: Create and implement a mobility incentive program to motivate pediatric, and young adult inpatients to remain as active as possible during their hospitalization.

Design/Method: Using a multidisciplinary approach from a team consisting of physicians, nurses, advanced practice providers, physical therapy, occupational therapy, child life, psychology, Arts in medicine, and volunteer services creating TEAM Me (Totally Excited about Moving, Mobility and Exercise). As standard practice, patients were encouraged by their care team to remain active during inpatient stay. As additional incentive, patients could earn stickers to display on TEAM Me door boards along with tickets to earn tiered prizes. Data including 6 minute walk test(6MWT) and staff/faculty survey evaluating perceptions of barriers to patient exercise were conducted both pre and post program implementation.

Results: 6MWT data was collected over a period of 4 months prior to program implementation and over 2 months following implementation. This included 96 Physical therapy encounters. Prior to implementation there was a total of 16 refusals to participate, Average 6MWT of 975.61 feet (Range 0-2045), average modified Borg score of 2.9(Range 1-6). Following implementation there was a total of 4 refusals, average 6MWT of 1128.57 feet(Range 0-2300) with average modified Borg score of 2 (Range 0-3). Faculty/staff survey was conducted prior to and following implementation. Survey entailed questions about perceived patient activity levels, patient motivators, physical and organizational barriers to patients' physical activity. Prior to implementation of TEAM Me, 26.7% of staff members reported their patients tend to walk daily compared with 65.1% post-implementation. Perception of patient motivation also improved: in the initial survey 30.2% of staff felt patients were motivated to stay active while inpatient compared with 69.8% post-implementation.

Conclusion: An innovative multidisciplinary program supporting patient mobility is feasible and may be beneficial to our patients. Initial results show improvement in average 6MWT, Borg scores, along staff perceptions of Inpatient participation in walking, and patient motivation. Future direction includes development of prospective clinical study.

THROMBOTIC MICROANGIOPATHY IN PATIENTS WITH NEUROBLASTOMA AFTER HSCT: THE ECULIZUMAB ERA

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Background: Transplant-associated thrombotic microangiopathy (TA-TMA) is an increasingly recognized complication of HSCT. TA-TMA most commonly affects kidneys resulting in proteinuria, hypertension and may progress to multi-organ failure in severe cases. Patients undergoing autologous HSCT for neuroblastoma require good organ function to complete post-transplant therapy. TA-TMA can significantly compromise planned therapy after HSCT and overall outcomes.

Objectives: The goal of our study was to examine the incidence of TA-TMA and its impact on organ function in patients with neuroblastoma undergoing HSCT at our institution.

Design/Method: Retrospective chart review was performed in all patients with neuroblastoma undergoing high dose chemotherapy and autologous stem cell transplantation (2005-2015) to identify incidence of transplant-associated TMA, outcome and therapy used.

Results: Sixty patients underwent HSCT during the study period using carboplatin/etoposide/melphalan (CEM) (n=42), busulfan/melphalan (Bu/Mel) (n=13) or tandem transplant (Cytosan/Thiotepa and CEM) (n=5). Twelve patients (20%) developed severe TA-TMA with multi-organ involvement at median day +15 after HSCT. TA-TMA occurred in 11 patients receiving CEM regimen and 1 after Cytosan/Thiotepa. There were no incidences of TA-TMA reported after Bu/Mel regimen. All patients had normal renal function, no proteinuria or hypertension before HSCT. At TA-TMA diagnosis 3 patients required hemodialysis and others had median GFR of 46 ml/min (by Cystatin C). All patients developed nephrotic range proteinuria and severe hypertension. Five of 12 patients with severe TA-TMA and multi-organ injury were treated with eculizumab. Patients received median of 9 eculizumab doses (range 4-18) using pharmacokinetic/pharmacodynamic (PK/PD) monitoring to maintain therapeutic drug level. Our PK/PD data indicated significant differences in eculizumab clearance based on TA-TMA activity. There were no side effects attributed to eculizumab. All treated patients recovered from multi-organ injury and were able to complete radiation and modified maintenance therapy. Out of 7 patients not receiving eculizumab, 2 died from TA-TMA complications, 3 progressed to end stage renal disease, 1 to chronic heart failure.

Conclusion: We report high incidence of TA-TMA after CEM regimen and conclude that eculizumab is well tolerated and effective treatment for TA-TMA, but PK/PD based dosing is required for best clinical response.

Platform Session #4015 (Young Investigator Award Recipient)

GERMLINE MUTATIONS IN CANCER PREDISPOSITION GENES IN A SUBSET OF PEDIATRIC ONCOLOGY PATIENTS UNDERGOING TARGETED SOLID TUMOR SEQUENCING USING MATCHED NORMAL DNA

Michael Walsh, Shukla Neerav, Joseph V, Kentsis Alex, Kevin Curran, Rachel Kobos, Angela Arnold, Megan Harlan, Kennedy Jennifer, Kasmintan Schrader, Zsofia Stadler, Nai-Kong Cheung, Shakeel Modak, Brian Kushner, Stephen Roberts, Michael LaQuaglia, Ira Dunkel, Yasmin Khakoo, Kim Kramer, Leonard Wexler, Paul Meyers, Alex Chou, Diana Mandelker, Liying Zhang, David Solit, Scott Armstrong, Marc Ladanyi, Mark Robson, Richard O'Reilly, Michael Berger, Kenneth Offit

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Background: 8.5% of pediatric patients and 12% of adult patients harbor pathogenic heritable genetic alterations predisposing them to cancer. Tumor-normal genomic sequencing is a means to target therapy and assess for cancer predisposition, however, definitive conclusions require proper sampling, standardized variant calling, and expertise to provide accurate curation of data.

Objectives: To determine the frequency of germline mutations in cancer predisposition genes and cancer pathways detected in a subset of pediatric oncology patients and to emphasize the potential therapeutic and preventive implications of these findings.

Design/Method: In a single-site, observational case series (July 2014-August 2015) 115 pediatric cancer participants underwent MSK-IMPACT testing, a 410-gene hybridization capture-based next-generation sequencing assay at Memorial Sloan Kettering Cancer Center. We analyzed whole blood DNA from (n=115) pediatric cancer patients [neuroblastoma 40% (47/115), brain tumors 12% (14/115), and other solid tumors 47% (54/115)]. Variants in these genes were evaluated by Ingenuity Variant Analysis software and manual curation to classify variants according to American College of Medical Genetics and Genomics (ACMG) standards and guidelines.

Results: Pathogenic or likely pathogenic germ line variants were detected in 9.5% (11/115) pediatric cancer participants studied. These included alterations in the mis-match-repair genes PMS2 (n=2) and MSH2 (n=1), in the RAS/MEK/NF pathway gene NF1 (n=2), the double-strand-break repair gene PALB2 (n=1), TGF- β pathway gene SMAD4 (n=1), cell cycle control genes RB1 (n=1) and CEBPA (n=2), and energy metabolism gene SDHA (n=1). In addition to syndrome associations, some of these finding may be relevant to radiation risk (RB1) or eligibility for trials of PARP inhibitors (PALB2) or immunotherapy (MSH2, PMS2).

Conclusion: We observed that 9.5% of a selected series of pediatric patients carry a germline variant of presumed pathogenic significance in known cancer predisposition genes. In addition to identifying etiologic pathways of cancer susceptibility in these cases, these findings have potential impact on prognosis, targeted treatment selection, toxicity, surgical planning and risk for second cancers. In particular, these results suggest that a subset of pediatric cancer patients will benefit from genetic counseling to better define syndromic phenotypes, to provide options for reproductive planning, and to target early detection and prevention in unaffected family members harboring inherited mutations.

LYSINE SPECIFIC DEMETHYLASE 1 AS A RATIONALLY CONCEIVED THERAPEUTIC TARGET IN T-CELL ACUTE LYMPHOBLASTIC LEUKEMIA

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Background: Growth factor independence 1 (GFI1) is a zinc-finger transcriptional repressor and regulator of cell growth, differentiation and survival. GFI1 is necessary for T-cell acute lymphoblastic leukemia (T-ALL) cell survival in vitro and in vivo, and GFI1 depletion leads to apoptosis and tumor regression. Transcriptional repression by GFI1 requires an interaction between its N-terminal SNAG domain and lysine specific demethylase 1 (LSD1), a histone H3K4 demethylase and dominant GFI1 effector. GFI1 derivatives lacking LSD1 binding are impaired as transcriptional repressors and fail to complement GFI1-depletion phenotypes. We hypothesize that LSD1 inhibition will act as a surrogate for GFI1 depletion to cause T-ALL cell death in vitro and in vivo.

Objectives: Define the pre-clinical activity of the HCI-25XX series of novel LSD1 inhibitors in T-ALL.

Design/Method: T-ALL human cell lines and primary patient isolates were treated in suspension cultures with HCI-25XX compounds, followed by determination of cell viability, induction of apoptosis, and colony formation in methylcellulose. T-ALL xenografts were established in NSG mice and treated daily with vehicle or HCI-25XX. GFI1 target gene expression, and markers of apoptosis and survival in vitro and in vivo were determined following HCI-25XX treatment. In vitro drug combination studies with HCI-25XX and standard T-ALL chemotherapy agents were performed to determine combination indices.

Results: HCI-25XX series LSD1 inhibitors display sub-micromolar IC₅₀ toward T-ALL cell lines and primary patient isolates. Relapsed patient isolates are also sensitive to HCI-25XX despite resistance to dexamethasone. T-ALL cell lines treated with HCI-25XX undergo apoptosis, and show clonal growth suppression in methylcellulose colony assays. In vivo, treatment with HCI-25XX reverses otherwise lethal tumor burden in a T-ALL mouse xenotransplant model. Levels of p21, a GFI1 target gene, decline in response to LSD1 inhibition, while enforced expression of p21 in T-ALL cells antagonizes LSD1 inhibition in cell viability assays. HCI-25XX series LSD1 inhibitors display synergy with standard chemotherapy agents used in T-ALL.

Conclusion: LSD1 inhibition promotes T-ALL cell death in vitro and in vivo, and its cytotoxic effects may depend upon p21 depletion. Targeting the epigenome via LSD1 inhibition offers a promising and novel approach to T-ALL therapy that warrants inclusion in early phase clinical trials.

PHASE I STUDY OF SELINEXOR, A SELECTIVE INHIBITOR OF NUCLEAR EXPORT, IN COMBINATION WITH FLUDARABINE AND CYTARABINE IN CHILDREN WITH RELAPSED OR REFRACTORY LEUKEMIA

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Background: Although overall survival rates are >90% for children with acute lymphoblastic leukemia (ALL) and >60% for those with acute myeloid leukemia (AML), patients with relapsed or refractory disease continue to have poor outcomes. Selinexor, an oral selective inhibitor of nuclear export, inhibits XPO1 and causes differentiation and apoptosis of a variety of leukemia subtypes while sparing normal hematopoiesis.

Objectives: We performed a phase I study to determine the safety of selinexor in combination with fludarabine and cytarabine in pediatric patients with relapsed or refractory leukemia.

Design/Method: Eighteen patients with relapsed or refractory acute leukemia were enrolled on the SELHEM clinical trial (NCT02212561). High-risk features included t(6;9), t(6;12), t(4;11), -7 (2 cases), and megakaryoblastic leukemia. Seven patients enrolled in second relapse. Selinexor was given orally on days 1, 3, 8, 10, 22, and 24 and escalated according to a rolling-6 design. Fludarabine (30 mg/m²) and cytarabine (2 g/m²) were administered on days 15-19.

Pharmacokinetic and pharmacodynamic studies were performed on days 1 and 22. Response evaluations were performed on day 15 and at the completion of course one.

Results: Seventeen patients were evaluable for toxicity. Three were treated at 30 mg/m², three at 40 mg/m², six at 55 mg/m², and five at 70 mg/m². Two cases of cerebellar toxicity were observed at 70 mg/m², thereby defining the dose limiting toxicity. The most common grade 3 non-hematologic toxicity was hyponatremia, which was easily corrected in all cases.

Pharmacokinetic parameters indicated that plasma exposure was dose proportional. Sixteen patients demonstrated increased XPO1 mRNA expression, which is upregulated in response to XPO1 protein inactivation. Seven out of fourteen evaluable patients achieved complete response or complete response with incomplete count recovery.

Conclusion: Selinexor, given sequentially with fludarabine and cytarabine, is tolerable at 55 mg/m² in pediatric patients with relapsed or refractory leukemia. Selinexor pharmacokinetic parameters are proportional to the dose given and similar to those seen in adult patients. All patients who received selinexor at ≥40 mg/m² demonstrated XPO1 target inhibition. Response rates are encouraging and we are currently enrolling an expansion cohort at a dose of 40 mg/m². Karyopharm Therapeutics Inc. provided study drug, pharmacokinetic and pharmacodynamics support.

THE ROLE OF CRM1 DIMERIZATION IN CRM1-AF10 LEUKEMOGENESIS

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Background: CALM-AF10 translocations are seen in 5-10% of childhood T-ALL (T-cell acute lymphoblastic leukemia), and are difficult to treat. Our lab recently demonstrated that the CRM1 nuclear export chaperone plays a critical role in CALM-AF10 leukemogenesis. To further study mechanisms by which CRM1 contributes to leukemia development, we created a CRM1-AF10 fusion vector, and showed that similar to CALM-AF10, CRM1-AF10 results in increased HOXA gene expression and induces leukemia in mice. Since it was recently shown that CRM1 is able to self-associate via a defined dimerization interface, we sought to determine whether CRM1 dimerization is important in leukemogenesis.

Objectives: Determine whether CRM1 dimerization is mechanistically involved in CRM1-AF10 leukemogenesis.

Design/Method: The CRM1 homodimerization interface includes seven specific amino acids between residues 346 and 481. We have created a CRM1-AF10 expression vector (CRM1dimmut-AF10) in which six of those seven residues have been mutated in order to impair dimerization. Using luciferase reporter assays, we measured HOXA gene transcription in NIH3T3 and HEK293 cells transiently transfected with the CRM1-AF10 or CRM1dimmut-AF10 constructs. Hematopoietic cells transduced with these fusion vectors have been transplanted into mice, and are being evaluated for leukemia in vivo.

Results: We found that the ability of CRM1dimmut-AF10 to activate the HOXA-luciferase reporter was significantly reduced compared to that of CRM1-AF10, by 30% in HEK293 cells and 15% in NIH3T3 cells. Mice were transplanted with CRM1-AF10 or CRM1dimmut-AF10 transduced cells in November 2015, and are being monitored for the development of leukemia. Since CRM1-AF10 usually induces leukemia in mice with a latency of ~100 days, we will report the effect of CRM1 dimerization on CRM1-AF10 leukemogenesis.

Conclusion: Our results demonstrate that the CRM1 homodimerization motif within CRM1-AF10 contributes to the ability of the fusion protein to activate HOXA transcription. This suggests that dimerization may be an important mechanism underlying CRM1-AF10 leukemogenesis. Future experiments will evaluate the ability of CRM1-AF10 to dimerize with CRM1 and with itself, using co-immunoprecipitation and GST pull-down experiments. We will also examine the role of CRM1 dimerization in CALM-AF10 leukemias. These studies could lead to new therapeutic options targeting the CRM1 dimerization interface.

NRF2 INHIBITION IS A NOVEL THERAPEUTIC APPROACH FOR AML VIA ENHANCING CHEMOSENSITIVITY

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Background: Chronic oxidative stress (COS) is the consequence of prolonged elevation of reactive oxygen species (ROS). In the context of AML, COS leads to sustained induction of Nrf2-dependent antioxidant pathways as compensatory mechanisms to COS. Sustained Nrf2-activation leads to a pathologic maladaptation referred to as Reductive Stress (RS). This RS promotes chemo resistance through counteracting chemotherapy-induced oxidative stress. In exploring this reductive stress, we found that Nrf2 inhibition abrogates RS and promotes chemo sensitivity in AML.

Objectives: To explore the role of Nrf2-mediated reductive stress in AML chemoresistance

Design/Method: Primary human AML samples and lines were used to characterize oxidative and reductive stress. Nrf2 inhibition through the pharmacologic inhibitor brusatol, or through exposure to the Notch ligand DLL1, were used to evaluate the potential of Nrf2/anti-oxidant inhibition as a therapeutic approach.

Results: High levels of Nrf2 are expressed in AML compared to normal PBMCs which correlates with increased reductive metabolites and reducing potential, i.e. reductive stress. Inhibition of Nrf2 through brusatol (or siRNA knockdown) leads to decreased antioxidant levels, increased oxidative stress and increased sensitivity to doxorubicin. In exploring the physiologic regulation of Nrf2, we uncovered a role for the Notch signaling pathway in repressing Nrf2 expression. Thus activation of the Notch pathway, through Notch ligand DLL1, leads to downregulation of Nrf2, recapitulating the effects of pharmacologic inhibition of Nrf2. Indeed Notch signaling induced >2-fold higher ROS levels along with decreased viability and synergy with doxorubicin.

Conclusion: In AML, the antioxidant master regulator Nrf2 contributes to chemoresistance. Our findings support a novel therapeutic approach whereby Nrf2-inhibition either via the small molecule brusatol or the novel mechanism of inducing Notch signaling, induces cell death in human AML via enhanced chemo sensitivity.

THE CLINICAL AND BIOCHEMICAL EFFECTS OF TREATMENT WITH OMEGA-3 FATTY ACIDS IN PATIENTS WITH HOMOZYGOUS SICKLE CELL DISEASE

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Background: Chronic inflammation, coagulation activation and oxidative stress are increasingly recognized as the major determining factors of acute and chronic clinical manifestations of sickle cell disease (SCD). Several lines of evidence indicate that the anti-inflammatory, anti-aggregatory and anti-oxidant long chain omega-3 fatty acids (n-3) could be a safe and effective modifying therapy for SCD.

Objectives: To demonstrate the clinical and biochemical effects of n-3 fatty acids (DHA and EPA) treatment on SCD.

Design/Method: One hundred forty patients with homozygous SCD (aged 2-24) were randomly assigned and received, daily, 1 (age 2–4 y), 2 (age 5–10 y), 3 (age 11–16), or 4 (age >17 y) omega-3 capsules containing 277.8 mg docosahexaenoic (DHA) and 39.0 mg eicosapentaenoic (EPA) or placebo for 1 year. The rates of clinical vaso-occlusive crisis, hemolytic events, blood transfusion rate, were assessed. The effect of n-3 treatment on markers of inflammation, blood cells adhesion, oxidative stress, coagulation and intravascular hemolysis was investigated.

Results: Omega-3 treatment reduced the median rate of clinical vaso-occlusive events ($P > 0.0001$), severe anemia ($P > 0.05$), blood transfusion (0.05), white blood cell count ($P > 0.05$), plasma lactate dehydrogenase (LDH), nuclear factor-kappa B (NF- κ B) gene expression in buffy coat, expression of monocyte integrin and D-dimer ($p > 0.05$). Omega-3 fatty acid group had significantly higher vitamin E plasma levels. Treatment with n-3 had no significant effect on plasma hs-CRP and plasma tumor necrosis factor- α (TNF- α), ($p > 0.05$).

Conclusion: These findings suggest that treatment with omega-3 fatty acids can be an effective therapeutic option for patients with sickle cell disease.

SUCCESSFUL UTILIZATION OF AN ELECTRONIC PAIN DIARY IN A MULTINATIONAL PHASE 3 INTERVENTIONAL STUDY IN PEDIATRIC SICKLE CELL ANEMIA

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Multinational, Multinational, Multinational, Multinational

Background: Patients with sickle cell anemia (SCA) experience recurrent painful crises that affect quality of life. Studies using patient diaries have shown that SCA pain is more prevalent and severe than previously reported based on healthcare facility utilization alone. DOVE was a multinational, study that assessed the efficacy and safety of prasugrel in reducing the rate of vaso-occlusive events in children with SCA (NCT01794000). DOVE incorporated an electronic patient reported outcome (ePRO) diary to assess daily sickle cell pain.

Objectives: To determine the feasibility of an ePRO diary to assess the frequency and intensity of daily sickle-cell pain and its impact on daily function in a large global study of children and adolescents with SCA.

Design/Method: DOVE utilized an hand-held ePRO device to collect daily data related to sickle cell pain, use of analgesics for pain and study drug adherence for up to 9 months in children ≥ 4 years of age. The diary content was translated into 11 languages and comprised of subjective (pain intensity, activity interference) and objective (analgesics used, school attendance) components. Pain intensity was measured using a modified version of the Faces Pain Scale-Revised. Data were transferred daily via cellular network to a central database that was accessible by study personnel to monitor compliance. Rates of patient compliance, as defined by a diary completion rate of at least 80%, were calculated. Completion was calculated as the number of daily diary entries divided by the total number of expected diary entries.

Results: A total of 311 patients received a diary and 268 patients provided up to 9 months of diary entries. Rates of diary compliance and completion were high throughout the diary collection period. For the subjective components, 92.6% of patients were compliant and the overall completion rate was 94.4%. For the objective components, 89.7% of patients were compliant and the overall completion rate was 93.3%. Data from the diary have been analyzed and reported (Heeney et al NEJM 2015).

Conclusion: With careful design, patient support and appropriate monitoring, an ePRO diary can successfully measure the impact of daily sickle cell pain in large global studies. Study sponsors Daiichi Sankyo and Lilly.

INDIVIDUALIZED PAIN PLANS SIGNIFICANTLY REDUCE HOSPITALIZATION IN PEDIATRIC SICKLE CELL PATIENTS WITH VASO-OCCLUSIVE CRISIS

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Background: Vaso-occlusive crisis (VOC) is a frequent event for children with sickle cell disease and creates a significant burden on emergency departments (ED). Previous reports showed decreased admission rates when individualized pain plans (IPP) are used in conjunction with day hospitals or sickle cell nurse practitioners embedded in the ED.

Objectives: To reduce the admission rate for children with sickle cell disease presenting to our pediatric ED with VOC by >20% within six months of initiating IPPs.

Design/Method: A quality improvement team was assembled including members of the hematology division, ED, and pharmacy. A Plan-Do-Study-Act (PDSA) format was employed. The IPP document was created in a unique folder within the electronic medical record. IPPs were initially created through retrospective chart review for our 80 highest resource users. Pediatric residents, ED residents, and ED attending physicians were instructed on access to and use of the IPPs. Our study measured the presence of an IPP, adherence to the IPP, and time to second opiate dose administration. Our primary outcome was admission rate. Length of stay and 72-hour return to the ED were assessed as balancing measures.

Results: IPPs were available for 73% of children with sickle cell disease who presented to our ED with VOC during the study period. The residents and attending physicians in the ED followed the IPP 84% of the time. The average time to administration of a second opiate dose was 60 minutes (CI 46.6-73.4) among patients discharged from the ED compared to 111 minutes (C.I. 76.5-145.5, p 0.008) among patients admitted to the hospital. Admission rate was 39% once IPPs were initiated compared to 57% prior to implementation (p = 0.03). Overall, admission rate decreased by 33% among patients with an IPP compared with 2014 (p = 0.038). Average LOS decreased from 4.7 days in 2014 to 3.4 days since initiating IPPs. There was no difference in 72-hour return rate to ED.

Conclusion: IPPs provide an effective strategy to reduce the admission rate for children with sickle cell disease presenting with VOC. Shorter time to second opiate dosing was also associated with a reduced risk of admission.

RETROSPECTIVE AND PROSPECTIVE RESULTS OF SIROLIMUS IN THE TREATMENT OF CAPILLARY LYMPHATIC VENOUS MALFORMATIONS

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Background: Capillary lymphatic venous malformations (CLVM) are rare vascular anomalies characterized by an abnormal network of capillaries, lymphatic vessels and veins. Patients with CLVM suffer from numerous complications such as soft tissue overgrowth, lymphedema, recurrent cellulitis, thrombosis and bleeding from the skin or other involved organs. Individuals also experience substantial psychological stress due to chronic pain, disfigurement and functional disabilities. Treatments have been largely symptom-based and typically do not result in significant disease improvement. Recent studies demonstrate an important regulatory function of the PI3-kinase/Akt/mTOR pathway in vasculogenesis and provide support for mTOR inhibition with sirolimus as a treatment option in CLVM.

Objectives: To evaluate the safety and efficacy of sirolimus in the treatment of patients with CLVM.

Design/Method: This study analyzed combined data from a multicenter systematic retrospective review of medical records of patients treated with sirolimus between January 2007 and June 2014 and from the prospective Phase 2 clinical trial assessing the efficacy and safety of sirolimus in the treatment of complicated vascular anomalies (NCT00975819). Disease improvement was determined by radiologic imaging, quality of life (QOL) measurements and clinical status assessments. Sirolimus dosing regimens, toxicities and side effect causality were evaluated.

Results: Of the evaluable patients, 26 had CLVM. No patients had complete resolution of symptoms and radiologic disease on sirolimus. Ninety-two percent of patients had improved QOL, 88% had improved clinical status and 42% had improved radiological response. All patients with coagulopathy had less bleeding complications with complete bleeding cessation in 85%. In patients with thrombotic events, symptoms improved in 94% with complete symptom resolution in 63%. Skin involvement and lymphedema improved in 76% and 67% of affected patients, respectively. No patients had disease progression while on sirolimus. Nine patients experienced grade 3 drug toxicities and did not require dose reduction. No grade 4 side effects attributable to sirolimus occurred. Most common side effects were bone marrow suppression and mild elevations of triglyceride, cholesterol and transaminase levels.

Conclusion: Sirolimus is a safe and well-tolerated treatment option that appears efficacious in reducing symptoms and improving QOL in patients with CLVM. Follow-up studies are necessary to assess long-term outcomes and monitor for possible late effects.

RNASEQ GENE EXPRESSION ANALYSIS IDENTIFIES MOLECULAR PATHWAYS IN NONMALIGNANT STROMAL CELLS AND ACUTE LYMPHOBLASTIC LEUKEMIA CELLS RELATED TO LEUKEMIA CELL SURVIVAL

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Background: Bone marrow stromal cells provide a favorable microenvironment for ALL cells and contribute to prevention of apoptosis in ALL cells. The mechanisms are poorly understood.

Objectives: Our objective is to delineate and therapeutically disrupt critical pathways in the leukemia marrow microenvironment that contribute to ALL cell survival. We hypothesize (1) that nonmalignant marrow stromal cells that efficiently prevent apoptosis of leukemia cells have a distinctive profile of gene expression, and (2) that productive interaction of nonmalignant stromal cells and ALL cells will induce changes in gene expression in relevant pathways in both stromal and leukemia cells.

Design/Method: We developed an in vitro system in which nonmalignant human marrow stromal cells prevent apoptosis in primary human high risk ALL cells. Prevention of leukemia cell apoptosis requires: (a) stromal cell-leukemia cell contact; (b) live stromal cells, i.e., fixed stromal cells do not prevent apoptosis; and (c) stromal cell protein synthesis. We conducted two classes of experiments. First, we compared RNASeq profiles of 17 cell lines that efficiently prevent leukemia cell apoptosis with the RNASeq profiles of 7 cell lines that do not. Second, we assessed global gene expression in both nonmalignant stromal cells and leukemia cells before and after 48 hours of coculture. RNASeq was performed using an Illumina platform. Cufflinks 2 was used to perform differential expression analysis with an FDR cutoff of 0.05. Functional annotation clustering of differentially expressed genes was performed using the Database for Annotation, Visualization and Integrated Discovery software (DAVID).

Results: We identified 409 genes differentially expressed in stromal cells that efficiently prevent apoptosis of leukemia. These genes are involved with cell surface interactions, cell matrix interactions, growth factor binding including PDGF, VEGF and IGF, regulation of cell death, and pathways related to oxidoreductases and purine nucleotides. Following interactions of ALL and stromal cells we identified 458 ALL genes related to regulation of apoptosis, cytokine responses, purine metabolism and extracellular matrix interactions.

Conclusion: We have identified pathways in stromal and leukemia cells that are related to prevention of leukemia cell apoptosis, providing opportunities to identify critical nodes in the networks that might be therapeutically targeted.

TARGETING THE LEUKEMIA NICHE: PRE-CLINICAL EVALUATION OF ENTRECTINIB, A POTENT TRK INHIBITOR, AS A NOVEL THERAPEUTIC APPROACH IN ACUTE MYELOBLASTIC LEUKEMIA (AML)

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Background: Emerging data indicates that dysregulated tropomyosin receptor kinases (TRKs) may also play a role in AML.

Objectives: To determine the therapeutic potential for TRK inhibition in AML

Design/Method: Existing datasets, AML lines and human stromal cells were used to assess TRKA and NGF expression, NGF-mediated signaling and therapeutic efficacy of TRK inhibition with entrectinib

Results: TRKA is highly expressed in normal human common myeloid progenitors suggesting a physiologic role in myelopoiesis. Analysis of a 516 AML patient sample dataset (with 71 controls) revealed expression of TRKA in 95% of AML samples, with 65% of samples expressing levels higher than mean CD34+ normal control expression, and 25% with significantly elevated levels of TRKA (i.e., >2 SD). Analysis of additional datasets revealed the highest expression of TRKA in erythroblastic (M6) and megakaryoblastic (M7/AMKL) leukemias, particularly Down Syndrome AMKL. In a panel of 9 human AML lines, TRKA was expressed in all lines at both the mRNA and protein level. Importantly, human bone marrow stroma cells express high levels of NGF, the ligand for TRKA, suggesting a novel role for NGF/TRKA in the AML-niche. Importantly, NGF stimulation induces MAPK and/or AKT signaling in 8 of 9 AML lines with potential effects on AML proliferation and chemoresistance. As a therapeutic approach, the TRK inhibitor entrectinib led to significant growth inhibition in 4 out of 9 lines with IC50s <200nM. Interestingly, the most sensitive cell lines were FLT3-ITD positive.

Conclusion: TRKA receptor is expressed at high levels in common myeloid progenitors, suggesting an important role for TRKA signaling in early myeloid development. Surprisingly TRKA receptor is expressed in the majority (95%) of human AML samples and lines. Human bone marrow stromal cells express high levels of TRKA ligand NGF, and exposure of AML cells to the TRKA ligand NGF potently induces survival signaling pathways in nearly all AML cells. Finally, a potent, clinically-active TRK inhibitor entrectinib inhibits the survival of nearly half of AML lines tested. These results reveal a novel AML niche-derived mechanism which can be targeted, and support the development of a clinical trial targeting TRK in AML patients using entrectinib.

IDENTIFYING CHILDREN AT INCREASED RISK FOR A CANCER PREDISPOSITION SYNDROME: THE MCGILL INTEGRATED PEDIATRIC ONCOGENETIC GUIDELINES (MIPOGG STUDY)

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Background: Inherited genetic syndromes have increasingly been associated with the development of pediatric tumors. A tumor may be the presenting sign of a genetic disorder and too often, this association goes unrecognized. Clues of an inherited cancer predisposition syndrome (CPS) may arise from the patient's personal or family history, or from the tumors' characteristics.

Objectives: To facilitate recognition of a CPS in patients with cancer, we created simple algorithmic criteria in the form of an educational tool, called the MCGILL INTEGRATED PEDIATRIC ONCOGENETIC GUIDELINES (MiPOGG). These criteria are based on an extensive literature review, and aim to identify children who warrant a cancer genetics referral. To assess the validity and feasibility of the criteria in the MiPOGG, here we have chosen to present those for children with renal tumors.

Design/Method: To determine which patients diagnosed with a renal tumor and subsequent CPS would have been identified using the MiPOGG criteria, we performed a retrospective chart review of all (n=38) pediatric patients with renal tumors between 1995 and 2015 at the Montreal Children's Hospital.

Results: Thirty-eight children were diagnosed with the following renal tumors: Wilms tumor (n=32), rhabdoid tumor (n=2), neuroblastoma (n=1), cystic nephroma (n=1), metanephric adenoma (n=1), renal cell carcinoma (n=1). Four patients had a proven CPS: Beckwith-Wiedemann (n=1), Rhabdoid tumor predisposition syndrome (n=1), Denys-Drash (n=1), Birt-Hogg-Dube (n=1). Of these, the malignancy was the presenting sign of a CPS in 3 patients. According to our criteria, 19/38 patients would have warranted a cancer genetics referral, with 68% of cases having > 1 reason for referral. While only 6 were sent for evaluation, all 19 had > 1 referral criteria. The interval from renal tumor diagnosis to cancer genetics referral ranged from 0 to 30 months.

Conclusion: The MiPOGG criteria would have identified 100% of children with renal tumors and a CPS, demonstrating strong sensitivity, although these criteria may lack stringency. While some children have been referred to genetics by physicians without the MiPOGG guidelines, several patients may have an undiagnosed CPS and would have benefitted from a cancer genetics referral.

ESTABLISHING A REGIONAL RETINOBLASTOMA PROGRAM IN LEBANON - SUCCESSES AND CHALLENGES

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Background: Survival of patients with intraocular retinoblastoma approaches 100% in developed countries, with salvage of the eye in more than 80%. Outcomes in developing countries are poorer, primarily due to delayed presentation, cost barriers, and lack of specialized personnel and equipment.

Objectives: A collaborative program was established to allow access of children with newly diagnosed intraocular retinoblastoma to centralized diagnosis and staging, and multidisciplinary approach to therapy, with local treatment delivered by a pediatric ophthalmologist at a tertiary care setting.

Design/Method: Disease staging was centralized and treatment was planned in a multidisciplinary setting. Patients received chemotherapy at the local hospital, while examination under anesthesia, focal therapy, enucleation, and radiation therapy were provided at no cost to families through a program development initiative by St Jude Children's Research Hospital (SJCRH) in Memphis, Tennessee, United States. Challenging cases were discussed with SJCRH team via teleconference.

Results: Over 2.5 years, 27 patients were evaluated; retinoblastoma was confirmed in 25. Nationalities were Lebanese (8), Syrian (16), and Iraqi (1). Two patients refused treatment. Twelve of the remaining 23 had unilateral disease; 11 underwent enucleation for Group D-E tumors. In 11 patients with bilateral disease, 12/22 eyes were eventually enucleated, 11 of which had presented with group D-E tumors. Six enucleated eyes had high-risk histologic features. Treatment coordination between the centers was feasible. Seventeen patients received chemotherapy. Twelve patients underwent cryotherapy/thermotherapy; two patients with bilateral disease required external beam radiation. One child with bilateral disease died of meningeal recurrence. Useful vision was preserved in 19/22 (86%) remaining patients.

Conclusion: Facilitating access to specialized multidisciplinary care, resolution of financial barriers, and close coordination among medical teams, all contributed to success of the program and vision salvage in affected children. The high rate of advanced intraocular disease at presentation necessitated frequent enucleation, demonstrating a need for raising awareness among pediatricians and ophthalmologists for earlier diagnosis and referral.

A MULTI-CENTER, PHASE-2 TRIAL OF LOSARTAN FOR THE NEPHROPATHY OF SICKLE CELL ANEMIA

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Background: Sickle nephropathy (SN) is a common and progressive manifestation of sickle cell anemia (SCA). Albuminuria indicates glomerular injury and portends renal failure. In a murine model of SCA, we found that increased TGF- β signaling underlies SN, and its downregulation by losartan, an angiotensin receptor blocker, reduced albuminuria and SN progression. The effect of losartan in humans with SCA is unknown.

Objectives: Determine the effect of losartan on SN in a phase-2, open-label study to inform the design of a phase-3 randomized trial.

Design/Method: Oral losartan was administered for 6 months to individuals with SCA (HbSS or S/ β 0-thalassemia) ≥ 6 years of age. Main exclusion criteria: chronic transfusions, GFR <60 mL/min/1.73m², hyperkalemia, and contraindications to losartan. Enrollment was in 3 groups defined by urinary albumin-to-creatinine ratio (UACR): no albuminuria (NoA: <30 mg/g); microalbuminuria (MicroA: 30-300); and macroalbuminuria (MacroA: >300). The primary endpoint was a $\geq 25\%$ reduction UACR from baseline. Sample size was calculated to detect the primary endpoint in $\geq 30\%$ of the MicroA group with $>80\%$ power. Secondary endpoints: urine osmolality, GFR, UACR classification and toxicity.

Results: There were 36 participants (mean age 24.1y; 53% female) in 3 groups (NoA=15; MicroA=13; MacroA=8). Four were non-evaluable (marked non-compliance and/or early termination). The primary endpoint ($\geq 25\%$ reduction in UACR) was met in 41% (13/32) overall [83% (5/6) of MacroA; 58% (7/12) of MicroA; 7% (1/14) of NoA]. Among MacroA and MicroA participants, 67% (12/18) met the primary endpoint. Overall, UACR classification improved in 28% but worsened in 9%. In MacroA and MicroA participants, UACR classification improved in 50% but worsened in 11%. Mean UACR was 202 mg/g (S.E.M. 59, median 50) before and 137 (S.E.M. 47, median 16) after losartan ($P=0.29$). Urine osmolality and GFR did not change significantly (393 vs 370 mosm/kg \cdot H₂O, $P=0.11$; 147 vs 139 mL/min/1.73m², $P=0.43$). Losartan was discontinued for leg cramps (N=1); GFR decline $>25\%$ (N=1); and serum creatinine rise $>50\%$ (N=1).

Conclusion: Losartan appeared to decrease SCA-related albuminuria in most participants. Those with baseline macroalbuminuria appear to have the greatest benefit, nearly all of whom showed a response. A phase-3, randomized, placebo-controlled trial is being designed to determine the efficacy of losartan.

SBDS KNOCKOUT IN ZEBRAFISH RESULTS IN NEUTROPENIA, DIMINISHED GROWTH, AND REDUCED VIABILITY, INDICATING THE ROLES OF SBDS IN EMBRYONIC AND POST-EMBRYONIC DEVELOPMENT

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Background: Shwachman-Diamond syndrome (SDS) is a multisystem disorder characterized by neutropenia, exocrine pancreatic insufficiency, and skeletal abnormalities. Individuals with SDS are also at increased risk for developing myelodysplastic syndrome and/or acute myeloid leukemia. SDS results from mutations in the SBDS gene. Genetic ablation of SbdS results in early embryonic lethality (ED 7.5) in mice. Zebrafish provide an attractive, alternative model organism with demonstrated relevance to mammalian hematopoiesis. Genome analysis of zebrafish (*Danio rerio*) revealed the presence of a single sbds gene, encoding a protein 90% identical to the human orthologue.

Objectives: Analysis of zebrafish sbds mutants will reveal new insights into the function of this gene during vertebrate development and into the pathophysiology of Shwachman-Diamond Syndrome.

Design/Method: We used CRISPR/Cas9 genome editing technique to generate indel mutations in sbds. To determine whether loss of sbds affects the number of neutrophils and macrophages, we used the transgenic lines Tg(mpx:Dendra)uwm4 and Tg(mpeg:Dendra)uwm12. Whole-mount o-dianisidine staining was used for erythrocyte staining.

Results: We created a zebrafish line null for sbds (sbds^{nu132/nu132}). Western blotting showed a decrease in SbdS levels until 8 dpf when the protein was absent. These results suggest that the presence of SbdS during early stages of the development is due to maternal deposition. SbdS knockouts showed reduced viability. Unlike SbdS^{-/-} mice, homozygous mutant sbds^{nu132} live up to 6 weeks. They display a marked growth retardation phenotype. Interestingly, growth retardation was not observed until 15 days post fertilization (dpf). We observed a significantly low number of neutrophils at 5 dpf and 15 dpf. However, no statistically significant difference in macrophage number was found. Also, no differences in hemoglobinized erythrocytes were found by 10 dpf. The structure of the pancreas, liver and eye was defective in homozygous mutants at 21 dpf.

Conclusion: We generated a zebrafish model of SDS, making it a highly relevant model to understand its pathophysiology.

CHILDREN'S HOSPITAL-ACQUIRED THROMBOSIS DATABASE (CHAT): A MULTI-INSTITUTIONAL DATABASE FOR PROSPECTIVE IDENTIFICATION OF INDEPENDENT PEDIATRIC VTE RISK FACTORS

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Background: Pediatric hospital-acquired venous thromboembolism (HA-VTE) incidence is rising and large sample sizes are needed for prospective epidemiologic risk factor studies.

Objectives: We formed the multi-institutional Children's Hospital-Acquired Thrombosis (CHAT) web-based REDCap registry to identify independent HA-VTE risk factors for clinical risk score development.

Design/Method: This IRB-approved, retrospective chart review reveals HA-VTE risk factors from children who developed VTE during admission at 3 pediatric hospitals from January 2012 - December 2014. We used descriptive statistics to summarize demographics, medical comorbidities, and central venous catheter (CVC) characteristics for the initial 400 patients entered into the database, as well as characteristics of the VTEs themselves.

Results: VTEs were diagnosed after a median of 9 (IQR 4-18) days, in patients with median age of 3.7 (IQR 0.4-13.8) years, with a slight (57%) male predominance. Sixty-three percent of subjects had significant past medical history and 8% were immobile at baseline. A majority of subjects were intubated at some point during their admission (60%), had at least one infection (59%) or surgery (48%) while hospitalized. The majority of VTEs were associated with a CVC (76%), were symptomatic at diagnosis (79%), and were diagnosed outside a critical care unit (65%). Distribution included arms/legs (81%), CSVT (7%), PE (5%), abdomen (4%), and intracardiac (4%).

Conclusion: Our initial results (phase 1) demonstrate a slight male predisposition, multiple associated chronic medical illnesses, and acquired hospital course co-morbidities, primarily CVC. Ongoing work includes incorporating subjects from multiple additional institutions and integrating data from control subjects to identify independent factors to develop a risk score model. Long-term goals include (phase 2) prospective validation of the risk score in a second cohort of children from other hospitals with the ultimate plan of using the scoring system to stratify children for (phase 3) future randomized clinical trials of the efficacy and safety of various risk-based prevention strategies to reduce pediatric HA-VTE incidence without unnecessary thromboprophylaxis exposure.

PREDICTORS OF REMISSION IN PEDIATRIC IMMUNE THROMBOCYTOPENIA (ITP): AN ANALYSIS OF THE INTERCONTINENTAL CHILDHOOD ITP STUDY (ICIS) GROUP REGISTRY II DATA

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Background: Pediatric immune thrombocytopenia (ITP) is a rare, acquired, autoimmune bleeding disorder that spontaneously remits in most children. Approximately 20% of children will develop chronic thrombocytopenia beyond 12 months and may have an increased bleeding risk. Predictors of remission have not been well defined.

Objectives: To identify factors which may predict disease remission in pediatric ITP.

Design/Method: Data from the ICIS Group Registry II, a large prospective cohort of pediatric patients with ITP, were analyzed to investigate factors that were associated with disease remission.

Results: In Registry II, 705 patients had data through 12 months, and 383 patients had data at both 12 and 24 months. By univariate analysis, younger age and pharmacologic treatment at diagnosis were associated with remission at 12 and 24 months ($p < 0.0001$, for both variables and times). Bleeding at diagnosis was also associated with remission at 12 ($p < 0.0001$) and 24 months ($p = 0.0213$). By multivariate analysis, remission at 12 months was associated with younger age (< 1 year OR 4.65 95% CI 2.04, 10.60; 1- < 6 years OR 3.24 95% CI 2.12, 4.95; 6- < 10 years OR 2.30 95% CI 1.50, 3.50), higher bleeding grade at diagnosis (OR 2.30 95% CI 1.50, 3.50), and combination treatment with intravenous immunoglobulin (IVIG) and corticosteroids at diagnosis (OR 1.94 95% CI 1.06, 3.58). Only younger age (< 1 year OR 6.97 95% CI 2.34, 20.75; 1- < 6 years OR 4.06 95% CI 2.24, 7.33; 6- < 10 years OR 2.12 95% CI 1.05, 4.27) and combination treatment with IVIG and steroids at diagnosis (OR 3.13 95% CI 1.48, 6.64) were associated with remission at 24 months. Patients < 1 year were most likely to achieve remission at 12 and 24 months. Gender and platelet count at diagnosis were not associated with remission.

Conclusion: Younger age, higher bleeding severity at diagnosis, and pharmacologic treatment with a combination of corticosteroids and IVIG at diagnosis are associated with remission at 12 months in ICIS Registry II. Patients < 1 year of age had the highest likelihood of remission at both 12 and 24 months. The relationship between bleeding and treatment at diagnosis in pediatric ITP requires further study to better understand whether these are independent predictors of remission.

HEMATOPOIETIC CELL TRANSPLANTATION FOR CHILDREN WITH OSTM1-OSTEOPETROSIS: BRIEF REPORT

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Background: Osteopetrosis (OP) is a rare genetic disease characterized by the dysfunction or deficiency of osteoclasts leading to increased bone mineral density (BMD) secondary to absent bone reabsorption. Children with malignant infantile osteopetrosis (MIOP), the lethal form of OP, exhibit an array of symptoms including pancytopenia, neurologic abnormalities, hepatosplenomegaly, growth deficiency, hypocalcemia, and respiratory compromise. Approximately 80% of children have an identifiable genetic mutation. Currently, there are 10 known mutations that are responsible for the OP phenotype. The most common mutations include TCIRG1 (50%), CICN7 (15%), and OSTM1 (5%) which all encode proteins involved in the acidification of osteoclast lacunae. Hematopoietic cell transplantation (HCT) is the only potentially curative therapy; however, only a subset of patients, depending on the mutation, respond to HCT.

Objectives: While children with TCIRG1 and CICN7 mutations should be considered early for HCT, an OSTM1 mutation in children presenting with neurologic symptoms has been regarded as a contraindication to HCT since it will not abrogate the associated neuropathologic progression to death. However, whether HCT can arrest the neuropathologic progression if a child undergoes transplantation prior to the onset of significant neurologic symptoms has not been reported.

Design/Method: In this report, we describe a 4 week old male who presented with tachypnea, increased BMD on chest x-ray, thrombocytopenia, and macrocytic anemia found to have two heterozygous mutations in the OSTM1 gene (Exon 2 and IVSI). Neurological testing, including brain MRI, ABER-auditory evaluation and electroretinogram, were normal. Given absence of significant neurologic signs and symptoms, and after careful discussion with family, decisions was made to move forward with HCT with his HLA-matched sibling. Patient underwent myeloablative conditioning with busulfan and fludarabine at 3 months of age.

Results: Transplant course was uneventful; however, two months after transplantation patient developed infantile spasms and a brain MRI showed diffuse cerebral atrophy. Despite his neurological progression, at 17 months of age he has reduced BMD and healthy reconstituted hematopoiesis.

Conclusion: The one-year follow-up of our patient suggests that early HCT in patients with an OSTM1 mutation does not prevent neurologic deterioration. Understanding his complete outcome requires longer follow-up.

TREATMENT OF DOCK8 IMMUNODEFICIENCY SYNDROME WITH HEMATOPOIETIC STEM CELL TRANSPLANT

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Background: Mutations in cytoskeleton regulators such as CD19, dedicator of cytokinesis 8 (DOCK8), and Wiskott-Aldrich syndrome protein (WASp) are often associated with immunodeficiency. Autosomal recessive mutations in DOCK8 results in DOCK8 immunodeficiency syndrome (DIDS). In the largest international retrospective survey of patients with DIDS, 36 underwent hematopoietic stem cell transplant (HSCT), suggesting a potential curative measure. Most recent literature review of patients with DIDS undergoing HSCT supports these findings. However, there are no consensus guidelines for therapy and optimal management remains unknown.

Objectives: Describe the outcome of HSCT in a patient with DIDS

Design/Method: Case report

Results: A 15-year-old Saudi Arabian male, a product of consanguineous marriage and a history of DIDS was referred to our center for HSCT. Medical history revealed multiple food allergies, eczema and asthma since age 4. Infectious complications included recurrent bacterial, fungal and viral skin infections besides sinopulmonary infections. Five family members died of DIDS. Lab workup revealed eosinophilia, CD4+ lymphopenia, high IgE (>3000 mg/dL) and low IgM level. Gene sequencing confirmed DOCK8 deficiency with a homozygous mutation. Patient received a 10/10 HLA-matched HSCT from his elder brother, heterozygous for the same mutation as the patient. Conditioning regimen included Fludarabine and Busulfan. Short course Methotrexate and Tacrolimus was used for Graft-versus-host disease (GvHD) prophylaxis. He engrafted on T+12. Peripheral blood chimerism on T+61 showed 7% recipient DNA. Following HSCT patient had good immune reconstitution. Post transplant complications include verruca plana and mild reactivation of HSV blepharitis which was treated appropriately. Presently, patient is T+75, on Tacrolimus without any signs of acute GvHD.

Conclusion: In summary, our case represents typical natural course of patients with DIDS. Timely referral and HSCT proved to be life saving for our patient while under treatment of patient's relatives proved fatal. Hence, we emphasize the importance of early recognition and screening of family members at risk of developing fatal complications. Our case highlights the need for large scale prospective clinical trials to evaluate the efficacy of HSCT in DIDS. For now, scientific insight based on remarkable resemblance between the clinicopathologic phenotype of WASp and DOCK8 mutations suggests a curative potential for HSCT in DIDS.

IFOSFAMIDE, GEMCITABINE AND VINOURELBINE (IGEV) IS AN EFFECTIVE SALVAGE REGIMEN WITH EXCELLENT STEM CELL MOBILIZATION IN RELAPSED AND REFRACTORY PEDIATRIC HODGKIN LYMPHOMA

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Background: With current upfront therapy, greater than 85% of children with Hodgkin Lymphoma (HL) can achieve long-term remission. However, there remains a challenging subset of patients with relapsed or refractory disease who fail first line therapy and require salvage therapy prior to consolidation with autologous stem cell transplant (ASCT). The combination of ifosfamide, gemcitabine, and vinorelbine (IGEV) has been used as a salvage regimen in adults with relapsed and refractory HL with high rates of disease response and of successful stem cell mobilization. Utilization of this regimen in pediatric HL has not been previously reported.

Objectives: To report the efficacy and toxicity of IGEV salvage chemotherapy regimen in pediatric patients with refractory or relapsed HL.

Design/Method: Eight pediatric patients aged 6 to 16 years with primary refractory (N=4) or first relapse (N=4) HL were included. The patients were treated at a single institution with 2-4 cycles of IGEV chemotherapy followed by ASCT and involved-field radiation therapy for those who had not received it during upfront therapy (N=7).

Results: The overall response rate was 100%: 4 patients obtained complete response, and 4 had partial response based on FDG PET/CT disease evaluations after IGEV therapy. At a median follow up of 74 months, seven out of eight patients are alive and in second remission. One patient had progressive disease after ASCT and has died. All patients had successful CD34+ stem cell mobilization after a single apheresis procedure. The median CD34+ cell count was $12 \times 10^6/\text{kg}$. The primary toxicities were hematologic and two patients had grade 3 infection. There were no grade 4 non-hematologic toxicities and no toxicity-related mortalities.

Conclusion: IGEV is an effective salvage regimen for children with relapsed or refractory Hodgkin Lymphoma due to high rates of disease response and successful facilitation of autologous stem cell collection, with an acceptable toxicity profile.

PREVALENCE OF IRON OVERLOAD IN PEDIATRIC HEMATOPOIETIC STEM CELL TRANSPLANTATION (HSCT) SURVIVORS

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Background: As hematopoietic stem cell transplantation (HSCT) techniques and supportive care have improved, more children are surviving their transplants. These patients require multiple transfusions, which may result in iron overload, though its prevalence in this population is unknown.

Objectives: To determine the prevalence and difference in prevalence of iron overload at 1 and 2 years after HSCT and predictors of iron overload in pediatric HSCT survivors.

Design/Method: We evaluated 107 children (median age at HSCT: 8 years, range 0-21; 54% male) who were diagnosed and underwent HSCT (68% allogeneic) between 2005 and 2012. Iron overload was defined as ferritin levels ≥ 1000 ng/mL. We used SAS 9.4 software to perform McNemar's chi-square test, sign test, and logistic regression to evaluate the difference in prevalence of iron overload, the change in ferritin level, and factors associated with iron overload at 1 and 2 years after HSCT.

Results: Sixty-one patients (57%) had a ferritin recorded 1 year post-HSCT and 43 (40%) at 2 years. Patients with a recorded ferritin were more likely to be male (63% vs. 37%, $p=0.02$), an allogeneic transplant recipient (82% vs. 44%, $p<0.01$), and have an underlying diagnosis of leukemia/MDS (53% vs. 28%, $p<0.01$). Between 1 and 2 years post-HSCT, there was a significant decrease in the mean ferritin level (1030 ng/mL vs. 908 ng/mL, $p=0.01$); however, there was no change in prevalence of iron overload (28% at both time points, $p=0.18$). Patients who received ≥ 300 mL/kg of packed red blood cells (pRBCs), approximately 20-30 transfusions, were more likely to have iron overload (OR 7.3, 95% CI 1.2-46.1). Other factors, including age, race, ethnicity, gender, underlying diagnosis, stem cell source, and ABO incompatibility, were not associated with risk of iron overload.

Conclusion: Over a quarter of patients had evidence of iron overload 2 years after HSCT. The lack of improvement in iron overload from 1 to 2 years post-HSCT highlights the need for regular iron overload screening and treatment in order to reduce severe morbidity, especially in survivors who receive at least 300 mL/kg of pRBCs. Larger studies are needed to assess other risk factors for iron overload in this population.

INDUCTION TOXICITIES AND DELAY IN THE START OF PLANNED POST-INDUCTION THERAPY IN CHILDHOOD ALL: A REPORT FROM DANA FARBER CANCER INSTITUTE ALL CONSORTIUM PROTOCOL 05-001

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Background: Children undergoing induction therapy for acute lymphoblastic leukemia (ALL) are at risk for treatment-related toxicities leading to morbidity, mortality and delays in planned post-induction therapy.

Objectives: We aimed to characterize treatment-related toxicities in ALL induction and to assess the association between induction toxicities and delay in the start of planned post-induction therapy. We explored whether delay in the start of planned post-induction therapy was ultimately associated with reduced disease-free survival (DFS).

Design/Method: Patients aged 1–18 years with newly diagnosed ALL from 11 consortium sites were enrolled on Protocol 05-001. All patients received identical 4-week induction therapy, including anthracycline, regardless of risk group. Induction toxicities were prospectively collected and graded according to Common Terminology Criteria for Adverse Events v3.0 (CTCAE). Post-induction treatment delay was assessed as follows: >7-14 days, >14-21 days or >21 days from date of complete remission (CR) to the start of the next treatment phase (0-7 days considered no delay.) DFS was compared between groups with the log-rank test and estimated with the Kaplan-Meier method.

Results: Between 2005 and 2011, 794 eligible patients were enrolled, of whom 95% achieved CR. During induction, 332 patients (42%) experienced Grade 3 or higher toxicity. The most common toxicities were infection (28% of patients), gastrointestinal (9%), metabolic (5%), cardiovascular (4%), hepatic (2%), and neurologic (2%). Sixteen patients (2%) died in induction, most commonly due to Grade 5 infection (N=11). Of 739 evaluable patients, 88 patients (12%) experienced delay in the start of planned post-induction therapy (4% >7-14 days, 2% >14-21 days, 6% >21 days.) The following induction toxicities were associated with delay: infection ($p<0.0001$), gastrointestinal (<0.0001), neurologic ($p=0.002$), cardiovascular ($p=0.006$), and metabolic ($p=0.01$). Within the gastrointestinal category, typhlitis ($p=0.03$), mucositis ($p=0.002$) and pancreatitis ($p=0.01$) were associated with delay. Hyperglycemia in induction was associated with reduced DFS ($p=0.003$). Other induction toxicities and each delay group were not associated with reduced DFS.

Conclusion: Grade 3 or higher toxicities are frequent during childhood ALL induction and are associated with treatment delay. However induction toxicities and delay in planned post-induction therapy do not appear to impact long-term DFS. Investigations to reduce treatment-related toxicities, such as antimicrobial prophylaxis, are warranted.

LOW LEVELS OF VITAMIN A ARE ASSOCIATED WITH INCREASED RISK OF ACUTE GRAFT VERSUS HOST DISEASE IN CHILDREN

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Background: Vitamin A and its metabolite retinoic acid directly influence the development and function of the immune system, enhancing differentiation of regulatory T-cells. In mouse models, vitamin A deficiency increased inflammatory cytokines in the GI-associated lymphoid tissue and draining lymph nodes. In contrast, other mouse models have shown that exogenous vitamin A exacerbated GI GVHD, increasing trafficking of T-cells to the gut and that genetic ablation of retinoic acid receptor signaling from donor T-cells also reduced severity of GVHD in the GI-tract and liver, suggesting that vitamin A can be pro and anti-inflammatory depending on context.

Objectives: We hypothesized that lower levels of vitamin A will lead to increased incidence of GVHD.

Design/Method: We conducted a cohort study of 114 children receiving allogeneic HSCT enrolled into our BMT repository. Blood samples and clinical data were collected prospectively, once weekly, from admission until 100 days post-transplant. Vitamin A levels were measured in patient plasma at baseline and Day 30 using the Human Vitamin A ELISA kit from MyBiosource. Univariate and multivariate analyses were performed with primary endpoints of development of GVHD

Results: The cumulative incidence of grades 2-4 and GI GVHD was increased in children with a vitamin A level below the median at Day 30 compared with those above the median (38.6 vs 12.4% at 100 days, $p=0.0008$; 30.4 vs 7% at 100 days, $p=0.002$). In a multivariate analysis, vitamin A level remained an independent risk factor for GVHD.

Conclusion: Our data show that vitamin A deficiency is associated with increased risk of acute GVHD, including GI GVHD. It is possible that this is due to a direct effect of vitamin A deficiency on the immune system, or that GVHD itself leads to reduced vitamin A levels. To attempt to address this, we looked at change in vitamin A level from baseline to day 30, no association was seen ($p=0.15$). Also, RBP4 levels were measured at Day +30 in patient plasma, no association with development of GVHD was seen ($p=0.68$). In future studies we will seek to replicate these current data in independent datasets and explore the mechanism of this finding.

MINIMAL RESIDUAL DISEASE (MRD) STRONGLY PREDICTS CLINICAL OUTCOME IN A REGIMEN COMBINING BORTEZOMIB WITH REINDUCTION CHEMOTHERAPY FOR FIRST RELAPSE PEDIATRIC ACUTE LYMPHOBLASTIC LEUKEMIA (ALL): A CHILDREN'S ONCOLOGY GROUP (COG) STUDY

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Background: Background: The COG conducted a phase 2, single-arm, reinduction study for first relapse pre-B or T-ALL, or T-cell lymphoblastic lymphoma (LL) relapse. The study combined bortezomib (bortez), a 26S proteasome inhibitor, with a standard COG three-block reinduction backbone (AALL01P2).

Objectives: Objective: The primary objective of this study was to compare reinduction (CR2) rates to historical control CR2 rate; the objective was successfully completed and previously presented.¹ Here we examine the effects of chemotherapy on MRD at each therapy block, and correlate MRD status with clinical outcome.

Design/Method: Methods: 146 eligible patients were stratified by age, disease immunotype and time to relapse. B-ALL pts ≤ 21 yrs. old were stratified as either early ($<18m$) (n= 49) or intermediate (18-36m) (n=61) risk medullary or combined medullary/CNS relapse. The trial also enrolled 22 evaluable T-cell ALL pts, 4 pre-B ALL pts >21 yrs., and 10 LL pts (no MRD). MRD was assessed following each therapy block. Event free survival (EFS) and overall survival (OS) were determined using Kaplan-Meier curves.

Results: Results: A total of 88, 49 and 31 evaluable B-ALL patients in Stratum 1 and 2 had successful MRD determinations at the end of Block 1, 2 and 3, respectively. Using an MRD sensitivity cutoff of 0.01%, the corresponding MRD-negativity rates were 31%, 57% and 74%. Percentages were similar using an MRD cutoff of 0.1% (43%, 59% and 75%). End-block 1 MRD (0.01%) was strongly predictive of outcome in both high ($<18m$) and intermediate (18-36m) risk patients. EFS (2y) was 70% in the MRD-neg vs. 3% in MRD-pos (p=0.0001). Similar results were seen in those relapsing 18-36m from diagnosis; 58% EFS if MRD-neg vs. 6% if MRD-pos (p<0.0001).

Conclusion: Conclusions: MRD was an excellent predictor of clinical outcome. Chemotherapy was effective at reducing MRD following each therapy block. Patients with positive MRD after induction block I, however had an exceedingly poor prognosis. ¹Horton SIOP 2014

THE SIGNIFICANCE OF RED BLOOD CELL ANTIGEN MATCHING ON BONE MARROW TRANSPLANT OUTCOMES IN PATIENTS WITH SICKLE CELL DISEASE

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Background: Hematopoietic stem cell transplant (HSCT) is the only potential curative therapy for sickle cell disease (SCD) currently. While significant research has been performed on the clinical impact of ABO-incompatible HSCT in patients with SCD, only preliminary studies have analyzed the outcomes of HSCT with non-ABO red blood cell (RBC) antigen discordance.

Objectives: To investigate the frequency and clinical significance of minor RBC antigen discordance on HSCT outcomes in patients with SCD.

Design/Method: This study is a retrospective analysis of a cohort of patients with SCD who received a HSCT from 1995 to 2015, at a single institution.

Results: Of the 48 patients with SCD who received HSCT, 17 (35.4%) had available data on minor RBC antigens for both donor and recipient. All 17 patients received transplants from HLA and ABO-matched related donors. There were 52.9% males, 88.2% African Americans, and the mean age at transplant was 8.4 years old. The majority (70.6%) of conditioning regimens were myeloablative. The primary indications for transplant were history of stroke (47%), vasoocclusive crisis (29.4%), and acute chest syndrome (17.6%). Prior to transplant, alloantibodies were present in 35.3% of the subjects, the majority being anti-Rh. All but two patients were followed for a minimum of 1 year post-transplant. The majority of patients (94.1%) had at least 1 minor RBC antigen discordant with their donor. Fourteen patients (82.4%) had 1 to 3 discordances. The most common discordant blood group systems were Rh (47%), MNS (35.3%), and Dombrock (29.4%). None of the subjects developed novel antibodies following HSCT, despite discordances. Overall, there was little correlation between the number of minor RBC antigen discordances and HSCT outcomes (overall survival, graft failure, transfusion requirements, time to engraftment, time to transfusion independence, and complications). However, patients with two or more minor RBC discordances had more chronic graft-versus-host disease (GvHD) (36.4%), while patients with one discordance were more likely to develop acute GvHD (50%).

Conclusion: There appeared to be a trend towards increasing chronic GvHD in patients with greater numbers of discordant minor RBC antigens, but no other association with clinical HSCT outcomes; however, given the limited size of this cohort, further studies are required.

PRELIMINARY RESULTS OF THE REDUCED BURDEN OF ONCOLOGIC THERAPY (REBOOT) TRIAL IN CHILDREN, ADOLESCENTS AND YOUNG ADULTS WITH INTERMEDIATE AND HIGH RISK AGGRESSIVE B-CELL NON HODGKIN LYMPHOMA

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Background: While highly curable, chemotherapy for B-NHL is associated with high rates of acute toxicity. The Children's Oncology Group ANHL01P1 study demonstrated safety and feasibility of adding six doses of rituximab to FAB Group B Stage III/IV and FAB Group C FAB/LMB96 based chemotherapy (Goldman et al, Leukemia 2013 and BJH 2014). An international trial randomizing children and adolescents with higher risk disease to rituximab was recently stopped prematurely following an observed improvement in 1 year EFS with the addition of rituximab (Gross, personal communication).

Objectives: To safely reduce therapy burden by reduction in anthracycline exposure and/or reduction of standard intrathecal therapy through use of intrathecal liposomal cytarabine (IT L-ARA-C) with addition of rituximab.

Design/Method: Intermediate (Group B) and high risk (Group C) mature B-cell lymphoma/leukemia patients, ages 3-30 excluding immunodeficiency and primary mediastinal patients are being enrolled on a multicenter study. All patients receive six rituximab doses during two induction (two doses/course) and two consolidation (one dose/course) courses with 60% doxorubicin dose reduction in intermediate risk patients. IT L-ARA-C (35mg 3-16 year and 50mg >16 years) is given with concurrent dexamethasone following methotrexate clearance in each induction cycle in CNS negative patients. CNS positive patients receive two additional doses during consolidation and maintenance.

Results: As of January 2016, 24 patients (median age 12 years (range 3-25)), 15 males, 11 Burkitt/13 DLBL, 18 Group B (1 Stage II, 17 stage III) and 6 Group C (4 CNS+) have been enrolled. There has been one reported rituximab related grade 3 anaphylaxis managed with steroids in subsequent dosing. The rate of grade III/IV mucositis and febrile neutropenia during induction in intermediate risk patients receiving reduced anthracycline dosing is 5.5%. There have been no notable neurological toxicities associated with IT L-ARA-C. With a median time from study entry of 54 weeks (range 6-152 weeks), the EFS and OS is currently 100%.

Conclusion: Results to date suggest we can safely reduce anthracycline exposure and subsequent acute chemotherapy related toxicity in intermediate risk B-NHL. No limiting side effects were observed with IT L-ARA-C given after methotrexate clearance. One year EFS remains high. Funded in part by Sigma Tau Pharmaceuticals.

PHARMACOKINETICS AND CLINICAL OUTCOMES OF INTRAVENOUS BUSULFAN ADMINISTERED TWICE DAILY DURING CONDITIONING IN PEDIATRIC RECIPIENTS PRIOR TO FAMILIAL HAPLOIDENTICAL(FHI) T-CELL DEPLETED (TCD) ALLOGENEIC HEMATOPOIETIC STEM CELL TRANSPLANTATION (AlloHSCT) IN HIGH RISK SICKLE CELL DISEASE (SCD)

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Background: Busulfan (Bu) is commonly used in AlloHSCT conditioning regimens; however, it requires plasma level monitoring due to narrow therapeutic window. We have previously reported that Bu dosed q12h IV has a comparable pharmacokinetic (PK) profile with q6hr dosing with 59% therapeutic first-dose Bu steady state concentration (C_{ss}) success in pediatric AlloHSCT recipients¹

Objectives: Determine the PK of Bu q12h IV and clinical outcomes related to Bu exposure in a cohort of patients with SCD undergoing FHI TCD AlloHSCT with CD34+ enrichment and T-cell addback.

Design/Method: Patients (2-21 y) with ≥ 1 high-risk SCD features were eligible. The myeloablative conditioning regimen included fludarabine, thiotepa, cyclophosphamide, R-ATG, Bu 1.6mg/kg/dose (2mg/kg/dose **Results:** Fourteen patients were evaluable. Median age 14(5-20)y, M/F (7/7), dosing weight 44.4(19.2-65.6) kg and follow-up was 383(156-643) days. PK analysis revealed mean \pm SEM Volume of distribution (V_d) of 0.66L/kg (± 0.03), Half-life (t_{1/2}) of 131(± 5.27) mins and Clearance (CL) of 3.45 mL/min/kg (± 0.16). Therapeutic first-dose Bu C_{ss} was achieved in 64% of recipients with mean \pm SEM of 657.5(± 29) ng/mL. Median neutrophil and platelet engraftment occurred at 9 and 16 days, respectively. No primary or secondary graft failures were seen. Severe SOS leading to death occurred in only one recipient with Bu C_{ss} 779 ng/mL/AUC of 2302 mmol*min/L, and one had grade 2 seizure on day-10. One-year median whole blood and RBC donor chimerism was 99% for both.

Conclusion: PK parameters of Bu q12h-dosing in this SCD cohort are consistent with previously reported q12h-dosing PK data in a non-SCD population and also with established q6h-dosing PK data. Favorable clinical outcomes and low incidence of toxicity suggest that Bu q12h-dosing in this population is safe, with a low incidence of SOS and 100% engraftment. 1. Gall, JB/Cairo, M et al. Bone Marrow Transplant 2013.

RACE AND ETHNICITY DO NOT IMPACT OUTCOMES AFTER RELAPSE OF CHILDHOOD B-LYMPHOBLASTIC LEUKEMIA: A REPORT FROM CHILDREN'S ONCOLOGY GROUP (COG) STUDY AALL0433

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Background: Relapsed childhood B-ALL has a poor prognosis, with timing and site of relapse being the best predictors of subsequent outcome. Race and ethnicity have previously been shown to impact survival of children with newly diagnosed ALL, but their effect on prognosis after relapse is unknown.

Objectives: We report updated outcome data and assess the prognostic impact of end induction minimal residual disease (MRD), race, and ethnicity for patients with relapsed B-ALL enrolled on COG AALL0433.

Design/Method: AALL0433 was a Phase-3 study for patients with intermediate-risk relapse of childhood B-ALL, defined as early CNS/testicular relapse (<18 months from diagnosis) or late BM/combined relapse (\geq 36 months). Race/ethnicity data were collected at enrollment. Therapy was based upon COG relapse protocols AALL01P2/P9412, and included randomization of vincristine dose (Arm-A 1.5mg/m² versus Arm-B 2mg/m²). Due to excess neurotoxicity resulting in early closure (ASPHO 2011), subjects on Arm-B were excluded from analysis. End-induction MRD was measured by flow cytometry in a central reference laboratory.

Results: 271 eligible patients enrolled overall. The distribution of patients by race/ethnicity (6% black; 23% Hispanic) was similar to that of front-line COG B-ALL trials. The 3-year EFS/OS for the BM relapse cohort were 69.9 \pm 3.7% and 78.4 \pm 3.3% respectively. Despite small patient numbers, race did not appear to predict outcome, with EFS of 88.9 \pm 11.2% for black versus 69.2 \pm 4.2% for white patients (p=0.55). Ethnicity also was not predictive, with 3-year EFS of 71.3 \pm 7.5% for Hispanic versus 69.2 \pm 4.3% for non-Hispanic patients (p=0.85). MRD was highly predictive, with 3-year EFS/OS of 84.9 \pm 4.2% and 93.8 \pm 2.9% for those with MRD <0.1%, versus 53.7 \pm 8.2% and 60.0 \pm 8.3% for MRD \geq 0.1% (p<0.0001).

Conclusion: Outcomes for patients with late marrow relapse of childhood ALL on AALL0433 are comparable to other recent international trials. MRD was a robust predictor of outcome. In contrast to newly-diagnosed B-ALL, race and ethnicity do not appear to impact subsequent relapse/survival rates after recurrence of leukemia. Differences in therapeutic intensity or disease biology after relapse could play roles in explaining the lessened impact of race and ethnicity on outcomes.

CORD BLOOD TRANSPLANTATION: A 20 YEAR PEDIATRIC EXPERIENCE AT A SINGLE INSTITUTION

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Background: Cord blood is used as an alternative stem cell source for hematopoietic stem cell transplantation (HSCT).

Objectives: We report a 20 year experience from a single institution and the impact of center experience, improved supportive care, and increasing number of banked cord units on outcome over time.

Design/Method: This is a retrospective chart review of all pediatric hematopoietic stem cell transplants over a 20 year period.

Results: Over 500 HSCT's were performed over a 20 year period. Ninety-five were performed using cord blood as the stem cell source. Four were from related donors (RD) and 91 were from unrelated donors (URD). Thirty-two were transplanted for non-malignant diseases (NMD) (31 URD; 1 RD) and 63 with malignant disease (MD) (60 URD; 3 RD). Patients transplanted with related donors for malignant (3) and non-malignant (1) conditions had 5 year event-free survival (EFS) and overall survival (OS) of 100% and 100% respectively. Incidence of acute GVHD grade II-IV was 50% and Grade III-IV was 0 with no chronic GVHD. Ninety-one patients were transplanted with unrelated donors using total body irradiation (TBI) and non-TBI containing regimens depending on disease. Immunosuppression for the majority (86%) consisted of cyclosporine (CSA) with prednisone. Patients were matched at 4 (13%), 5 (64%) or 6 (23%) of 6 loci (high resolution at DRB1). EFS and OS were measured at 100 days (67%/70%), 1 year (58%/65%) and greater than 3 years (58%/61%). Incidence of acute GVHD grade II-IV was 36% and grade III-IV was 22%. Chronic GVHD was absent in 88% of evaluable patients, but limited in 10% with 2% having extensive.

Conclusion: Cord blood offers a viable alternative to bone marrow as a source of hematopoietic stem cells for transplantation. During the more than 20 years that cord blood has been used at our institution, significant improvement in survival was appreciated over time likely do to a number of factors including center experience, improvements in supportive care, more cord units available to select from and better appreciation of factors important in choosing the optimal graft. These results compare favorably with matched bone marrow transplant controls.

PROFILE OF PEDIATRIC CHRONIC MYELOID LEUKEMIA IN THE ERA OF IMATINIB- A STUDY FROM A DEVELOPING COUNTRY

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Background: Pediatric Chronic myeloid leukemia (CML) is very rare. Long term medications, toxicity, family support, education and parents' psychosocioeconomic statuses are areas to be studied, especially in developing countries.

Objectives: To study the clinicohematologic profiles, diagnostic, therapeutic methods, follow-up, impact of the disease on education and the psychosocioeconomic compromise of the parents.

Design/Method: Demography, clinical and hematological features at presentation, treatment, compliance, toxicity and follow up details of all the patients with CML were done from 2011. The parents answered a validated questionnaire to assess the psychosocioeconomic impact.

Results: Seven pediatric patients were diagnosed with CML (2011-2014). Incidence: 5.6% of pediatric leukemias and 9 % of CML. 1 patient opted out; 6 are undergoing treatment and follow-up. Male: female is 2:1. The symptoms were abdominal pain, fever, weight loss. 67% had splenomegaly. All patients presented with chronic phase. One patient (17%) had hyperleukocytosis. FISH and karyotyping detected t(9;22). RT-PCR for bcr-abl was done. All patients were given standard dose of T.Imatinib. Toxic symptoms like gastrointestinal intolerance, skin rashes, hyperpigmentation, bone pain, myalgia and cramps were tolerable in 5 (83%) patients. Five patients (83%) were compliant. Complete molecular response (CMR) was obtained in 12- 18 months, 83% maintaining CMR at 4 1/2 years of follow up. One (17%) patient showed treatment failure due loss of compliance. Four (66%) patients lost 1 year of schooling. Five (83%) middle socioeconomic class patients travelled by bus, met medical expenses by insurance or support from friends. One (17%) upper class patient met expenses by himself. Of the parents evaluated, 33% responded to feeling guilty including interpersonal relationships. 50% were depressed with 33% felt gloomy and worried about future. 50% showed difficulty in coping and burdened. Nobody chose drugs / alcohol. 33% had economic constraints; 17% had to sell assets.

Conclusion: Pediatric patients with CML responded well with minimum toxicity to Imatinib. Schooling was affected. Parents were depressed with difficulty in coping. Government and organizations should initiate strategies to provide psychosocioeconomic support to family members and patients with CML.

ACUTE COMPLICATIONS OF THIOTEPA, BUSULFAN, FLUDARABINE CONDITIONING FOR CHILDREN ACUTE LYMPHOBLASTIC LEUKEMIA

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Background: Total body irradiation (TBI) is associated with many acute and chronic complications but is the standard therapy as conditioning for allogeneic stem cell transplantation (AlloSCT) in children acute lymphoblastic leukemia (ALL). Thiotepa is an alkylating compound with anti-neoplastic and myeloablative activity and can mimic effect of radiation. The use of thiotepa, busulfan, fludarabine (TT-BU-FLU) in acute leukemia is frequent in Europe for adults and children, we report our experience in terms of security for an alternative probably less toxic conditioning in children ALL.

Objectives: To evaluate the rate of acute complications, graft failure, acute GVHD and transplant related mortality in AlloSCT children ALL conditioning with TT-BU-FLU.

Design/Method: We performed a retrospective analysis of consecutive patients with ALL, transplanted with TT-BU-FLU conditioning in a single pediatric stem cell transplantation center with a median follow of 8.3 months (1-28)

Results: From September 2013 to December 2015 21 patients received allogeneic stem cell transplant after TT-BU-FLU conditioning the median age at SCT was 9.1 years (1-15) the percentage of patients in CR1, CR2 y CR3 was 28%, 52% and 20% respectively. 11 patients received unrelated cord blood and 10 match sibling bone marrow. Primary engraftment of donor cells was present in 21 (100%) of patients, acute GVHD grade II-IV was observed in 33% of patients, no patient developed severe mucositis, hemorrhagic cystitis or VOD, 3 patients died because of bacterial sepsis (TRM 14%). In this short follow up period 2 patients have relapsed.

Conclusion: TT-BU-FLU is a myeloablative conditioning safe, with excellent rate of engraftment and low acute toxicity, graft versus host disease is similar to the expected for TBI. With a longer follow up we can conclude if it is as effective as TBI and with less late effects in children ALL.

PRIMARY HEMOPHAGOCYTTIC LYMPHOHISTIOCYTOSIS: THE EXPERIENCE OF A TERTIARY CARE CENTRE IN SOUTH INDIA

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Background: Hemophagocytic lymphohistiocytosis (HLH) is a rare, often life threatening syndrome characterized by reactive, systemic proliferation of benign histiocytes throughout the reticuloendothelial system. In a tropical developing country, the diagnosis may be missed as there are other more common causes for the triad of high fever, splenomegaly and cytopenia.

Objectives: We describe the profile and outcome of children with primary HLH in a pediatric unit of a developing country.

Design/Method: Retrospective review of all cases of Primary HLH diagnosed over a 3 year period in the Pediatric hematology oncology unit.

Results: Fifteen cases of primary HLH were diagnosed as per the HLH 2004 diagnostic criteria. All the cases were referred as cases of pyrexia of unknown origin (PUO). A syndromic diagnosis was made in 8 patients; 7 had Griscelli syndrome and 1 had Chediak Higashi. All were treated as per HLH 2004 protocol. Two children had neurological involvement of HLH. Twelve children responded to induction therapy. One expired before treatment could be initiated and three expired due to refractory HLH while on induction chemotherapy. Stem cell transplant was advised to all patients once HLH was under control but the only child who underwent SCT at another centre, succumbed to sepsis. Seven cases are on continuation therapy and on follow up. Four were lost to follow up while on continuation therapy.

Conclusion: HLH should be considered as a diagnostic possibility in a child who presents with PUO, especially if there are dysmorphic features suggestive of Griscelli or Chediak Higashi syndromes. While therapy with HLH 2004 protocol is successful in the majority of cases, access to stem cell transplant is still a challenge in the developing world.

INCIDENCE AND OUTCOMES OF PERICARDIAL EFFUSION IN PEDIATRIC PATIENTS WHO UNDERGO STEM CELL TRANSPLANT

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Background: Stem cell transplant (SCT) is an established therapy for numerous malignant and non-malignant conditions in the pediatric population. It is associated with significant morbidity and mortality. Acute cardiac complications are rare but can be life-threatening conditions. Pericardial effusion (PE) is a frequent complication that may not be related to cardiac toxicity per se, but may have significant impact in the overall survival of these patients.

Objectives: To assess risk factors for pericardial effusion in pediatric patients after hematopoietic stem cell transplant and its impact on mortality.

Design/Method: We conducted a retrospective chart review of a cohort 158 pediatric patients less than 21 years of age who were admitted to an academic, tertiary hospital in Miami, Florida between 2004 and 2015 who underwent SCT either due to malignancies or other hematological disorders.

Results: Of 158 patients 47 who did not have an echocardiogram prior to transplant were excluded. The total incidence of PE was 38%; 95% CI 29-47%. Our study showed different outcomes between conditioning regimen and infections in patients who developed PE. Of 25 patients who received total body irradiation, 11 (44%) developed PE ($p=0.03$). Graft-versus-host-disease was also significant ($p=0.02$). Among infections, adenovirus ($p=0.017$), and HHV6 infection ($p=0.041$) were significant risks for PE. There was no statistical significance between the incidence of PE and donor source, however the incidence among marrow, peripheral, and cord blood stem cells recipients were 26% (15 of 56), 22% (13 of 59), 37% (14 of 38) respectively which shows an important trend. The length of stay after SCT in patients with no effusion was 44.2+4.43 days compared to 65.1+6.5 days in those who developed PE ($p<0.05$). Overall, there was 22.5% mortality rate during the initial admission for conditioning and stem cell infusion. In those who had PE the mortality rate was 38% ($p<0.05$).

Conclusion: In this cohort we found statistically significant risks for developing PE such as GVHD which has already been reported. In addition HHV6 infection in our opinion is yet to be described. Overall, patients who developed PE had higher morbidity and mortality.

TREATMENT AND SURVIVAL ANALYSIS FOR PEDIATRIC PATIENTS WITH LANGERHANS CELL HISTIOCYTOSIS - A SINGLE INSTITUTION REVIEW

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Background: Langerhans cell histiocytosis (LCH) is an inflammatory disease characterized by proliferation and accumulation of dendritic cells in a background of reactive macrophages, T lymphocytes and eosinophils. The current classification of LCH has a broad spectrum based on extent of organ involvement at diagnosis. Those patients with multifocal disease and risk organ involvement at presentation usually carry a worse prognosis. Another important prognostic factor is initial response to therapy.

Objectives: Determine the incidence, treatment and outcome data of LCH patients diagnosed at Children's hospital New Orleans during the time period (2005-2014).

Design/Method: Retrospective Chart Review

Results: A total of 41 patients were diagnosed during 2005-2014. Twenty patients presented with single system (SS) and 21 presented with multisystem (MS) disease. Of those with MS disease 13 presented with risk organ involvement (RO+ve) and 8 patients with no risk organ involvement (RO-ve). 10/21(48%) patients with MS disease had reactivation/progression with mean follow up of 3.2 years. 4/8(50%) patients with RO-ve disease had reactivation/progression with mean follow up of 2.7 years. As discussed previously one of the most significant prognostic factor for MS RO+ve LCH is response to therapy. Out of the 13 patients with RO+ve disease, no active disease was noted in one patient after 6 weeks(8%), 3 patients after 3 months(23%) and 9 patients after 12 months(69%). 6/13 patients(46%) with RO+ve disease had either reactivation/progression with mean follow up of 3.5 years. When further analyzing it by duration of therapy 3/5(60%) patients who received 6 months therapy had reactivation/progression. In contrast only 3/8 patients (38%) who received therapy for 12 months had reactivation/progression. In this group Histiocyte Society study LCH III reported a 5-year reactivation rate of 27%.

Conclusion: Our data represents a relatively small sample size from a single institution. There was no mortality noted in patients with SS disease and 80% of these patients were event free with mean follow up of 3.7 years. Patients with MS disease had overall event free survival of 52% with mean follow up of 3.2 years. There was one mortality in this group. The major prognostic factors were involvement of CNS risk lesions and duration of therapy.

INHALED CIDOFOVIR FOR ADENOVIRUS PNEUMONITIS IN A PEDIATRIC HEMATOPOIETIC STEM CELL TRANSPLANT RECIPIENT

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Background: Children undergoing hematopoietic stem cell transplant (HSCT) are at increased risk of having potentially fatal viral infections including adenovirus which is a major cause of morbidity and mortality in this population. Cidofovir is a nucleotide phosphate analogue that competitively inhibits the incorporation of deoxycytidine triphosphate into DNA by viral DNA polymerase thereby disrupting further chain elongation. It has demonstrated in-vitro activity against a number of DNA viruses including adenovirus, herpesvirus, poxvirus, papillomavirus and polyomavirus when given intravenously (IV). Recent case reports have described the safe and successful administration by inhalation for the treatment of respiratory viral infections.

Objectives: To report the case of a pediatric hematopoietic stem cell transplant recipient treated with inhaled cidofovir for adenovirus pneumonitis.

Design/Method: Case report and literature review

Results: A 5 year old Hispanic female with past medical history of Fanconi anemia who developed multi-organ failure requiring dialysis and respiratory support for adenovirus pneumonitis 90 days after umbilical cord stem cell transplant. Tracheal aspirate at the time of intubation was positive for adenovirus by PCR. Despite maximal doses of IV cidofovir (adjusted for renal failure) her viral load continued to trend up and she was clinically deteriorating. After obtaining parental consent, she was treated with inhaled cidofovir 40mg diluted in 20mls of normal saline administered daily via ET tube for a total of 12 doses based on a previously published case report. She progressively improved clinically, eventually requiring minimal ventilator support and the adenovirus viral load in tracheal aspirate dropped progressively from 112,000 to 800 DNA copies/mL. No immediate complication was observed.

Conclusion: Though adenovirus pneumonitis is a major cause of morbidity and mortality among pediatric HSCT recipients, its treatment can be challenging. Inhaled cidofovir offers an alternative to IV cidofovir for patients with renal failure in whom IV cidofovir might be contraindicated due to nephrotoxicity. Further well designed studies are needed to assess the safety and efficacy inhaled cidofovir.

UTILITY OF (1→3)- β -D-GLUCAN ASSAY TO DETECT INVASIVE FUNGAL INFECTIONS IN PEDIATRIC PATIENTS WITH ACUTE MYELOID LEUKEMIA

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Background: Invasive fungal infections (IFI) are life-threatening complications in neutropenic children being treated for acute myeloid leukemia (AML). While early diagnosis is crucial, non-specific clinical signs such as isolated prolonged fever often make correct identification of IFI a challenge. (1→3)- β -D-glucan (BDG) is a major cell wall component of invasive fungi and is detectable in the serum to facilitate diagnosis of IFI. While BDG positivity has been validated for diagnosis of IFI in adult populations, correlation between BDG and IFI remains unproven in pediatric cancer.

Objectives: To assess the correlation between detectable serum BDG (via Fungitell© assay) and IFI in at-risk pediatric populations with AML.

Design/Method: This is a retrospective cohort study of pediatric subjects with AML <21 years at diagnosis treated at Miller Children's & Women's Hospital Long Beach with at least one reported BDG assay. Antifungal prophylaxis, quantity of detectable BDG, and any associated IFI evaluation (cultures, radiographic imaging, Aspergillus galactomannan antigen, pathology) were collected and independently reviewed for this study. "Positive" IFI was defined as probable/proven according to the 2008 consensus EORTC/MSG guidelines (excluding BDG). Multiple receiver operating characteristic (ROC) curves were generated with varying BDG thresholds ranging from 60 to 500 pg/ml. Using the best fit curve, we analyzed specificity, sensitivity, and true positive likelihood ratio (LR+) across thresholds to determine the optimal boundary limit of serum BDG associated with an IFI in this pediatric oncology population.

Results: A total of 228 reported BDG assays and IFI evaluations were reviewed from 53 chemotherapy cycles administered to 18 eligible subjects. Routine antifungal prophylaxis was administered to all subjects (fluconazole or echinocandin); "positive" IFI was diagnosed in 6/18 subjects (33%). Inspection of the best fit ROC curve (AUC 0.856) identified a BDG threshold of ≥ 80 pg/ml as associated with the highest "correct classification" (89%, LR+ 9.2) and balance of specificity (92.2%) and sensitivity (73.0%). Increasing the threshold to 120 pg/ml decreased correct classification (86.4%), and markedly affected sensitivity (51.4%) with only a minor improvement in specificity (93.2%).

Conclusion: Detection of BDG at a threshold of ≥ 80 pg/ml is sufficiently specific to aid in the diagnosis of IFI in pediatric populations with AML.

NEONATAL ABSTINENCE SYNDROME AND LEUKOPENIA

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Background: Chronic administration of opioids has been associated with lymphocyte abnormalities and can affect immune system function. Little is known about the effect of maternal drug use on the neonatal immune system and lymphocyte counts. We hypothesized that maternal drug use during pregnancy can lead to neonatal lymphopenia. Recognizing this possible increased risk of infection in this population can allow for appropriate counseling and precautions.

Objectives: Identify if newborns exposed to intrauterine drugs experienced hematologic abnormalities, specifically lymphopenia.

Design/Method: Retrospective chart review of neonates born between 2003 and 2014 with a documented drug withdrawal syndrome was conducted. Medical records obtained by an electronic search for infants with the following ICD-9 codes: 779.4 (drug reactions and intoxications specific to newborns), 779.5 (drug withdrawal syndrome in newborn), and 305.5 (nondependent abuse of opioids); gestational age of the infant at birth, birth weight, type of maternal drug used, duration of hospitalization, treatment for neonatal abstinence syndrome (NAS), infant's absolute lymphocyte count, documented co-morbidities, and duration of drug exposure were recorded.

Results: 81 neonates had a documented diagnosis of NAS during the time period reviewed. 31 had complete blood counts drawn (mean time of 6 hours of life) available for review. Manual differentials were utilized when available. By using an ALC cut-off of 3400/uL (<10th percentile), 14/31 neonates (45%) with the diagnosis of drug withdrawal syndrome were lymphopenic. Lymphopenic infants were noted to have longer NAS treatment duration (12.7 days vs. 8.9 days) as well as longer length of hospitalization (29 days vs. 16 days). 36% of lymphopenic infants were preterm (<37 weeks gestation.) 86% of infants were exposed to opioids; exposure was confirmed by a positive maternal drug screen or positive neonatal meconium drug screen.

Conclusion: 45% of infants with the diagnosis of drug withdrawal syndrome were lymphopenic and these infants required longer duration of treatment for NAS. We are investigating the possible relationship between severity of NAS and neonatal lymphopenia. Further analysis is needed to determine if this correlation is noted in a larger study population, if the effect is transient, and how the child's clinical status during the neonatal period and throughout childhood may be affected.

USE OF THE CUMULATIVE BURDEN APPROACH TO ASSESS CARDIOVASCULAR MORBIDITY AMONG PEDIATRIC HODGKIN LYMPHOMA (HL) SURVIVORS: A REPORT FROM THE ST. JUDE LIFETIME (SJLIFE) COHORT STUDY

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Background: Morbidity associated with individual cardiac chronic health conditions is severe among pediatric HL survivors. Estimation of total cardiac disease burden, however, remains incomplete.

Objective: To describe the cumulative burden of cardiac disease among pediatric HL survivors using medically ascertained SJLIFE cohort data.

Methods: Of 670 HL survivors who met the SJLIFE eligibility (treated at St. Jude Children's Research Hospital, survived $\geq 10+$ years and $\geq 18+$ years old as of June 2014), 348 participated (mean age=40.8, range 21.1-67.3) and underwent longitudinal clinical evaluation for 21 different cardiac chronic health conditions. Longitudinal assessments were combined with retrospective clinical assessments and classified using a modified Common Terminology Criteria of Adverse Events (CTCAE) grading schema (grades: 1=mild, 2=moderate, 3=severe/disabling, 4=life-threatening). The CTCAE grades for 322 SJLIFE non-participants were imputed by multiple imputation, sampling SJLIFE participants matched on gender, race, age at diagnosis, treatment era, anthracycline dose and chest radiation exposure. The mean cumulative count (treating death as competing risk) was used to estimate cumulative burden.

Results: At 20 years post-diagnosis, our cohort experienced on average, 97.9 (95% confidence interval, 83.5-112.4) grade 1-4 and 8.8 (4.5-13.0) grade 3-4 conditions per 100 survivors. At 35 years, the grade 1-4 and 3-4 cumulative burdens increased to 338.0/100 (299.7-376.3) and 84.2/100 (60.4-108.0), respectively; with myocardial infarction, cardiovascular dysfunction (comprising cardiomyopathy and pulmonary hypertension) and dyslipidemia/essential hypertension each contributing 29.3%, 15.8% and 15.6% to grade 3-4 cumulative burden, respectively. From 20 to 35 years post-diagnosis, the average annual increase in grades 1-4 cumulative burden among survivors exposed to chest radiation rose from 10.5 to 20.0/100, with grades 3-4 increasing from 1.1 to 7.9/100. The equivalent increase among non-irradiated survivors was 4.0 to 7.5 (grades 1-4) and 0.1 to 2.4 (grades 3-4). Among anthracycline-exposed survivors the average annual increase changed from 17.6 to 15.1 (grades 1-4) and 1.9 to 9.2 (grades 3-4).

Conclusion: The cumulative burden of cardiac morbidity among pediatric HL survivors climbs rapidly over time with multiple cardiac chronic health conditions contributing to the total cardiac disease burden. The cumulative burden metric provides a more comprehensive approach to evaluating overall morbidity and will better assist in designing future trials and refining screening guidelines.

OUTCOMES OF MILD TO MODERATE ISOLATED NEUTROPENIA

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Background: Patients with absolute neutrophil count (ANC) <1500 are frequently referred to Pediatric Hematology Oncology, yet scant literature exists on outcomes and treatment for mild or moderate isolated neutropenia.

Objectives: To better understand the outcomes of referrals for isolated mild to moderate neutropenia.

Design/Method: Four year, IRB-approved retrospective chart review of patients referred to a Pediatric Hematology-Oncology clinic for neutropenia. Neutropenia was categorized as: Mild: ANC: 1.001-1.500x10⁹/L, Moderate: 0.501-1.000 x10⁹/L, Severe: 0.201-0.5 x10⁹/L and Very Severe ≤0.2 x10⁹/L. Descriptive statistics and univariate analysis were performed using JMP 10.

Results: Among 1579 referred patients, 142 had neutropenia. Of those, 112 (79%) had isolated neutropenia (mean ANC: 0.696x10⁹/L (s.d.0.388)). Twenty three patients (21%) had mild neutropenia, 47 patients (43%) moderate neutropenia, 30 patients (27%) severe neutropenia, and 10 patients (9%) with very severe neutropenia. Patients with isolated mild (mean age 8 years) and moderate (10 years) neutropenia were significantly older than patients referred with severe (2 years) and very severe neutropenia (3 years). (p<0.0001) No significant difference in ANC was found among genders (60% males). Four patients had positive anti-nuclear antibody, 18 had positive anti-neutrophil antibody, two had ELA mutation and no HAX mutation. Among 23 referred patients for initial mild isolated neutropenia, only three (13%) progressed during their course to an ANC in moderate range. Currently, 20 patients (87%) have normal ANCs, three patients (13%) remain mildly neutropenic (mean ANC 1.157x10⁹/L), and no patients currently have moderate, severe, or very severe neutropenia. Among 47 patients with moderate neutropenia at referral, seven (15%) progressed to severe neutropenia during their course including three with autoimmune neutropenia, two with viral illness, and two with idiopathic neutropenia. Currently, three of these patients remain severely neutropenic. Five patients received GCSF, four patients with severe/very severe neutropenia; a two month old with moderate neutropenia received GCSF during hospitalization for infection. Finally, among all patients referred to outpatient clinic diagnosed with cancer, none presented with isolated neutropenia.

Conclusion: Most patients referred for mild, isolated neutropenia resolved to normal and did not require subspecialty interventions. Patients referred for moderate isolated neutropenia were identified with autoimmune neutropenia and viral illnesses.

FACTORS PREDICTIVE OF PULMONARY DYSFUNCTION AMONG CHILDHOOD HODGKIN LYMPHOMA SURVIVORS

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Background: Pulmonary fibrosis (PF) is a progressive disorder without curative options. Adult survivors of Hodgkin lymphoma (HL) are at increased risk of PF due to therapeutic exposures that include bleomycin and pulmonary radiation; however, few studies have investigated subclinical pulmonary dysfunction in pediatric survivors of HL. We examined the effects of known clinical risk factors for PF upon off therapy pulmonary function tests (PFTs) in a uniformly treated pediatric HL cohort. We hypothesize that abnormal off therapy PFTs evidence a subclinical pulmonary dysfunction that may predict development of PF in survivors of HL exposed to pulmonary toxic therapies.

Objectives: To characterize the relationship between patient demographics and therapeutic exposures and PFT abnormalities in pediatric survivors of HL.

Design/Method: We obtained demographic, exposure, and outcome data on local survivors of HL < 5 years off treatment by retrospective chart review. The association between survivor variables and DLCOc (diffusion capacity of lung for carbon monoxide, corrected for hemoglobin) was evaluated using multivariable linear regression models, controlling for relevant treatment and patient characteristics.

Results: We identified 46 subjects (mean age at diagnosis = 14.3 years, range: 4-18) with DLCOc results available who were ≥ 5 months after treatment completion (mean = 25.1 months, range: 5 – 65). All subjects received a combination of bleomycin chemotherapy (mean cumulative dose = 60.2 IU/m², range: 0 – 80) and/or pulmonary radiation (71%). The mean post-treatment DLCOc was 66.5% (range: 45 – 85%). In adjusted regression models, post-treatment DLCOc was positively associated with age at diagnosis (1.49% per 1 year increase in age; 95% confidence interval [CI]: 0.72, 2.26) and inversely associated with female gender (-6.76%; 95% CI: -11.34, -2.18) and pulmonary radiation (-4.97%; 95% CI: -9.97, -0.05).

Conclusion: In this uniformly treated HL cohort, risk factors associated with off therapy subclinical pulmonary dysfunction included younger age at diagnosis, female gender, and exposure to pulmonary radiation. Expanding this cohort may reveal additional clinical factors influencing pulmonary outcomes. Furthermore, investigation of potential biomarkers of PF, such as telomere length and serum inflammatory markers, may identify individuals at risk for progression to severe pulmonary dysfunction, and create opportunities for therapeutic interventions.

FATIGUE IN PEDIATRIC IMMUNE THROMBOCYTOPENIA (ITP): BASELINE PREVALENCE IN PATIENTS STARTING SECOND LINE THERAPIES IN THE FIRST ITP CONSORTIUM OF NORTH AMERICA RESEARCH STUDY (ICON1)

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Background: Adult patients with ITP report significant fatigue, but fatigue has not been assessed in any large pediatric studies.

Objectives: To describe patient-reported fatigue and correlation with clinical characteristics in pediatric patients with ITP initiating second line treatments.

Design/Method: A longitudinal observational cohort of 108 children with ITP, starting second line treatments, were enrolled from 2013-2015 at 21 ICON centers. Enrollment requirements included age >1-<18 y and starting a second line treatment (not IVIG, steroids or anti-D) as monotherapy. Bleeding was assessed using the ITP Bleeding Score (IBLS). Fatigue Scale-Child (FS-C) age 7-12, adolescent (FS-A) age 13-18, and the Fatigue Scale Parent (FS-P, all ages) were administered. Using this scale, 34% of children and 21% of adolescents with cancer report high fatigue (J Pain Symptom Manage. 2010). Fatigue scores were re-scaled to 0 (no fatigue) to 100 (highest fatigue).

Results: Median age was 11.2y (SD 4.3y), and 55/108 (51%) had chronic ITP; median number of prior ITP treatments was 4 (1-9). At enrollment, the median FS-C score (n=45) was 17.5 (range 0-85). The median FS-A score (n= 38) was 19.2 (0-73), and the median FS-P (n= 94) score was 36 (7-81). During the prior week, more than half the time, 40% of children reported being tired and 58% of adolescents reported their "body felt tired". High fatigue was self-reported in 36% of children and 37% of adolescents, not significantly different than reported in pediatric cancer (p=0.81 and 0.08, respectively). Parent report of child fatigue was significantly higher than patient report in paired analysis (p<.0001). The fatigue score was significantly associated with current and "worst ever" IBLS only for the oral site, p=0.02 and p=0.01, respectively. There was no correlation between fatigue and platelet count. Fatigue was not correlated with age, number of prior therapies, race, or ethnicity.

Conclusion: Fatigue is common in children with ITP starting second line therapy and similar in severity to that reported in pediatric cancer. Longitudinal follow up on the ICON1 study will assess change in fatigue on second line therapies.

ASSOCIATION BETWEEN INFLAMMATORY CHARACTERISTICS IN BLOOD COUNTS AND RELAPSE IN PEDIATRIC LYMPHOMA

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Background: Hodgkin's Lymphoma is known to be associated with eosinophilia in approximately 10-15% of patients. No other significant blood count changes have been associated with other forms of lymphoma, and characteristics of the complete blood count in pediatric lymphoma patients have not been well studied, especially with regard to relapse and monitoring. We have noticed that children with other types of lymphomas may also have "inflammatory" changes reflected in the blood counts.

Objectives: Determine if indeed this anecdotal impression is correct, and whether these changes may aid in prognostication, and monitoring of relapse.

Design/Method: This is a retrospective case note review of all pediatric patients diagnosed with lymphoma who were seen at NUH from 2000-2015. All aspects of the Full Blood Count (FBC) at diagnosis and relapse were obtained and analyzed, along with the type of lymphoma, stage, and relapse outcome of the patients. Laboratory features of inflammation on the FBC include leukocytosis, neutrophilia, eosinophilia and thrombocytosis.

Results: We examined 89 pediatric patients up to 18 years of age with lymphoma. 51.7% (n=46) presented with at least one biochemical feature of inflammation while 48.3% (n=43) had none. There is a greater association of relapse (20.9%) for patients with absence of initial inflammation on the FBC compared to those with presence of inflammation (10.9%). For the relapsed patients who showed initial FBC inflammation at diagnosis, 80% (n=4) of them continued to show FBC inflammation at relapse. For relapsed patients who did not show initial FBC inflammation, 100% (n=9) continued to have absence of inflammation on relapse.

Conclusion: An inflammatory picture at diagnosis may be correlated with less relapse. If a patient presents with initial FBC inflammation, the presence of an inflammatory picture subsequently may indicate relapse and hence regular routine FBCs would be useful in monitoring disease status. For patients who had absence of initial FBC inflammation, it would not be useful to use subsequent FBCs to monitor progress and relapse. Using FBC to monitor for relapse in appropriate cases would be especially attractive for pediatric oncologists in low income countries. We plan to extend our studies to include more patients including adult patients.

SIROLIMUS AS AN EFFECTIVE AGENT IN THE TREATMENT OF AUTOIMMUNE THROMBOCYTOPENIA (ITP) & EVANS SYNDROME: A SINGLE INSTITUTIONAL EXPERIENCE

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Background: Autoimmune cytopenias are characterized by immune-mediated destruction of hematopoietic cell lines. Idiopathic thrombocytopenic purpura (ITP) is a single-lineage disorder causing thrombocytopenia while Evans Syndrome (ES) causes anemia and thrombocytopenia. Most patients adequately respond with steroids, intravenous immunoglobulin, and/or WhinRho. For patients with refractory disease, limited options for effective and well-tolerated therapies exist.

Objectives: The purpose of this study was to describe our institutional experience with sirolimus as therapy for pediatric patients with refractory ITP and ES.

Design/Method: We identified all patients in the last decade treated at our institution for refractory ITP or ES with sirolimus. We collected demographic data and assessed response to therapy. Responses were categorized as complete (CR), partial (PR), or modest (MR). CR was defined as resolution of all cytopenias (platelet count ≥ 75 K/ul and hemoglobin ≥ 8 g/dl) for at least 2 months with ability to taper steroids, PR as improvement in cytopenias by at least one grade for at least 2 months with the same or tapering dose of steroids or stable cell count while tapering steroids by at least 50%, and MR as increased platelet count from <10 K/ul to 10-20 K/ul and asymptomatic.

Results: Of the 17 patients meeting inclusion criteria, 12 (70%) had ITP and 5 (30%) had ES. Median age at diagnosis was 2.6 years (range 0.6–20.3) for ITP and 10 years (range 6.8–17.3) for ES. Fifty-eight percent (n=7) of patients with ITP achieved CR by 3 months, 25% (n=3) initially achieved PR followed by CR by 12-18 months of therapy. No durable response was identified in 17% (n=2). Eighty percent (n=4) of ES patients achieved a CR by 3 months. One patient with ES achieved MR but discontinued therapy due to hematuria, which was the only identified adverse event. Of the 14 patients in CR, 71% remain in CR off therapy for a median of 2 years (range 1–6). The remaining 29% remain in CR on therapy for a range of 3-15 months.

Conclusion: Our institutional experience has been that sirolimus is safe and effective as a steroid-sparing agent in the treatment of children with refractory ITP and ES.

T-CELL LYMPHOBLASTIC LYMPHOMA IN A PATIENT WITH FAMILIAL PLATELET DISORDER WITH PROPENSITY TO ACUTE MYELOGENOUS LEUKEMIA (FPD/AML) DUE TO A NOVEL GERMLINE RUNX1 MUTATION

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Background: Familial platelet disorder with propensity to acute myelogenous leukemia (FPD/AML) is an autosomal dominant disorder characterized by thrombocytopenia, abnormal platelet function, and a propensity to develop myelodysplasia (MDS) and/or acute myeloid leukemia (AML). It is caused by heterozygous mutation in RUNX1 (also known as AML1 or CBFA2), on chromosome 21q22. RUNX1 is a key regulator of hematopoiesis, megakaryopoiesis and myeloid differentiation. Patients with inherited RUNX1 mutations have a 35 to 50% lifetime risk of myeloid malignancy. Childhood acute lymphoblastic leukemia has been described in FPD/AML. T-cell lymphoblastic lymphoma has not been reported in association with FPD/AML.

Objectives: This is the first report of a pediatric patient who developed T-cell lymphoblastic lymphoma due to inherited RUNX1 mutation

Design/Method: Case report

Results: An 8-year-old boy was referred to the pediatric hematology for evaluation of thrombocytopenia since birth. His platelet count was 70,000/uL at initial evaluation. He did not report bruising or bleeding symptoms. The patient's father had been diagnosed with chronic idiopathic thrombocytopenia, his paternal grandmother died of AML at 26 years and his paternal great uncle died of lymphoma at 24 years. Familial RUNX1 mutation was suspected due to the significant family history of malignancy and chronic thrombocytopenia. Molecular testing revealed a previously unreported variant of unknown significance in RUNX1, p.Thr178Pro (c.532A>C), in both the patient and his father. Prediction software labeled the mutation as "probably damaging" and "not tolerated". The patient was monitored yearly and then presented to the Emergency Department at age of 11 years with a large anterior mediastinal mass. Pleural fluid testing was diagnostic of T- cell lymphoblastic lymphoma. His bone marrow was negative for malignancy and myelodysplasia. He is currently in maintenance chemotherapy and is in complete remission.

Conclusion: This is the first report of T- cell lymphoblastic lymphoma in association with FPD/AML due to inherited RUNX1 mutation.

INFLUENCE OF INTRAVENOUS IMMUNOGLOBULIN AND METHYLPREDNISOLONE ON CYTOKINES SECRETED BY T LYMPHOCYTE IN CHILDREN ITP

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Background: Studies have shown that patients suffering from ITP have polarized Th1 or Th2 response and cytokine deregulation. The Th1/Th2 balance was well known to regulate the immune system under normal conditions and to be impaired in autoimmune diseases like ITP. In order to study the mechanism of T lymphocyte abnormalities in children ITP, we should ensure the homogeneity of the objects. Due to children ITP often have abrupt and severe onset of thrombocytopenia, we prescribe intravenous immunoglobulin (IVIG) at the first day of hospitalization to prevent hemorrhage, as well as methylprednisolone (MP), which is often be used when exclusion of malignancy. For this reason, T lymphocyte function evaluation involved detection of cytokines secreted by Th1, Th2 and Th17 etc. might be interrupted by treatment we mentioned above.

Objectives: Our study was designed to explore the influence of intravenous immunoglobulin (IVIG) and methylprednisolone (MP) on cytokines secreted by T lymphocyte in children ITP.

Design/Method: We enrolled 62 patients with first diagnosed ITP and ultimate duration was less than 3 months without recurrence (38 boys and 24 girls, age range 2-178 months, median 33 months). We enrolled children ITP at the onset of their disease from our department between December 2011 and March 2013. We followed them until 12months of their whole duration, choosing the patients whose ultimate duration less than 3 months and no recurrence. Cytokines measurement by cytometric bead array included IL-2, IL-4, IL-6, IL-10, TNF, IFN and IL-17. We divided patients into 3 groups according to the treatment they received before testing cytokines level, then we compared T cell cytokines' level among these groups.

Results: We enrolled 62 patients with first diagnosed ITP and ultimate duration was less than 3 months without recurrence (38 boys and 24 girls, age range 2-178 months, median 33 months). We found IL-2 level is decreased in both group treated with MP for 1 day (N=29, P=0.042) and group in which patients treated with IVIG for 1 day (N=18, P=0.048) compared with group without any treatment (N=15). While the other cytokines' level have no difference among groups.

Conclusion: As for children ITP, although pathways of MP and IVIG in treating thrombocytopenia were different, they both could decrease IL-2 in children ITP ultimately. As a representative cytokine of TH1 cell, IL-2 has been demonstrated to be important in lymphocyte activation and mobilization. So we considered that MP and IVIG can reduce the T cell activation and production of auto-antibodies by decrease IL-2.

ROMIPLOSTIM FOR TREATMENT-RELATED THROMBOCYTOPENIA IN PEDIATRIC MALIGNANCIES

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Background: Therapy-related thrombocytopenia (TRT) is common in the treatment of pediatric malignancies due to chemotherapy and radiation therapy. In some instances thrombocytopenia can be dose-limiting and cause significant therapy delays leading to suboptimal treatment of the underlying malignancy. Romiplostim, a thrombopoietin receptor agonist, is FDA-approved as a second-line treatment for immune-mediated thrombocytopenia in children and has shown to be well-tolerated. Romiplostim has also been successfully used for therapy-related thrombocytopenia in adults, but there are no data on its use for this indication in children.

Objectives: We report a series of 3 pediatric patients treated with romiplostim for TRT.

Design/Method: A retrospective chart review of 3 pediatric patients who received romiplostim for TRT at Nationwide Children's Hospital in 2014-2015.

Results: Two of 3 patients had dose-limiting, prolonged TRT while undergoing treatment for solid tumors; patient 1 following pelvic radiation for localized pelvic Ewing sarcoma and patient 2 following MIBG therapy for high-risk neuroblastoma. Romiplostim was initiated at a dose of 1 mcg/kg in patient 1 and 3 mcg/kg in patient 2. Dose was increased by 1 mcg/kg weekly until platelet goal to continue chemotherapy was achieved and continued at a steady dose. Maximum dose was 7 mcg/kg in both patients. Duration of therapy was 9 weeks in patient 1 and 13 weeks in patient 2. Due to a religious objection to blood products, patient 3 received three weekly 2-3 mcg/kg doses over a month period to maintain platelet count $> 100 \times 10^9/L$ while receiving salvage therapy for relapsed parameningeal rhabdomyosarcoma. All patients maintained platelet counts above goal following discontinuation of romiplostim. No adverse effects from romiplostim injections were observed.

Conclusion: Romiplostim successfully treated TRT without any adverse effects in this case series. While possible risk of leukemic clone proliferation may limit use of romiplostim for TRT in children with hematologic malignancies, romiplostim could be a very beneficial treatment for TRT in children with solid tumors. It may limit treatment delays and dose reductions, ultimately leading to improved overall survival. Prospective studies on this use of romiplostim are warranted.

MSH6 HAPLOINSUFFICIENCY AT RELAPSE CONTRIBUTES TO THE DEVELOPMENT OF THIOPURINE RESISTANCE IN PEDIATRIC B-LYMPHOBLASTIC LEUKEMIA

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Background: Outcomes for patients with relapsed B-lymphoblastic leukemia remain suboptimal. Understanding biological mechanisms underlying drug resistance is essential. We previously noted relapse-specific deletions in MSH6 in approximately 8% of relapsed patients. MSH6 forms a crucial part of the DNA Mismatch Repair (MMR) pathway that recognizes base pair mismatches.

Objectives: Our aim was to distinguish two hypotheses: 1) MSH6 deletion results in a hypermutation phenotype associated with generation of secondary mutations involved in drug resistance; 2) MSH6 deficiency leads to failure to initiate apoptosis directly in response to chemotherapeutic agents.

Design/Method: Stable cells were generated in mismatch proficient (697, Raji) and deficient (Reh, RS4;11) cell lines, using short hairpin RNA (shRNA) constructs targeting MSH6 and non-targeting (NT) controls. Cells were exposed to 7 chemotherapeutic agents for 5 days. Thioguanine nucleotide (primary cytotoxic thiopurine metabolite) incorporation (DNA-TGN) was assessed using liquid chromatography tandem mass spectrometry. Hypermutator phenotype was assessed by microsatellite instability (MSI) and mutation rates in the PIG-A gene, determined by loss of CD55, CD59 and FLAER staining.

Results: Upon knockdown of MSH6 (MSH6-KD), MMR proficient cell line 697 showed a manifold increase in IC50 to thiopurines (IC50 ratio KD/NT: 6TG 35.23, 6MP 9.08), reflecting resistance, which was not seen in the MMR deficient control cell line Reh (IC50 ratio KD/NT: 6TG 1.04, 6MP 1.12). MSH6-KD did not cause resistance to other chemotherapeutic drugs, in any cell line. MSH6-KD in 697 cells increased DNA-TGN incorporation at 96 hours (NT 1722.4 vs KD 3070.86 fmol/ug DNA), which was not observed in Reh. MSI was not observed in cell lines or MSH6 deleted patient samples. As expected MSH6 KD had no effect on mutation rate in Reh cells but curiously a 35% reduction in mutation rates was seen in 697 cells.

Conclusion: Loss of MSH6 function contributes to development of selective resistance to thiopurines, but not other agents, probably reflecting compromised apoptosis. Thus, MSH6 focal deletions can be added to a growing list of genetic alterations associated with resistance to purine analogues highlighting the critical role of maintenance therapy.

TWO NOVEL GERMLINE JAK2 MUTATIONS COOPERATIVELY CAUSING FAMILIAL ESSENTIAL THROMBOCYTHEMIA

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Background: Essential thrombocythemia (ET) is a myeloproliferative neoplasm characterized by thrombocytosis with increased risk of thromboembolic events, progression to myelofibrosis and leukemic transformation. Mutations of the Janus Kinase 2 (JAK2) gene, most commonly JAK2V617F, are known driving factors of ET pathogenesis. ET is rare in children and only a few familial cases have been reported due to germline JAK2 mutations with autosomal dominant inheritance. Two siblings presented in our clinic with platelet counts $>1200\text{K}/\mu\text{L}$; one had a history of stroke at 2 months of age. Both were found to be compound heterozygous for two novel germline JAK2 variants, JAK2L815P and JAK2V1123G. The father and two unaffected siblings carrying JAK2L815P and the mother carrying JAK2V1123G have normal platelet and red blood cell counts.

Objectives: To explore causality and the signaling mechanism(s) of the two novel JAK2 variants for ET.

Design/Method: Wild-type (WT) and mutated forms of JAK2 were transduced in Ba/F3 cells stably expressing the thrombopoietin receptor (Ba/F3-MPL) and the JAK-STAT signaling pathway, proliferative capability and response to the JAK2 inhibitor, ruxolitinib, were studied. JAK-STAT signaling was also evaluated in patients' platelets and in megakaryocytes produced in vitro from patients' CD34+ cells.

Results: Ba/F3-MPL transduced with both JAK2L815P and JAK2V1123G mutants demonstrated increased STAT5 phosphorylation compared to WT-JAK2 and to JAK2V617F; in contrast JAK2V617F had higher JAK2 and STAT1/3 phosphorylation. These findings paralleled the phosphorylation changes in our patients' platelets, where increased STAT1/STAT5 phosphorylation was noted compared to normal control while platelets from a pediatric ET-JAK2V617F patient had increased pJAK2 and pSTAT1/3. Megakaryocytes produced in vitro from patients' CD34+ cells showed increased STAT5 activation compared to those from normal volunteers. Proliferation studies of IL-3-dependent Ba/F3-MPL under cytokine starved conditions indicated that Ba/F3-MPL cells with the JAK2L815P and JAK2V1123G had a higher proliferation rate and a decreased sensitivity to ruxolitinib compared to the JAK2V617F Ba/F3-MPL cell line.

Conclusion: The mutations JAK2L815P and JAK2V1123G appear to function cooperatively to produce the ET phenotype via a mechanism that appears to be distinctly different from that of JAK2V617F. Further in vitro and in vivo studies are warranted to gain further insight into JAK2 activation and regulation.

DISCOVERY OF NOVEL EFFECTOR GENES REGULATED BY CALM-AF10 IN PEDIATRIC LEUKEMIAS

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Background: CALM-AF10 translocations, seen in 5-10% of childhood T-ALL (T-cell acute lymphoblastic leukemia), are difficult to treat. CALM-AF10 leukemias share many characteristics with leukemias involving Mixed-Lineage Leukemia (MLL) gene translocations. CALM-AF10 and MLL fusion leukemias exhibit similar gene expression profiles, characterized by elevated levels of proleukemic HOXA genes. Improving the outcome of patients with these leukemias depends on the development of targeted therapies with increased efficacy. While HOXA genes are known drivers of leukemogenesis, they are also important in normal hematopoiesis, making them less suitable as drug targets. We previously determined that the CRM1 nuclear export protein tethers CALM-AF10 to its target genes, and that exposure to leptomycin B (LMB), a compound that disrupts the CRM1/CALM-AF10 interaction, abrogates the ability of CALM-AF10 to activate its transcriptional targets.

Objectives: To discover novel CALM-AF10 target genes that are involved in the pathogenesis of CALM-AF10 leukemias.

Design/Method: Using RNA-sequencing, we identified genes with increased expression in hematopoietic progenitors transduced by a CALM-AF10 expression vector. To identify genes whose expression is dependent on CRM1, we performed Affymetrix microarrays using murine CALM-AF10 leukemia cells briefly treated with LMB (1 nM). Genes of interest were validated using qRT-PCR.

Results: We determined the intersection among genes selectively expressed in CALM-AF10 transduced bone marrow progenitors (502 genes), and genes decreased in CALM-AF10 leukemia cells following a two-hour exposure to LMB (1441 genes). We identified twenty-three genes likely to be direct targets of CALM-AF10. Reassuringly, nine of these genes were in the HOXA family, validating our previous observations. Three novel genes, HELLS, SHISA2, and SIX1, all of which have roles in development and malignancy, were selected for further study, and their increased expression was validated using qRT-PCR.

Conclusion: Using gene expression profiling, we identified several novel candidate transcriptional targets of the CALM-AF10 oncoprotein. Three of these genes, HELLS, SHISA2, and SIX1, have previously been implicated in development and malignancy, and might play a role in CALM-AF10 leukemogenesis. We are currently examining the effects of overexpression and knockdown of these genes on CALM-AF10 leukemia cell lines in vitro and in vivo.

RETROSPECTIVE AND PROSPECTIVE RESULTS OF THE USE OF SIROLIMUS IN THE TREATMENT OF GENERALIZED LYMPHATIC ANOMALY AND GORHAM STOUT DISEASE

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Background: Generalized Lymphatic Anomaly (GLA) and Gorham-Stout Disease (GSD) are rare lymphatic anomalies characterized by the abnormal development of lymphatic vessels in multiple body sites that may cause effusions, organ dysfunction, pathologic fractures, pain and disfigurement. Affected individuals frequently experience progressive clinical symptoms with worsening quality of life (QOL). Unfortunately, treatment options are limited and often ineffective. Surgery is generally reserved for localized disease while conventional medical treatments like steroids and chemotherapeutic agents produce substantial side effects with variable results. Current evidence demonstrates an important regulatory function of the PI3-kinase/Akt/ mTOR pathway in vasculogenesis and supports mTOR inhibition with sirolimus as a therapeutic target.

Objectives: To evaluate the safety and efficacy of sirolimus in the treatment of patients with GLA and GSD.

Design/Method: This study analyzed combined data from a multicenter systematic retrospective review of medical records of patients treated with sirolimus between January 2007 and June 2014 and from the prospective Phase 2 clinical trial assessing the efficacy and safety of sirolimus in the treatment of complicated vascular anomalies (NCT00975819). Disease improvement was determined by radiologic imaging, QOL measurements and clinical status assessments. Sirolimus dosing regimens, toxicities and side effect causality were evaluated.

Results: Of the evaluable patients, nineteen had GLA or GSD (13 GLA, 6 GSD). As expected, no patients had complete resolution of clinical symptoms and radiologic disease with sirolimus. Overall partial disease response was 84% (92% GLA, 67% GSD) with 79% of patients with improved QOL, 63% with improved clinical status and 39% with improved radiological response. Improvement occurred in 83% of patients with pleural effusions and 50% with pericardial effusions; no patients with pre-existing pleural or pericardial effusions worsened on therapy. Disease progression occurred in 1 GSD patient due to reported decreased QOL. Five patients experienced grade 3 or 4 drug toxicities without requiring dose reductions. Most common side effects were bone marrow suppression, mucositis/stomatitis and hypertriglyceridemia.

Conclusion: Sirolimus is a safe and well-tolerated treatment that appears to reduce symptoms and/or stabilize disease in patients with GLA and GSD. Given the significant morbidity and mortality in patients with complicated lymphatic malformations, future treatment studies need to address these specific phenotypes.

THE REGULATION OF BCL2 FAMILY PRO-SURVIVAL PROTEINS AND THE EFFICACY OF TARGETING THIS PATHWAY IN PH-LIKE B-ALL WITH HIGH LEVELS OF CRLF2

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Background: Genetic alterations causing overexpression of the cytokine receptor, CRLF2, are associated with a form of high-risk Ph-like acute lymphoblastic leukemia (CRLF2 B-ALL). Activation of the CRLF2 receptor by the cytokine, TSLP, results in activation of the JAK/STAT and PI3/AKT/MTOR pathways, both of which have been associated with chemoresistance and upregulation of Bcl2 family pro-survival genes.

Objectives: To determine the effect of TSLP-CRLF2 mediated signals on expression of Bcl2 family proteins and the efficacy of targeting Bcl2 family pro-survival proteins in CRLF2 B-ALL.

Design/Method: Flow cytometry and Western blot were used to evaluate Bcl2 family protein expression in CRLF2 B-ALL cells cultured with and without TSLP. Flow cytometry was used to for Annexin V/7-AAD and Caspase 3/7 assays of apoptosis following treatment of CRLF2 B-ALL cells with Mcl-1 inhibitor (Mim-1) in the presence and absence of TSLP.

Results: TSLP increased expression of the Bcl2 family pro-survival protein, Mcl-1, in CRLF2 B-ALL cell lines with activating JAK mutations (MUTZ5 and CALL4). Treatment with Mcl-1 inhibitor (Mim-1) reduced cell counts by >90% and this reduction was maintained in the presence of TSLP. Reductions in cell number were due to a dose-dependent increase in caspase-mediated apoptosis reaching >95% cell death after 3 days in concentrations of Mim-1 over 15 uM, even when TSLP was present. We saw increased expression of Bcl-xL and Bcl2 when doses of Mcl-1 inhibitor were 30 uM or higher, but very little change at lower doses, suggesting that observed increases are more likely to be selective survival of cells expressing high levels of these alternative Bcl2 family pro-survival molecules rather than compensatory upregulated expression.

Conclusion: These data suggest that TSLP can contribute to chemoresistance via upregulation of the Bcl2 family protein, Mcl-1, even in cases of CRLF2 B-ALL with activating JAK mutations. These results provide evidence that therapy to target Mcl-1 could be an effective treatment for Ph-like ALL where CRLF2 is overexpressed.

COAGULATION MANAGEMENT IN CHILDREN WITH VASCULAR MALFORMATIONS (VM): PRACTICE HETEROGENEITY AMONG MEMBERS OF THE AMERICAN SOCIETY OF PEDIATRIC HEMATOLOGY-ONCOLOGY (ASPHO) SPECIAL INTEREST GROUP (SIG) VASCULAR ANOMALIES (VA)

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Survey to ASPHO SIG VA Members; Web-based Questionnaire was distributed, New York City, Columbia University Medical Center, United States

Background: Vascular Anomalies (VA), including patients with vascular malformations (VM), is an emerging field in pediatrics with growing recognition of coagulation-related complications specific to this population. To date, no specific guidelines exist.

Objectives: To describe clinical practices related to pediatric VM patients with coagulation disturbances in North America, in order to facilitate future development of standards of practice and the identification of research gaps.

Design/Method: The ASPHO SIG-VA conducted an Institutional Review Board approved online survey of SIG-VA members that included general practice questions and clinical vignettes describing coagulation-related issues. Items for the survey were derived from the expert experience, literature review, and suggestions from the survey committee.

Results: To date, 19/38 (50%) members responded [all 5 highest ranked centers (US), 2 largest (Canada)], and ~80% have practiced for ≥ 6 years. Around 85% of the respondents work in a multidisciplinary clinic, seeing between 5-800 simple VM/yr and between 3-1,500 combined VM/yr. All have used anticoagulants [ie. low molecular weight heparin (LMWH)] or aspirin (ASA) for coagulopathies before [last 12 months: >10 pts (30%), 1-3 pts (~25%), none (0%)]. Three basic scenarios were included: a) periprocedural management in a combined VM with hypofibrinogenemia and D-dimer elevation, ~63% would prescribe anticoagulants vs. 32% not, (5% were indecisive); enoxaparin was the agent of choice (92%, dose: 0.5-1.0 mg/kg/dose, x1 or x2/day, up to 2 wks pre-/post-procedure); b) simple VM with isolated D-dimer elevation and no symptoms, 20% would prescribe anticoagulants vs. 75% not, (5% were indecisive); enoxaparin was the agent of choice (60%, similar regimen); and c) simple VM with isolated D-dimer elevation and local pain, ~58% would prescribe anticoagulants vs. 16% not, (26% were indecisive); the agents of choice were ASA/NSAIDs (81%, and compression garments). Most common reasons to avoid LMWH were paucity of literature, perceived increased bleeding risk and needle phobia.

Conclusion: Despite the prevalence of VM in children our survey highlights the expected practice variability in the management of coagulopathies. Lack of evidence was recognized as the main obstacle for the use of anticoagulants. Further characterization of coagulation complications, as well as risk stratification for both bleeding/thrombosis can pave the way towards future guidelines.

CDC42 IS OVEREXPRESSED IN ACUTE LYMPHOBLASTIC LEUKEMIA AND REGULATED BY IKAROS TUMOR SUPPRESSOR

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Background: Ikaros, a protein encoded by the IKZF1 gene, acts as a tumor suppressor in acute lymphoblastic leukemia (ALL) by regulating expression of its target genes. Using chromatin immunoprecipitation coupled with next-generation sequencing (ChIP-Seq), we showed that Ikaros binds to the promoter of the CDC42 gene in human ALL. The CDC42 gene encodes a small GTPase that acts as an oncogene in solid tumors, but it has not been associated with leukemia. We hypothesize that Ikaros regulates CDC42 expression and that CDC42 is involved in ALL pathogenesis.

Objectives: 1) To determine the role of Ikaros in regulating CDC42 expression in ALL. 2) To define the significance of CDC42 expression in ALL and 3) To test the therapeutic efficacy of targeted inhibition of CDC42 in ALL.

Design/Method: Ikaros overexpression and knock-out was by transduction with retroviral vector containing Ikaros and Ikaros shRNA, respectively. Luciferase reporter assay was used to evaluate Ikaros effects on the CDC42 promoter. Gene expression was assessed using quantitative real-time PCR (qRT-PCR) and Western blot. DNA binding was measured by quantitative chromatin immunoprecipitation (qChIP). Cell proliferation was assayed by WST and synergistic cytotoxic effects of compounds was analyzed using CalcuSyn.

Results: Gain-of-function and loss-of-function experiments showed that Ikaros represses CDC42 transcription. CDC42 is overexpressed in B-ALL and T-ALL as compared to normal bone marrow. CDC42 overexpression correlates with high white blood cell count in ALL. Treatment of ALL with a specific CDC42 inhibitor (ML141) produced a cytotoxic effect. In leukemia, Ikaros binding to the CDC42 promoter and its ability to repress CDC42 is impaired due to phosphorylation by pro-oncogenic Casein Kinase II (CK2). Inhibition of CK2 with a clinically-tested inhibitor, CX-4945, restored Ikaros binding to the CDC42 promoter and transcriptional repression of CDC42. The use of CX-4945 in combination with the CDC42 inhibitor, ML141, produced a synergistic cytotoxic effect in both B-ALL and T-ALL.

Conclusion: Our results demonstrate that CDC42 is overexpressed in ALL and is a potential therapeutic target in leukemia. Expression of CDC42 in ALL is regulated by Ikaros and CK2. Targeting CK2 in combination with CDC42 inhibitors is a potential novel treatment for ALL.

SIROLIMUS FOR THE TREATMENT OF CERVICOFACIAL LYMPHATIC MALFORMATIONS

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Background: Lymphatic malformations (LMs) are challenging to manage, particularly those involving the cervicofacial region and airway. Primary therapy is sclerotherapy and/or resection, while the role of sirolimus is evolving for the treatment of cervicofacial LMs.

Objectives: To review our experience with sirolimus medical therapy for cervicofacial lymphatic malformation for efficacy and safety/tolerability.

Design/Method: An IRB-approved retrospective review of 19 patients treated with sirolimus for cervicofacial LMs from November 2012 to October 2015.

Results: Five patients have completed therapy (duration 5, 9, 17, 25, and 26 months) and 14 remain on sirolimus (range 4-35 months). Age at initiation ranged from 2 months to 34 years. Nine patients had microcystic LM and ten had mixed macrocystic-microcystic LMs. All patients have serial photographs and 10 patients have serial imaging to gauge response. All patients demonstrated some reduction in LM bulk, ranging from dramatic to visually modest. Younger patients with mixed macrocystic-microcystic disease with less prior therapy demonstrated more significant responses. 94.7% (18) patients reported subjective improvement on sirolimus including decreased LM bulk, softening tissue, decreased bleeding/leaking related to mucosal vesicles, and decreased rates of cellulitis. All patients (n=13) with mucosal vesicles present at initiation of sirolimus resolved or improved. Median time to initial response was 1 month (range 5 days to 4 months). Of six patients with tracheostomies, one was decannulated after maxillofacial surgery and two are tolerating capping while on sirolimus. Six patients developed cellulitis within the LM during treatment; none progressed to sepsis or had more episodes of cellulitis on sirolimus. No opportunistic infections occurred. Two patients have undergone surgical debulking following sirolimus treatment to decrease residual remaining tissue with wound healing issues.

Conclusion: The use of sirolimus in the management of cervicofacial LMs appears to be efficacious, especially in younger patients and for mucosal disease, with limited adverse events. Long-term follow-up, durability of response, and coordination of sirolimus around procedural therapies need further evaluation.

NNAT EXPRESSION IS CORRELATED WITH CLINICAL FEATURES IN CHILDHOOD PRECURSOR-B ACUTE LYMPHOBLASTIC LEUKEMIA

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Background: We have shown previously that the neuronatin gene (NNAT) undergoes aberrant DNA hypermethylation associated with transcriptional silencing in a majority of childhood acute leukemia cases. The clinical significance of loss of NNAT expression in childhood leukemia, however, is unknown.

Objectives: The goal of our study was to correlate clinical characteristics and outcomes with NNAT expression in precursor B – acute lymphoblastic leukemia (ALL).

Design/Method: Sixty seven consecutive cases of non-infant precursor B-ALL presenting between 2005 and 2011 were analyzed retrospectively utilizing bone marrow samples obtained at diagnosis and data from the medical record. For each sample, site-specific NNAT methylation was quantitated by combined restriction/bisulfite analysis (COBRA) and NNAT mRNA expression was qualitatively determined by end point RT-PCR. Clinical characteristics including age at presentation, white blood cell count (WBC) at presentation, immunophenotype, induction response, and survival were compared between NNAT hypermethylator and normal methylator groups and between NNAT expressor and nonexpressor groups.

Results: NNAT methylation and expression status was determined for 28 cases.

Hypermethylation (defined as site-specific methylation > 60%) was identified in 16/28 ALL samples. NNAT silencing (loss of expression) was identified in 15/28 samples). We found cases exhibiting loss of NNAT expression were more likely than expressors to be associated with a WBC > 50,000/mm³ at diagnosis (p=0.037). Also the EFS for the high-risk group approached statistically significant difference between the expressor and non-expressor groups.

Conclusion: Loss of NNAT expression was associated with an elevated WBC count (>50,000/mm³) at presentation. While EFS and OS did not differ significantly between expressor and non-expressor groups in the overall analysis, when we restricted the analysis to patients exhibiting high-risk characteristics of elevated WBC or age > 10 years, the EFS advantage of expressors over non-expressors approached statistical significance. Given the relative stability of the tails of these EFS curves, analysis of additional patients may yield a statistically significance difference. While NNAT has been shown to regulate endoplasmic reticulum calcium homeostasis in some cell types, the biological basis for clinical features associated with loss of NNAT expression in childhood PB-ALL remains to be determined.

HEPATIC HEMANGIOMAS: A CASE COMPARISON BETWEEN CLASSIC AND ATYPICAL PRESENTATIONS

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Background: Hepatic hemangiomas are the most common benign liver tumor of infancy. The typical presentation usually involves a palpable abdominal mass with or without signs of anemia and heart failure. Despite their relatively common occurrence, confusing nomenclature is still affecting the medical literature. Classification schemas based on growth pattern, immunostaining and clinical behavior have emerged in an attempt to better standardize management.

Objectives: We present a case of an infant with atypical clinical course of a hepatic hemangioma and contrast it with other patients that presented with a similar diagnosis. Our aims are to contribute to the growing data surrounding these common vascular lesions in hopes of standardizing diagnostic criteria and outcomes, as well as better guide therapeutic options.

Design/Method: A retrospective chart review was performed on a 2 month-old baby boy at Texas Children's Hospital and compared to previous cases and published reports of this diagnosis.

Results: The patient was a boy born at 32-weeks' gestation who presented with respiratory failure secondary to acute abdominal distension at 2 months of age. Ultrasound prior to delivery had shown a 6.9cm left hepatic lobe mass, and MRI confirmed a 7cm x5.2 cm left hepatic lobe hemangioma. On presentation, repeat ultrasound showed the hepatic mass to be stable in size without significant shunting or compression of hepatic vessels, with a large amount of ascites present. Alpha-fetoprotein (AFP) levels were within range for age (2090-4520). Further workup failed to reveal a primary etiology for his ascites. Due to his critical status, decision was made to excise the mass. Pathology revealed a GLUT-1 negative vascular lesion consistent with a hepatic congenital hemangioma. Post-operatively the baby recovered well the ascites did not re-accumulate.

Conclusion: There is a wide range of clinical presentations for focal hepatic hemangiomas, from asymptomatic to critically ill. These lesions require close follow up from birth to identify development of complications and initiate prompt treatment.

THE ROLE OF NUP98 IN CALM-AF10 AND CRM1-AF10 LEUKEMOGENESIS

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Background: The t(10;11) CALM-AF10 translocation occurs in patients with T-ALL and AML and is associated with a poor prognosis. CALM-AF10 leukemias are characterized by upregulation of HOXA gene expression, which is a known driver of leukemogenesis. Interaction of the CALM-AF10 oncoprotein with the nuclear export factor CRM1/XPO1 is essential for upregulation of HOXA expression. We have previously demonstrated that CRM1 interacts directly with Hoxa chromatin, suggesting that CRM1 recruits CALM-AF10 to its target genes. However, other mediators may also be involved. In particular, NUP98 is a component of the nuclear pore complex that interacts with CRM1 during nucleocytoplasmic transport of macromolecules. Translocations fusing NUP98 with multiple different partners have been described in high-risk leukemias. NUP98 fusion oncoproteins can bind to and activate the transcription of HOXA genes.

Objectives: To determine whether NUP98 cooperates with CRM1 and CALM-AF10 to transactivate HOXA genes.

Design/Method: We previously created retroviral CALM- and CRM1-AF10 fusion vectors and demonstrated their ability to activate the transcription of a Hoxa7-luciferase reporter. We designed an inducible shRNA retroviral vector targeting Nup98. We performed transient co-transfections of the Hoxa7-luciferase reporter with Nup98 shRNA vectors, together with CALM-AF10, CRM1-AF10 or an empty vector in HEK293 cells. We also stably expressed the inducible NUP98 shRNA vector in NIH3T3 cells.

Results: Luciferase assays showed that knockdown of NUP98 increased the baseline level of Hoxa7 transcription but had limited effect on the transcriptional activity of CALM-AF10 and CRM1-AF10. Inducible knockdown of Nup98 also caused an increase of endogenous Hoxa levels in NIH3T3 cells.

Conclusion: Surprisingly, silencing of NUP98 increases Hoxa7 transcriptional activation and endogenous Hoxa transcripts. Since NUP98 is important for nuclear export, impeding NUP98 function likely results in nuclear retention of critical proteins and may indirectly deregulate Hoxa transcription. Experiments are underway to determine the role of NUP98 on Hoxa levels in cells expressing CALM-AF10 and CRM1-AF10. Of note, a recent report demonstrated Crm1-dependent direct binding of Nup98-Hoxa9 to Hox genes (Oka et al., Elife 2016). This further highlights the important interactions among CRM1, NUP98, and Hox loci as a molecular basis for leukemogenic Hox gene dysregulation.

TREATMENT OF INFANTILE HEMANGIOMAS AND PULMONARY HYPERTENSION WITH SIROLIMUS IN A PEDIATRIC PATIENT

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Background: Infantile hemangiomas (IH) typically are benign vascular neoplasms that spontaneously involute over time. They are most commonly found on the head, neck and trunk, but can also involve internal organs such as the liver, lung and central nervous system. Oftentimes these lesions can be treated conservatively. Medical management, when needed, consists of laser treatments, surgical excisions and medications including propranolol and steroids.

Objectives: To describe a pediatric patient with diffuse hepatic and cutaneous IH and failure to thrive with progressive pulmonary hypertension (PH) due to pulmonary hemangiomas treated with sirolimus.

Design/Method: The patient is a three year old African American female who presented shortly after birth with diffuse cutaneous hemangiomas, hepatomegaly, splenomegaly and anemia. Abdominal MRI/MRA noted replacement of the entire liver parenchyma by numerous nodular lesions consistent with IH, as well as signs of early heart failure. Skin biopsy confirmed IH. She was started on propranolol and prednisolone for her hemangiomas, as well as medical management of her heart failure. Hepatic and cutaneous hemangiomas improved over time. At 23 months of age, however, she developed severe idiopathic PH diagnosed by right cardiac catheterization with systemic pulmonary artery (PA) pressures at rest responsive to oxygen and nitric oxide. Computed tomography scan of her thorax noted multiple enhancing pulmonary nodules scattered throughout both lungs, suspicious for pulmonary arteriovenous malformations.

Results: The patient was started on sildenafil. Given the severity of her PH likely from pulmonary hemangiomas and persistence of her liver and cutaneous hemangiomas despite previous therapy, she was subsequently started on sirolimus. Repeat cardiac catheterization two months after initiation of sirolimus noted improvement in her PH, as well as in her liver hemangiomas. Unfortunately the patient developed significant hypoglycemia resulting in her demise.

Conclusion: Pulmonary hemangiomas are rare in the pediatric population. Sirolimus acts by inhibiting the mTOR pathway and thus decreases vascular endothelial proliferation. Steroids and propranolol are first line medical management of IH; however, sirolimus may be an effective treatment option for hemangiomas refractory to conventional therapeutic options.

EFFECT OF POLY I:C TRANSFECTED STROMAL CELLS ON ACUTE LYMPHOBLASTIC LEUKEMIA CELL SURVIVAL

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Background: While the cure rate for acute lymphoblastic leukemia (ALL) is >90%, relapse occurs in about a quarter of cases, particularly with high risk disease. T cell immunomodulation may be a valuable adjunct to standard therapy. However, studies to date have only demonstrated direct effects of immunomodulation on tumor cell survival. Our work explores methods of manipulating the microenvironment to treat ALL. Poly I:C is a dsRNA analog that has demonstrated a direct effect on tumor growth via IFN pathways, and giving it anti-leukemic effects. However, this siRNA has not been studied on primary stroma in the ALL population, thus no complete understanding of its genetic microenvironmental effect has been offered.

Objectives: To determine whether Poly I:C is an siRNA that (1) upregulates IFIT1 gene expression as a measure of activation of interferon pathways and (2) indirectly induces acute lymphoblastic leukemia cell tumor cell death by way of altering primary stromal gene expression.

Design/Method: (1) Reverse transfection of 3 different stromal cell lines, RNA extraction, cDNA synthesis, followed by quantitative PCR to determine poly I:C siRNA mediated upregulation of IFIT1 gene expression. (2) Transfection of three primary stromal cell lines with poly I:C, followed by cell washing, and subsequent ALL cell plating. ALL cell survival will then be measured by flow cytometry.

Results: (1) Poly I:C induced IFIT1 gene expression in stromal cells. (2) ALL cells underwent apoptosis in the presence of Poly I:C treated stromal cells.

Conclusion: Poly I:C dramatically reduces the capacity of nonmalignant stromal cells to support the viability of primary ALL cells. This finding suggests that drug targeting of marrow stromal cells may provide new approaches to control ALL. Current studies in the lab are exploring the key changes in gene expression pathways induced by Poly I:C in nonmalignant stromal cells that lead to ALL cell death.

CONDITIONAL KNOCKOUT OF ATG5 IN BONE MARROW LEPTIN-RECEPTOR-EXPRESSING PERIVASCULAR STROMAL CELLS CAUSES LEUKOPENIA

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Background: Bone marrow (BM) niche cells, specifically the Leptin-receptor-expressing perivascular stromal cells (LepR⁺), CXCL12-abundant reticular cells (CAR), and endothelial cells, play an essential role in the maintenance and self-renewal functions of hematopoietic stem cells (HSCs). A number of secretory-related molecules like stem cell factor (SCF), CXCL12 and Angiopoietin mediate this maintenance function. In addition, functional autophagy within HSCs is known to play a critical role for maintaining HSC homeostasis, as the loss of ATG7 in HSCs leads to loss of normal HSC functions and severe myeloproliferation. However, it remains unclear as to how hematopoiesis will be affected if autophagy is selectively blocked in bone marrow niche cells.

Objectives: To investigate the effect of autophagy deficiency within bone marrow niche cells on hematopoiesis.

Design/Method: A knockout mouse model was generated allowing for a selective ablation of an autophagy-essential protein, ATG5, in LepR⁺ perivascular stromal cells. The deletion of Atg5 is indeed restricted to LepR⁺ cells, and this loss of ATG5 is sufficient to block autophagic function, was evident by accumulation of p62 protein.

Results: The white blood cell count (WBC) is significantly reduced in 16-week old male ATG5 KO mice compare to wild type (wt) control mice ($p < 0.05$). Further, the myeloid population (CD11b⁺Ly6G⁺) in both bone marrow and peripheral blood is significantly decreased in ATG5 KO mice (p value < 0.05 , ATG KO vs. wt control). WBC count continued to decline in 24 week old ATG5 KO male mice. Both LSK (Lin-Sca-1⁺c-Kit⁺) and long term HSC (LT-HSCs, CD150⁺CD48⁻LSK) populations are decreased in both 16-week and 24-week old male mice; however, this trend did not reach statistical significance. . Although the absolute cell count of lymphocytes, including B and T cells (CD19⁺ and CD3⁺, respectively) in peripheral blood, is significantly dropped in ATG5 KO mice compared to wt controls, there is no significant change of mature B and T cells in bone marrow.

Conclusion: Preliminary results suggest deletion of a key autophagy regulator in LepR⁺ bone marrow niche cells will cause leukopenia. The underlying mechanism is currently under investigation and it will help us to better understand the role of autophagy in hematopoiesis within the BM microenvironment.

BCR-ABL DRIVES IMMUNE EVASION VIA ACTIVATION OF CALCINEURIN

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Background: Immunologic evasion is one of the hallmarks of cancer, but the mechanisms by which leukemia evades the immune system are incompletely understood. Our lab has found that calcineurin in BCR-ABL+ leukemia cells acts as a potent mediator of immune evasion during leukemogenesis. When the essential subunit of calcineurin is knocked down, immune competent hosts are able to suppress leukemia outgrowth but immunodeficient hosts succumb to disease. We hypothesize that BCR-ABL activates calcineurin and NFAT (Nuclear Factor of Activated T cells).

Objectives: To determine BCR-ABL's role in the activity of calcineurin, as measured by NFAT activity.

Design/Method: Baf3 cells were transduced with either empty vector MiG or p190 (BCR-ABL+). Cells were kept in culture and exposed to varying doses of PMA and ionomycin in order to stimulate them. Calcineurin activity was measured via analysis of NFAT, a known downstream effector of calcineurin. Experiments to measure NFAT expression include western blot to assess protein and phosphorylation, real time PCR to assess NFAT dependent transcripts and an NFAT reporter assay to assess transcriptional activity.

Results: NFAT activity is increased in BCR-ABL+ cells as compared to control MiG cells, as is evidenced by increased total protein as well as activated protein. Increasing doses of PMA and ionomycin also lead to higher levels of NFAT in both MiG and BCR-ABL+ cells, but is more pronounced in the BCR-ABL+ population.

Conclusion: There is more total NFAT and activated NFAT protein present in BCR-ABL+ leukemia cells vs control, suggesting that BCR-ABL activates calcineurin. Studies are ongoing to determine if higher levels of protein lead to an increase in NFAT transcriptional activity and mRNA in BCR-ABL+ leukemia cells as compared to MiG. This increased activity may play a role in the ability of BCR-ABL+ leukemia cells to evade the immune system.

IDENTIFYING GENOMIC AND PROTEOMIC MODIFIERS OF VON WILLEBRAND DISEASE

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Background: Von Willebrand disease (VWD) is a common inherited bleeding disorder characterized by incomplete penetrance and variable expressivity. We phenotypically and genetically characterized a 2,000-member Amish pedigree with autosomal dominant VWD type 2M. Sequence analysis of VWF revealed heterozygosity for a missense mutation at position c.4120 (C>T) in 134 individuals. Even with an identical genetic mutation in VWF, these individuals show great variability in bleeding tendencies as measured by a quantifiable score provided by bleeding assessment tools (BAT).

Objectives: To identify biologic and genetic variants outside of VWF that influence bleeding in VWD.

Design/Method: Whole exome sequencing was performed in 16 members of the family (age and sex matched) that carry the R1374C mutation (7 with the least severe bleeding and 9 with the most severe bleeding). ANNOVAR, a software tool used to functionally annotate genetic variants, was utilized to analyze each variant and predict the effect on protein expression. Concurrently, we analyzed plasma from 12 of the above individuals using SomaLogic proteomics technology to quantify >1,100 proteins that are potentially associated with processes that are involved in bleeding. Ingenuity Pathway Analysis (IPA) was used to interpret results.

Results: IPA analysis revealed differential protein expression within several pathways, of which the most significant include cellular movement (p-value 5.46 E-03), immune cell trafficking (p-value 8.44 E-03), and hematologic system development and function (p-value 9.61E-03). Within these pathways, proteins involved in cell adhesion (i.e. MMP2, VCAM1 and FN1), coagulation (i.e. PLG), and inflammation (i.e. IL1A, IL17A, and CD86) were differentially expressed between high and low bleeders. Analysis of whole exome sequencing revealed 93 genetic variants that were enriched in one group compared to the other. Interestingly, several of these variants correlated to pathways identified in the proteomic data, including KNG1, SELPLG, FGB, STAB2, C4BPA, and GP6.

Conclusion: Preliminary analyses show a high prevalence of genes involved in inflammation, cell adhesion and the hematologic system that may be associated with bleeding variability within this Amish family. Further work will focus on replicating these variants in the rest of the members of the family, both affected and unaffected, as well as in hundreds of available unrelated cases with VWD.

STROMAL CELL GAS6 PROTECTS LEUKEMIA CELLS FROM MERTK INHIBITION

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Background: Inhibition of MERTK with the small molecule inhibitor MRX-2843 decreases tumor burden and prolongs survival in acute leukemia cell line and patient-derived xenograft models. However, while treatment with MRX-2843 reduces leukemia in peripheral blood and spleen, it is less effective in clearing the bone marrow of leukemic blasts. Gas6, a MERTK, Axl, and Tyro3 ligand, is a poor prognostic factor in AML, mediates increased resistance to cytotoxic chemotherapy in leukemia cells, and is present in the bone marrow stroma.

Objectives: To determine if bone marrow stromal cell Gas6 induces resistance to MRX-2843.

Design/Method: Acute leukemia cell lines were cultured in the presence of Gas6-producing fibroblast-like cell lines or bone marrow derived stromal cells (BMDSCs) from wild type or Gas6 knockout mice. Axl-Fc was added to co-cultures to bind and deplete Gas6. Induction of apoptosis and cell death was determined by flow cytometry after treatment with MRX-2843 or vehicle. Expression of MERTK and related kinases AXL and TYRO-3 was determined by immunoblot.

Results: Co-culture with Gas6-expressing cell lines significantly reduced leukemia cell death in response to treatment with 300 nM MRX-2843 compared to leukemia cells alone (18.25% versus 93.09%, $p < 0.001$). The protective effect was dose-dependent and reduced by titration of Gas6 with 1 $\mu\text{g}/\text{mL}$ Axl-FC (7.4% versus 16.5%, $p = 0.022$). Similarly, BMDSCs from wild-type mice protected leukemia cells from MRX-2843 induced cell death more effectively than BMDSCs from Gas6 knockout mice (4.28% versus 72.39%). Immunoblot analysis demonstrated increased expression of TYRO-3 in leukemia cells in response to co-culture.

Conclusion: The MERTK ligand Gas6 is produced by fibroblast-like cell lines and BMDSCs and mediates protection of leukemia cells from cell death induced by MERTK inhibition with MRX-2843. Gas6 depletion using genetic (GAS6 knock-out mice) and biologic (Axl-Fc) strategies decreased resistance of leukemia cells to MRX-2843 in the presence of stroma. These data are consistent with a mechanism by which increased expression and activation of Tyro3 and/or Axl promotes cell survival and resistance to selective MERTK inhibition. Further, combined treatment with MRX-2843 and a bone marrow mobilizing agent may be an effective therapeutic strategy.

EVALUATION OF OFTEN MULTIPLE BLEEDING DISORDERS IN PATIENTS WITH NOONAN SYNDROME: A SYSTEMATIC REVIEW

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Background: Noonan Syndrome (NS) is a genetic condition (1 in 1,000-2,500 individuals) that involves characteristic facial features, short stature, congenital heart defects, skeletal anomalies, developmental delays, and bleeding problems. Hematologists may be called upon to evaluate children with NS for bleeding abnormalities, particularly since many of the patients may undergo multiple surgeries beginning in early childhood.

Objectives: The aim of this systematic review was to identify specific laboratory findings and bleeding disorders in NS to inform the appropriate scope of diagnostic workup.

Design/Method: Publications reviewed were from 1965-2014 including trials, case reports/series, and reviews identified via Medline, EMBASE, and Scopus. NS patients included in the analysis were from studies where a presumed bleeding disorder or bleeding phenotype were described. All available patient data were abstracted including demographics, bleeding symptoms, lab abnormalities, bleeding score and specific disorders reported.

Results: From 45 studies identified, 31 had relevant data from 428 NS patients. Nearly half (49%) were male; 43% had reported bleeding, 26% no reported bleeding, and 31% had no data on bleeding. Most (90%) had some reported bleeding laboratory test abnormalities, but only 45% had a specific diagnosis reported. Abnormal laboratories included prolonged PT (6.8%), aPTT (17%), PT/aPTT (5%) and platelet-related (10%). While 153 (79%) had single factor deficiencies, vWD or platelet disorders, 41 (21%) had multiple deficiencies. Overall, factor XI deficiency was most common (81) followed by platelet abnormalities (46), factor XII (34), and factor VIII (28). Factors XI+XII (11) and XI+VIII (7) were the most common combined disorders.

Conclusion: These results support the importance of identifying bleeding disorders in patients with NS early in childhood, and particularly pre-operatively. The wide span of disorders and frequent presence of multiple disorders, from factor deficiencies to platelet function disorders and vWD, suggests screening needs to go beyond PT/aPTT and platelet count and should include assessment of platelet function. These results highlight the importance of early consultation with a pediatric hematologist specializing in coagulation disorders, and the need to rigorously document the extent of the work-up to accurately describe the types of disorders ruled-out.

THE PROGNOSTIC SIGNIFICANCE OF RECEPTOR FOR HYALURONIC ACID MEDIATED MOTILITY (RHAMM) EXPRESSION IN PEDIATRIC ACUTE LEUKEMIAS

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Background: The receptor for hyaluronic acid mediated motility (RHAMM, CD168) has been identified as one of the leukemia associated antigens. There have been studies in which RHAMM alone or in association with CD44 and other proteins promote invasion and inhibition of apoptosis. Paediatric acute lymphoblastic leukemia (ALL) has good prognosis whereas acute myeloid leukemia (AML) does not. There is a lacunae in the study of RHAMM expression and its prognostic significance in pediatric acute leukemias.

Objectives: To study the expression of RHAMM in paediatric acute leukemias and its prognostic significance.

Design/Method: Paraffin blocks of 73 bone marrow trephine biopsies of paediatric acute leukemias were processed for immunohistochemistry by standardized automated technique. The primary antibody used was ABCAM USA. The relative proportion (percentage) of positively stained tumor cells was quantified by three observers. Blast percentage was done in the bone marrow aspirate taken at day 8 of induction to assess the immediate response. The percentage of RHAMM positive cells and the response to induction therapy were correlated. The clinical follow up of the cases with Kaplan-Meier plot and the initial RHAMM expression were also correlated.

Results: AML: ALL ratio was 1:5 and the male: female ratio was 2:1. The mean age was 9.2 years (ALL) and 8.8 years (AML). The expression of RHAMM in AML was more than the expression in ALL. The blast percentage after induction therapy, relapse and the prognosis when correlated showed statistically significant negative correlation in both types of leukemia. The presence of more than 10% RHAMM positive cells in the initial biopsy correlated with residual disease, relapse and bad outcome.

Conclusion: Significant negative prognostic effect of RHAMM expression is evident in acute pediatric leukemias. The expression was more in AML than ALL. Hence this marker maybe included in the diagnostic panel so that the parents of the patients can be counselled and the treatment can be intensified for a better prognosis. Evolution of an inhibitor for this marker as a promising targeted therapy for these patients warrants further research.

PROSPECTIVE VALIDATION OF A RISK STRATIFIED SCREENING TOOL FOR HOSPITAL-ASSOCIATED VENOUS THROMBOEMBOLISM IN CHILDREN IN A TERTIARY CARE CENTER

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Background: Hospital-associated VTE (HA-VTE) is associated with increased morbidity. There is a paucity of prospectively validated risk stratification tools for venous thromboembolism (VTE) in hospitalized children.

Objectives: To evaluate the performance an electronic VTE risk assessment in pediatric patients

Design/Method: In August 2013, a VTE screening tool was incorporated into the computerized admission order sets for patients < 21 years hospitalized at the Johns Hopkins Children's Center. NICU patients were excluded. Assessment of mobility, VTE risk factors and bleeding risk was required for patients >14 years, and in all ages with prior VTE history or provider concern for VTE. Patients were stratified into 3 risk groups based on a score that incorporated age, immobility and risk factors. Pharmacologic prophylaxis was recommended for patients at high VTE risk, mechanical prophylaxis for moderate VTE risk or high VTE risk with bleeding risk, and no prophylaxis for low VTE risk. HA-VTE was defined as 1) VTE diagnosed \geq 48 hours after hospital admission or 2) VTE diagnosed within 90 days of hospital discharge. Patients with HA-VTE were identified by ICD9 coding and chart review.

Results: During 16 months from August 2013 to January 2015, a total of 13,067 patients underwent electronic VTE risk assessment. Provider compliance with completion of screen within 24 hours of admission was 97%. We identified 38 HA-VTE cases for a rate per 10,000 admissions of 29 (95%CI 21-40), similar to a rate of 25 (95%CI 21-29) observed from 2006 to 2013, prior to implementation of the screening tool. The rate of HA-VTE per 10,000 admissions increased with VTE risk: low risk rate was 17 (95%CI 11-26); moderate risk 78 (95%CI 21-199); high risk 350 (95%CI 188-592). Bleeding was assessed during a 4 month period; the relative risk for patients receiving pharmacologic prophylaxis was 9.9 (95%CI 3.8-25.3) for all bleeding and 6.8 (95%CI: 2.2-20.6) for major bleeding.

Conclusion: An electronic VTE risk assessment tool identified patients at increased risk of HA-VTE. However, VTE rates have not significantly decreased with implementation of the screen, and increased bleeding was associated with pharmacologic prophylaxis. Additional studies are needed to improve risk assessment and prevention strategies.

NO IMPROVEMENT IN CLINICAL TRIAL ENROLLMENT FOR ADOLESCENTS AND YOUNG ADULTS WITH CANCER AT A CHILDREN'S HOSPITAL

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Background: Our group has previously published results from July 2001 to June 2006 showing a significantly lower portion of adolescent and young adult (AYA) patients, aged 15 to 22, being treated on a clinical trial when compared to younger patients. The most common cause was the lack of an open clinical trial.

Objectives: To determine if the enrollment of AYA oncology patients on therapeutic studies at our institution has improved in recent years with a greater focus on this population locally and nationally.

Design/Method: We retrospectively analyzed cancer registry data at the Children's Hospital of Pittsburgh (CHP) for all new oncologic diagnoses from January 2010 through December 2014. This data included age, gender, diagnosis, race, whether the patient was enrolled on an open treatment study, and if not, why. Univariate analyses were done to compare demographic data between AYA patients who enrolled on study and those who did not. Fisher's exact test was used to analyze differences in AYA patients who did and did not enroll on study.

Results: 865 new oncology patients were seen at CHP during this time, 669 (77%) under 15 years and 196 (23%) 15 years or older. 33% of all patients were treated on a clinical trial, including 34% of younger patients and 24% of older patients, which was statistically significant ($P=0.002$). The differences between these rates and those from prior years in both age groups (38% and 27%, respectively) were not statistically significant ($P=0.15, 0.53$). In our current data, the most common reason for the low enrollment rates was once again the lack of an open therapeutic trial. There were no statistical differences between the groups when other factors were analyzed.

Conclusion: Despite initiatives at CHP and on the national level to enroll more AYA patients on clinical trials, our most recent data shows no improvement. The cause is multifactorial, but the primary reason we have found in our institution is the lack of an open clinical trial. This is a potentially remediable factor that needs to be prioritized nationally by the pediatric and medical oncology community.

PROPHYLACTIC ENOXAPARIN USE IN PEDIATRICS: PHARMACOLOGIC, RADIOGRAPHIC AND CLINICAL OUTCOMES

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Background: Enoxaparin is the most commonly used agent to treat thrombosis in pediatrics. Although its off-label use for this purpose is standard practice in pediatric referral centers, there is a paucity of data and recommendations in the literature regarding its administration for primary thromboprophylaxis.

Objectives: This study was designed to characterize the clinical care and course of patients who received enoxaparin for primary thromboprophylaxis at Texas Children's Hospital.

Design/Method: This was a retrospective chart review of patients who received at least one dose of enoxaparin for primary thromboprophylaxis during the 6-month study period, January through June, 2014. Data collected included demographic information, course duration and details, and clinical and radiographic outcomes. Data are reported using percentages, mean and standard error of the mean. Patients were categorized into two groups: 1) immediate post-operative administration and 2) all others (e.g., immobility as risk factor).

Results: Of forty patients who received enoxaparin for thromboprophylaxis, 26 (65%) were immediate post-operative (group 1; age 16.09 ± 0.44 years) with an average treatment duration of 4.07 ± 0.77 days. Fourteen other (35%) patients (group 2; age 13.74 ± 1.43 years) received enoxaparin as thromboprophylaxis for other reasons, over an average of 42.35 ± 8.06 days. 69% of group 1 patients were started on "adult" dosing of enoxaparin (either 40 mg daily or 30 mg BID) compared to 36% of group 2. Group 1 patients had an average 1.53 ± 1.42 dose changes (median 0, range 0-7) while group 2 had 2.92 ± 0.56 (median 1, range 0-6). Anti-Xa levels were monitored 0.69 ± 0.22 times in group 1 (median 0, range 0-5) and 4.92 ± 1.34 times in group 2 (median 3, range 0-17). Twenty-seven (67.5%) patients had enoxaparin initiated by a surgical service. No bleeding or thrombotic complications were identified, although 17.5% of patients reported bruising with injections.

Conclusion: Although limited in scope, these findings support use of enoxaparin as a safe and possibly effective measure for preventing clots in children and adolescents. Use of fixed dose regimens with minimal laboratory monitoring should be further explored, especially in selected populations, such as post-operative patients.

ALTERNATIVE RNA SPLICING OF CSF3R IN PROMOTING MYELODYSPLASTIC SYNDROMES

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Background: Myelodysplastic syndromes (MDS) constitute a heterogeneous group of bone marrow disorders frequently terminating in acute myeloid leukemia (AML). Mutually exclusive mutations were recently identified in splicing factors U2AF1, SF3B1, SRSF2, SF3A1, ZRSR2, and LUC72 in 50-85% of MDS cases. The granulocyte colony stimulating factor receptor (CSF3R) is indispensable for normal production of neutrophils. Two of the seven isoforms of CSF3R have clinical relevance: Class I (full-length form) and Class IV (alternatively spliced form). Compared to Class I, Class IV isoform is differentiation-defective and mediates enhanced proliferation. Increased expression of the Class IV isoform has been found in MDS/AML patients. Hypothesis: Aberrant splicing of the CSF3R promoted by mutations in splicing factors drives abnormal granulopoiesis in MDS due to increased expression of the differentiation defective Class IV CSF3R.

Objectives: To understand the role of cellular phosphorylation status and the influence of mutation (S34F) in the U2AF1 splicing factor on CSF3R splicing, specifically related to Class I vs Class IV.

Design/Method: To study the effect of splicing factor mutations on CSF3R splicing, we constructed a minigene consisting of 5' exon of the CAT gene with an ATG site and a partial intron fused to intron region of CSF3R upstream of Exon 17. The retained intron is present in the exon 17 of CSF3R. We transduced 293FT cells with the minigene ± wild-type U2AF1 or U2AF1 S34F mutant. Cells were treated with sodium orthovanadate (Na₃VO₄) or phorbol myristic acetate (PMA). Na₃VO₄ inhibits tyrosine phosphatases, whereas PMA promotes activation of the protein kinase C pathway. qPCR was used to determine the expression of Class I and Class IV expression.

Results: U2AF1, SRSF2 and SAM68 sites were identified in the nucleotide sequence of the spliced intron. We found that inhibition of tyrosine phosphatase activity by Na₃VO₄ resulted in increased intron excision, but PMA did not. The data suggest that tyrosine phosphorylation is important for intron excision. Exogenous expression of U2AF1 S34F showed a decrease in intron excision, suggesting that the mutation inhibits Class IV transcript formation.

Conclusion: CSF3R splicing is regulated by post-translational modifications and U2AF1.

DECREASED INPATIENT LENGTH OF STAY AND INTENSIVE CARE UTILIZATION AFTER THE JOINT OUTCOMES STUDY

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Background: Prophylactic factor replacement therapy is increasingly utilized to prevent bleeding complications in severe hemophilia. Increased prophylaxis utilization may lead to decreased admissions for bleeding complications and may alter inhibitor epidemiology. Publication of the “Joint Outcomes Study” (JOS) a phase 3 randomized controlled trial of primary prophylaxis in 2007, demonstrated that prophylaxis significantly improves joint outcomes in children with moderate to severe hemophilia A. The high-impact nature of the JOS offers an opportunity to study the epidemiological consequences of increasing prophylaxis use.

Objectives: To determine differences in admissions for bleeding episodes and inhibitor bypassing therapies (a surrogate marker for inhibitors) as well as length of stay (LOS) and intensive care (ICU) utilization between timeframes before and after publication of the JOS.

Design/Method: Hospitalizations were identified from the Pediatric Health Information System (PHIS) database for children ages 2-7 years old with hemophilia A or B. Hospitalizations from 2002-2006 (pre-JOS) and 2009-2013 (post-JOS) were compared. Data from PHIS institutions which participated in the JOS (14) were not included to avoid bias related to randomized prophylaxis during the active study period. Data from the remaining hospitals (43) were evaluated. Discharge diagnoses, defined by ICD-9-CM (international classification of diseases, 9th revision, clinical modification), along with medication charges were utilized to define bleeding episodes and bypassing therapies.

Results: There was no significant trend in bleeding episodes (bleeding diagnosis and use of factor replacement) or bypassing therapies. The overall LOS was shortened from 5.1 days to 4.5 days ($P=0.0009$) and ICU stays decreased from 7% to 3.5% of admissions ($P=0.002$) in the post-JOS era.

Conclusion: This study demonstrates a decrease in overall hospital LOS and ICU utilization in the post-JOS era. There was no increase in bypass therapy utilization, suggesting that the incidence of inhibitor formation remained stable. These findings cannot be directly attributed to changes in practice resulting from publication of the JOS, since hemophilia severity and utilization of prophylaxis cannot be directly determined from PHIS. However, they suggest that increasing utilization of primary prophylaxis may decrease inpatient utilization without altering inhibitor epidemiology.

EXPLORING CONNECTIONS BETWEEN THE EPIGENETIC FACTOR CHD1 AND THE SPLICEOSOMAL FACTOR SF3B1 IN MYELODYSPLASTIC SYNDROME/AML THROUGH CREATION OF ZEBRAFISH MUTANTS USING CRISPR/CAS 9 TECHNOLOGY.

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Background: Myelodysplastic syndrome (MDS) is a heterogenous spectrum of malignant hematologic disorders, characterized by dysplastic and ineffective hematopoiesis and propensity to transform to acute myeloid leukemia (AML). Though uncommon in children, risk of MDS is increased in children with inherited bone marrow failure syndromes and in those surviving cancer treatment. Human genomics studies have revealed that genetic mutations in spliceosomal components or epigenetic regulators are present in the majority of MDS patients. The relevant connections between spliceosomal and epigenetic factors in this disease is poorly understood.

Objectives: Here we describe the use of CRISPR (clustered regularly interspaced short palindromic repeats)/Cas9 technology to create mutants in the epigenetic regulator *chd1* (chromodomain helicase DNA-binding protein 1) in zebrafish. *Chd1* is known to interact with the spliceosome. Our studies will determine the *in vivo* importance of this interplay in hematopoiesis.

Design/Method: To create double-strand breaks in the *chd1* gene in zebrafish, *in vitro* transcribed guide RNA specific for *chd1* and Cas9 protein were microinjected into fertilized zebrafish embryos. These injected F0 founder fish were then mated to generate F1 carriers. The F1 progeny were screened for the presence of a mutated *chd1* by performing polymerase chain reaction (PCR) to amplify the target region followed by a T7 endonuclease assay for detection of indels. Exact mutations were identified by cloning and Sanger sequencing followed by bioinformatics analysis.

Results: From 13 screened F1 fish, 10 were found to carry mutations in *chd1*. Of those with mutations, 7 had mutations that are predicted to disrupt protein function through introduction of premature stop codons. Trans-heterozygous *chd1* mutant F1 fish were incrossed and no defects in overall morphology or survival were noted, in line with our previous observations using morpholino-antisense oligonucleotide knockdown of *chd1*. Homozygous mutants for *chd1* are now growing and will be characterized for hematopoietic defects and interactions with spliceosomal factors.

Conclusion: Use of Crispr/Cas9 technology in zebrafish is an effective way of creating gene-specific mutations in MDS/AML factors to determine their *in vivo* contribution to disease. Understanding the pathophysiology and interaction between spliceosomal mutation and epigenetic factors will help identify prognostic factors and potentially guide treatment in MDS and AML.

SUPERIOR VENA CAVA SYNDROME: AN EVIDENCE-BASED ANALYSIS OF REPORTED CASES IN THE ENGLISH-LANGUAGE LITERATURE FROM 1990 TO 2015

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Background: Superior Vena Cava Syndrome (SVCS) is obstruction of venous return from the head/neck that may lead to rapid development of vascular obstruction, respiratory compromise and/or neurologic manifestations with significant morbidity and mortality. Pediatric SVCS typically occurs due to external mass compression, thrombosis or related to congenital heart disease or cardiac transplant. Current knowledge is limited to single center experience with limited evaluation of outcomes and prognostic factors.

Objectives: Determine the association of clinical, radiological and therapeutic factors on morbidity and mortality of pediatric SVCS, particularly thrombosis and cardiac-related SVCS.

Design/Method: A systematic comprehensive search of literature pertaining to pediatric SVCS from 1990 to 2015 was performed. We conducted extensive data extraction from all detailed case reports/series. Data was included in the analysis only when mentioned in the articles. Descriptive statistics were performed, while related variables were evaluated using Fisher's exact test and linear-by-linear test, with p-values < 0.05 considered significant.

Results: A total of 142 patients (age 0-18 years) from 101 articles were included in the analysis, with a slight male predominance (64%) and a bimodal age distribution during infancy and mid adolescence. Long-term morbidity (30%), mortality (18%) and acute complications (55%) were assessed as outcomes. Cancer-related SVCS (31% of cases) correlated with worse outcomes (p-value 0.073), while cardiac-related SVCS (47% of cases) correlated with better outcome (p-value 0.102) but increased recurrence rate (p-value 0.068). Thrombosis was present in 36%, with multi-modal anti-coagulation showing improved outcome by > 50% (p-value 0.004). Age < 1 year (p-value 0.121), > 2 signs/symptoms on presentation (p-value 0.063), lack of collaterals on imaging (p-value 0.007) and presence of acute complication at presentation (p-value 0.005) correlated with poorer outcome, while the use of general anesthesia (89% of cases) had no implications except for one sedation-related mortality.

Conclusion: We have conducted a comprehensive evidence-based analysis of pediatric SVCS. Identified factors such as infant age, multiple signs/symptoms on presentation, lack of collaterals and presence of acute complications may have prognostic utility that can influence clinical advice and surveillance practices. Future studies may benefit from our subgroup analysis and should focus on elucidating outcome-based guidelines for the treatment of pediatric SVCS.

INHIBITION OF JQ1 ON MYELOID LEUKEMIA CELLS

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Background: AML is a hematologic malignancy that despite recent advances in management and therapy, has a treatment and disease relapse related death rate of approximately 40% in children. Aberrant chromatin states are a hallmark of AML, making this a possible therapeutic target for AML. Myeloid blasts also show constitutive tyrosine-phosphorylation of signal transducer and activator of transcription 5 (STAT5) in 69% of patients with AML. Bromodomain and extra terminal domain proteins (BET) regulate gene expression via binding to acetylated chromatin and activating transcriptional activities. JQ1 is a BET inhibitor that prevents the binding of bromodomain 4 (BRD4) to acetylated histones, resulting in inhibition of gene transcription. It has also been reported that JQ1 decreases STAT5 activation (pSTAT5) in lymphoblastic leukemia cells.

Objectives: We hypothesize that JQ1 suppresses myeloid leukemia cell growth by inhibiting aberrant BET protein function and activation of STAT5.

Design/Method: TF-1a myeloid leukemia cells were treated with JQ1 at concentrations of 0-500nM and cell proliferation rate was evaluated using AlamarBlue® at 72 hours. Colony forming assay (CFU-GM) was established in 0.3% agar and McCoy's 5A Medium, with TF-1a cells and varying concentrations of JQ1. Flow cytometry (FACS) was used to detect the levels of the activated form of STAT5 (pSTAT5). JQ1 was also tested in mononuclear cells from cord blood (CB) in order to determine the toxicity of JQ1 on normal cells.

Results: AlamarBlue® assay indicated that TF-1a cell proliferation significantly decreased at doses of JQ1 of 31.25nM ($p=0.002$) or higher ($p<0.001$), but at doses of 125nM or greater ($p<0.001$) in CB, suggesting that leukemia cells are more sensitive than CB cells. CFU assay suggested that JQ1 significantly inhibited TF-1 colony formation in a dose dependent fashion ($p<0.001$). FACS analysis indicated that pSTAT5 significantly decreased in TF-1a cells after 2hrs of 500nM JQ1 ($p=0.011$).

Conclusion: Our Preliminary data suggests that JQ1 significantly decreases STAT5 activation in myeloid leukemia cells and significantly inhibits leukemic cell proliferation at levels not toxic to CB cells. Should this be confirmed in further studies, JQ1 may be an alternate therapy for treatment of myeloid leukemia. Woods, *Pediatr Blood Cancer* 2012. Birkenkamp *Leukemia* 2001. Wyce *Oncotarget* 2013. Ott, *Blood* 2012.

PREDICTORS OF THROMBOSIS RESOLUTION IN PEDIATRIC PATIENTS

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Background: As the incidence and knowledge of deep venous thrombosis in children increases, so does the awareness of long-term complications from DVT. Post-thrombotic syndrome is one of the potential outcomes of DVT, and can be a debilitating consequence of a DVT causing pain, swelling, and limb discoloration. An incompletely resolved DVT often can lead to PTS, though what percentage of DVT resolve with anticoagulation has been understudied.

Objectives: To evaluate the characteristics of patients who develop DVT and to assess the rate of resolution, rate of PTS, and predictors of both.

Design/Method: The study was a retrospective chart review of all children diagnosed with a DVT over a two-year period (2012-2013) in a single large academic center. Information regarding patient age, sex, radiographic imaging, presence of a central line, DVT location and extension, thrombophilia testing, and outcomes were extracted. Logistic regression analyses were performed to evaluate for predictors.

Results: There were 105 cases that met eligibility criteria. Median age at presentation was 1.3 years of age (range, 0 – 18 years). Primary clot location was as follows: 5% abdominal, 41% upper extremity, 54% lower extremity. Seventy-seven percent of clots were associated with a central venous catheter. Thrombophilia testing was performed in 49 patients, and was positive in 39% of patients that were screened. Fifty-nine percent of DVTs resolved with anticoagulation. However, there were no statistically significant predictors of thrombosis resolution. PTS was assessed in clinical follow-up in 94 cases, with 14% reporting symptoms. There was no significant difference in the development of PTS by age, sex, primary site, or presence of an inherited or acquired thrombophilia.

Conclusion: Our study is one of the larger studies looking at thrombosis resolution and PTS development in children. Though 41% of DVTs did not resolve, only 14% of subjects reported symptoms of PTS at clinic follow-up. There were no statistically significant predictors of either outcome, suggesting that other factors not commonly assessed may be playing a role in adverse outcomes in the treatment of DVTs. Large prospective cohort studies need to be performed to better delineate these findings.

SORAFENIB COMBINED WITH NON-CONVENTIONAL CHEMOTHERAPY PRODUCES DEEP REMISSIONS IN FMS-LIKE TYROSINE KINASE-3 GENE/ INTERNAL TANDEM DUPLICATION POSITIVE (FLT-3/ITD+) POSITIVE ACUTE MYELOID LEUKEMIA (AML) PATIENTS

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Background: FLT-3 mutations are present in nearly 25% of AML patients and have been associated with poor prognosis when treated with conventional chemotherapy. In vitro and in vivo studies have demonstrated beneficial effects of sorafenib in FLT3/ITD+ pediatric AML

Objectives: To assess the outcome of sorafenib in combination with various chemotherapy regimens in FLT3/ITD+ AML in children

Design/Method: We retrospectively analyzed initial outcomes of 14 FLT-3/ITD+ AML patients who received various chemotherapeutic regimens + sorafenib from May 2013 to December 2015. Patients were treated with either daunorubicin 60mg/m² /cytarabine 100 mg/m² (3+7) or/and high dose ara-C 18 G/m² (HDAC) or/and/or metronomic therapy (MCT) (etoposide + 6-thioguanine +/- prednisolone) or/and cladribine (2CDA) (9 mg/m²) + ara-C (500 mg/m²) d1 to d5. Sorafenib was given orally in the dose of 150 to 200 mg/m² twice a day.

Results: There were 13 children with newly diagnosed and one with relapsed FLT-3/ITD+ AML; 10 males, 4 females. The median age at presentation was 11 years (range 2 to 19) with median WBC count of 109 x 10⁶/L (range 30-308). MRD negativity (by flow) was achieved in 7/7 patients post 2CDA/ara-C + sorafenib; 4/8 patients post (MCT) + sorafenib; 1/1 patient post 3+7 + sorafenib. Only 1/7 patients receiving HDAC + sorafenib achieved MRD negativity. 11/14 (77%) patients achieved deep remission post treatment with chemo + sorafenib, while the remaining 3 patients have not yet received 2CDA/ara-C + sorafenib. There have been 3 relapses till date, all of whom had received only 1 cycle of 2CDA+araC as part of therapy. There were 3 remission deaths, 1 due to sepsis post 2CDA+ ara-C and 2 at home (village) due to unknown cause. At a median follow-up of 10 months (range 4 to 19 months), 7/14 patients are alive. Sorafenib was well tolerated with only 2 patients having Grade III skin toxicity.

Conclusion: Our preliminary data suggests that patients with FLT-3/ITD+ AML may benefit with 2CDA/ara-C + sorafenib as induction and consolidation regimen followed by oral MCT + sorafenib as maintenance.

IS THERE AN INCREASE INCIDENCE OF PEDIATRIC VENOUS THROMBOEMBOLISM AT ALTITUDE?

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Background: Venous thromboembolisms (VTEs) are cited to occur in 0.07-1 per 10,000 children annually based on databases collected mainly from populations at sea level. Denver, CO has an elevation of 1600m and is considered intermediate altitude. Higher incidences of adult VTEs at altitude have been reported, but there are no studies on the incidence of pediatric VTE at higher altitudes. We hypothesize that children at altitude also have an increased incidence of VTE compared to children at sea level.

Objectives: To investigate the incidence of pediatric VTE at intermediate altitude.

Design/Method: After obtaining COMIRB approval, a retrospective case control study was performed investigating the pediatric VTE incidence at intermediate altitude. The incidence was determined by identifying patients with distinct ICD-9 diagnoses for VTE seen at Children's Hospital Colorado during 2010-2014. Diagnostic validation was performed through chart review. Patients presenting from outside the Denver area were excluded.

Results: 540 unique patients were identified with ICD-9 codes for VTE (males 54%, females 46%). Median age was 13.26 years (range: 1 day to 18.84 years). Patients presenting with primary diagnosis of VTE comprised 29.4% (159 patients) of the population. Patients diagnosed with a secondary VTE within 48 hours of admission made up 30.7% (166 patients) and patients with hospital-acquired VTE diagnosed 48 hours after admission made up another 39.8% (215 patients). The gender distribution of primary VTE patients favored females (59.1%) over males (40.9%) with 75% of patients presenting between 14.73-18.13 years. In consideration of risk factors, 42% had positive family history for thrombophilia or "blood clots," 39% had evidence of inflammation such as a viral illness in the previous 4 weeks before diagnosis, 18% had significantly reduced mobility, 22% of patients took oral contraceptives and 15% were obese.

Conclusion: This epidemiologic study of pediatric VTEs diagnosed at a single institution at intermediate altitude suggests that there is an increased rate of VTE at moderate altitude. The incidence was 2 per 10,000 children, which is doubled from the upper limit incidence of 1 child per 10,000 cited by studies at sea level. Comparison of data to other institutions at altitude and additional screening for confounding factors are needed.

DEVELOPMENT OF CHIMERIC ANTIGEN RECEPTORS FOR NATURAL KILLER CELL-BASED TREATMENT OF T-CELL MALIGNANCIES

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Background: Relapsed T-cell leukemia overall has a poor prognosis. Chimeric antigen receptor (CAR) therapy could potentially be used; however targeting T-cell disease without a T-lymphoblast specific antigen is difficult. Use of natural killer (NK) cells as the effector cell and CD5 as our target antigen allows us to overcome this problem. We created a novel CAR by substituting the single chain variable fragment (scFV) of traditional CARs with a variable lymphocyte receptor (VLR) as our antigen recognition sequence. VLRs represent the functional unit of the adaptive immune system in jawless vertebrates (lamprey and hagfish) and are analogous to immunoglobulins. VLRs exist naturally as single chain structures and demonstrate high specificity via repeating sequences termed leucine rich repeats.

Objectives: Our objective was to develop a VLR-CAR-NK cell against T-cell leukemia using an anti-CD5 sequence.

Design/Method: We constructed a second generation CAR using a VLR sequence targeting CD5 as our antigen recognition sequence and high titer CD5 VLR CAR self-inactivating lentivirus was produced. To test the CAR construct, CD5 expressing Jurkat cells were transduced with various doses of lentivirus, and activation was measured. For cytotoxicity studies, NK-92 cells were used as the effector cell with CCRF-CEM being the target cell. Cytotoxicity was measured at different effector: target ratios using a flow cytometry based assay.

Results: Activation directly correlated with lentiviral copy number and CAR expression in Jurkat cells. NK-92 cells expressing the CD5 VLR CAR showed a ~two fold increase in cytotoxicity towards CCRF-CEM cells when compared with naïve NK-92 cells; however, low transduction efficiency and copy numbers (<0.5) were problematic. To improve, we created a bicistronic vector expressing GFP and CD5 VLR CAR. Jurkat cells with the new construct showed a direct correlation between GFP expression and activation, thus confirming dual expression and function of both proteins. Transduced NK-92 cells with the new construct were sorted and expanded. These cells expand robustly, demonstrate CAR expression and have the functional characteristics for targeting T-cell disease.

Conclusion: Our studies show the usefulness of VLR-derived CARs and provide the foundation to move these studies into preclinical testing as a treatment for relapsed childhood T-ALL.

CLINICAL DATA OF THE PATIENTS WITH HEMOPHILIA PRESENTED IN A TERTIARY CARE HOSPITAL OF A DEVELOPING COUNTRY

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Background: Hemophilia is a rare X-linked recessive clotting factors deficiency disorder. Overall incidence is 1 per 10,000 male live births. Patients present with bleeding tendency and severity correlates with the level of factor deficiency. Late diagnosis and improper management can lead to lifelong complications.

Objectives: To analyze the clinical data of disease in a developing country with limited resources so that we can predict how can we prevent morbidity and improve the quality of life in our set up.

Design/Method: A total of 55 patients of Hemophilia A and B were reviewed retrospectively who presented in Children's Hospital & Institute of Child Health, Lahore in last one year. Data was analyzed on basis of clinical features, age at first presentation, age at diagnosis, severity of disease, factor replacement, and life threatening bleed. PT/APTT, mixing studies and factor assays were also noted.

Results: Among these 55 patients all were male. Around 93% were diagnosed as Hemophilia A and 7% as Hemophilia B. Mostly (96.4%) diagnosed after 1 year of age although 62% were symptomatic before 1 year of age. About 49% were having moderate disease, 18%, with mild and rest were with severe disease. Family history was positive in 51% and in all the patients who presented before 6 months of age had severe hemophilia. APTT was prolonged in all the patients with the mean value of >1 minute. Severity of disease and family history has significant relation at $p < 0.005$, while relation between severity of disease and the age at diagnosis is significant but compromised at $p = 0.05$, i.e. critical line. Post circumcision bleed (45.5%) was observed prominently as primary symptom followed by bruises and epistaxis, respectively. Life threatening bleed was reported in 9% and about 66% developed hemarthrosis. Only 2 patients had APTT done before circumcision. Most of the patients were on demand factor replacement therapy (74.6%) and only 5.4% of them were on primary prophylaxis.

Conclusion: On the basis of early presentation and family history we can predict the severity of the disease. Performing PT/APTT before circumcision in all children is cost effective screening investigation as early diagnosis, adequate and timely prophylaxis can prevent early and late complications.

AMPLIFIED KILLING OF LEUKEMIA BLASTS BY CAR-T CELLS USING A NOVEL FACS BASED CYTOTOXICITY ASSAY

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Background: The continued emergence of cellular therapies to treat precursor-B cell ALL has evolved to include patient-derived T cells that have genetically modified to express chimeric antigen receptors (CAR) which bind to CD19 on lymphoid leukemic blasts. There are reports of using CD19 expressing cell lines in chromium release or FACS assays, however the use of patient derived blasts in such experiments has been elusive.

Objectives: To identify a rapid assay to assess cytotoxicity for development of future CAR-T cells

Design/Method: Cytotoxicity assays were set up with populations of effector and target cells. Effector cell populations were T cells collected from 2 pediatric pre-B ALL patients and 2 healthy donors. CAR-T cells were manufactured using T cells from the same 2 healthy donors transduced with a retroviral vector containing CD19-CAR. Target cell populations: 1) CD19+ cell line (Nalm6), 2) bone marrow from 2 patients with pre-B ALL, and 3) T cells from 2 healthy donors. Effector and target cells were co-cultured for 4 hours at increasing effector to target (E:T) ratios (0:1 to 20:1). Co-cultures were stained to identify dead cells and analyzed by FACS. The percentage of living target cells (LC) in each assay was averaged and the percent difference ($d = LC0 - LC20 / LC20$) in killing was calculated using these averages.

Results: Nalm6 cells when co-cultured with the 4 untransduced effector populations had 80 percent difference in killing (LC0 75%, LC20 15%). 2 populations of CAR-T cells had an 89 percent difference in killing of Nalm6 cells (LC0 83%, LC20 9%). Target cells from a healthy donor showed no difference in percent killing when cultured with untransduced effector cell populations and CAR-T cells ($d = 6\%$). Leukemic blasts from bone marrow had a 21 percent difference in killing when cultured with untransduced effector cells from E:T of 0:1 to 20:1 (LC0 82%, LC20 65%) compared with 30 percent difference in killing with CAR-T cells (LC0 87%, LC20 60%).

Conclusion: There is amplified killing of a patient's leukemic blasts by CAR-T cells compared with untransduced cells. We have plans to continue to use this novel assay to specifically measure the cytotoxicity of iPS derived CAR-T cells against CD19 blasts collected from pediatric patients.

SUBCUTANEOUS DDAVP USE IN PEDIATRIC VON WILLEBRAND DISEASE AND HEMOPHILIA A

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Background: DDAVP is used in treatment and prevention of bleeding in von Willebrand Disease (VWD) and Hemophilia A (HA). DDAVP can be administered intravenously, subcutaneously or intranasally. The majority of data on effectiveness of DDAVP are from adults receiving intravenous infusions. There is a paucity of data regarding subcutaneous administration in children.

Objectives: Determine response rate and side effect profile in children with VWD or HA receiving subcutaneous DDAVP.

Design/Method: We conducted a single-centre retrospective study of patients who received subcutaneous DDAVP from January 2004 to December 2015. Response for patients with HA was defined as Factor VIII (FVIII) ≥ 0.3 IU/mL and an increase of \geq twofold over baseline, after one hour. Response for patients with VWD was defined as VWF:RCo and FVIII ≥ 0.3 IU/mL and an increase in both of \geq twofold over baseline after one hour.

Results: We studied 16 patients with mild HA (median age 7.1 years, range 2-14 years) and 13 with VWD (median age 8.1 years, range 3-16 years, 54% male, 11/13 type 1 and 2/13 type 2M). Among patients with HA, 11/16 (69%) responded to DDAVP. Median age was 8.5 years for responders and 4.2 years for non-responders. Of patients with VWD, 7/13 (54%) responded. All responders had type 1 disease. Patients with HA with baseline FVIII level ≤ 0.1 IU/mL, and patients with VWD with VWF:RCo ≤ 0.1 IU/mL, were all non-responders. Side effects included: facial flushing (6/29), headache (1/29), asymptomatic hypotension (7/29), and tachycardia (3/29). No serious adverse events were reported.

Conclusion: Response rate for patients with mild HA in our cohort was higher than reported in a comparable cohort receiving intravenous DDAVP, using the same response criteria (69% vs. 57%). However, in patients with type 1 VWD, we observed a lower response rate than reported with intravenous DDAVP in a similar cohort (64% vs. 80%). Older patients and those with higher baseline factor levels were more likely to respond. Subcutaneous DDAVP was safe and well tolerated with only mild side effects, making it a valuable therapeutic option for pediatric patients who demonstrate response, especially given the ease of administration and potential use at home.

PARENT PERCEPTION OF PEDIATRIC INTENSIVE CARE UNIT DECISION MAKING FOR CRITICALLY ILL CHILDREN WITH CANCER

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Background: Parents of children with cancer face challenging decisions while in the Pediatric Intensive Care Unit (PICU). Few studies identify these decisions and how parents perceive their support and satisfaction with decision making in the PICU.

Objectives: To identify decisions faced in the PICU by parents of children with cancer and parents' perception of their involvement and satisfaction with the decision making process.

Design/Method: Parents completed a written questionnaire upon their child's admission and discharge from the PICU. The admission questionnaire requested basic demographic information. The discharge questionnaire asked parents to: identify the most important decision made for their child in the PICU; indicate if someone helped communicate with doctors about decisions; complete the decision regret scale (a 5-item tool scored from 0 "least regret" to 100 "most regret"); and complete the Decision Making component of the pediatric family satisfaction with intensive care unit (pFS-ICU) scale (a 10-item tool scored on a scale from 0 "least satisfied" to 100 "most satisfied").

Results: We received admission and discharge questionnaires from 20 parents of 16 patients. Patients ranged in age from 1 to 17 (mean 8.9) years. Of the patients enrolled, 44% of patients (n=7) had hematologic cancers and 56% (n=9) had solid tumors. Parents identified that important decisions made for their child involved: medications; use of radiation; use of medical devices; surgical procedures; and general care plans. 65% (n=13) of parents reported receiving help communicating with doctors about decisions. Parents identified bedside nurses (n=8); residents (n=2); fellows (n=3); social workers (n=3); chaplains (n=2); and doctors or subspecialties (n=2) as helpful in their decision making process. The average decision regret score was 9.4 (range 0-50), and the average pFS-ICU DM score was 81.5 (range 51 – 100).

Conclusion: Parents face complicated decisions for critically ill children with cancer. Over half of parents identified a member of the healthcare team who helped them communicate about decisions, most commonly bedside nurses. These data highlight a potentially important role for bedside nurses in supporting communication and decision making for parents in the PICU. While decision regret scores were low and pFS-ICU DM scores were high, room for improvement exists.

TWO MOLECULAR DEFECTS IN HOMOZYGOUS PROTEIN C DEFICIENCY WITH ATYPICAL PRESENTATION: CASE SERIES AND REVIEW OF LITERATURE

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Background: Homozygous protein C deficiency (HPCD) is a rare hereditary thrombophilia caused by a genetic mutation involving the PROC gene with estimated incidence of 1 per 4 million births. The classical presentation of HPCD is purpura fulminans (PF) developing shortly after birth. The diagnosis is usually made based on genetic analysis and protein C level.

Objectives: We aim to discuss the clinical presentation, associated molecular defects, and outcome of five pediatric patients with HPCD as well as review related data in the literature.

Design/Method: Data were collected from the medical records of five pediatric patients with HPCD treated at our institution. Literature review included 82 patients with HPCD. We included only papers written in English that provided at least clinical presentation and/or outcome for the cases they studied.

Results: Our sample includes two males and three females with median age of two years (2-14 y). Three cases were positive for c.1163 C>T (Ala388Val) mutation while the other two had c.1297 G>A (Gly433Ser). In all cases, PF was atypically delayed beyond the first year of life. Only one case we found in the literature with PF beyond one year and this was positive for c.8514 G>A (Ala267Thr) mutation. Protein C activity was reported less than < 1% in all cases. Blindness was seen in four of our cases in comparison to 16/82 (20%) cases in the literature reviewed. Of the four cases who developed blindness, two were found to have the rare congenital ophthalmic finding of Peter's anomaly. One case had intraocular bleeding shortly after birth preceding PF which occurred 16 month later. In contrast 17/82 (21%) cases in reviewed literature found to have ocular bleeding simultaneously with PF. All patients are survived.

Conclusion: We defined two genetic defects causing HPCD with atypical presentation of late-onset PF and isolated intraocular bleeding. No previous reports have provided clinical data for these particular mutations. Whether these molecular defects contributed to this atypical expression is yet to be answered. The association between Peter's anomaly and HPCD has never been reported. This observation merits further study in a large center.

CARE CLOSER TO HOME: THE IMPACT OF A COMMUNITY-BASED PEDIATRIC ONCOLOGY CENTER ON BURDEN OF CARE

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Background: Childhood cancer treatment in the US is typically offered at tertiary centers, located in large urban settings. For children who reside in outstate areas, travel increases the family burden of care. Greater distance from the treating hospital is associated with greater economic hardship, emotional stress and family burden.

Objectives: The purpose of this study was to examine the impact of a community-based pediatric cancer center on burden of care as measured by travel distance, cost and time.

Design/Method: For pediatric cancer patients diagnosed from 2008-2014 roundtrip distance and travel time to the treating community-based pediatric cancer center (CBPCC) and nearest tertiary care treatment center (TCTC) were identified. Gasoline cost was computed using miles per gallon for new cars during diagnosis month and mean price per gallon. Three Children's Oncology Group treatment scenarios were applied to all patients from diagnosis through protocol end or death: 1) Leukemia (53 visits), 2) Lymphoma (10 visits), and 3) Sarcoma (56 visits). Paired t-tests compared CBPCC and TCTC for a single visit and the three treatment scenarios.

Results: A total of 84 patients, ages 0-19 years (median=9.0) were included; 61.9% were rural residing. All comparisons were significant at $p < 0.001$. For a single round trip visit, difference in travel distance (CBPCC-TCTC) was -263.4 miles, travel time -3.6 hours, and gasoline cost - \$36.63. For the leukemia treatment scenario, difference in travel distance was -13,960.6 miles, travel time -189.1 hours, and gasoline cost -\$1,862.53. Similar results were seen for lymphoma and sarcoma, proportional to the number of scheduled visits in each treatment scenario.

Conclusion: Community-based pediatric cancer centers can reduce the burden of care for families by minimizing their travel time and its associated hardships. This analysis does not include travel for unscheduled visits or off-therapy visits, nor does it consider the additional expenses generated by travel (housing, food, child care, missed work). Over the course of a child's cancer treatment, care closer to home magnifies the savings of time and costs, reducing the overall burden of care for families.

THE INCIDENCE OF POSTOPERATIVE BLEEDING IN PEDIATRIC PATIENTS WITH MILD BLEEDING DISORDERS WHO RECEIVED PREOPERATIVE DESMOPRESSIN (DDAVP)

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Background: Von Willebrand's disease (VWD) and platelet function disorders (PFD) are the most common mild bleeding disorders seen in children and young adults. These patients usually have good responses to IV DDAVP and are often prophylactically treated with it prior to surgeries. Few studies have analyzed the prophylactic use of IV DDAVP in preventing postoperative bleeding in these patients.

Objectives: Our goal was to evaluate if patients with VWD and PFD who were prophylactically treated with IV DDAVP had a lower rate of postoperative bleeding than historical controls who did not receive DDAVP.

Design/Method: We performed a retrospective chart review of pediatric patients seen in the coagulation clinic for a DDAVP challenge at the Children's Hospital of Pittsburgh from January 2011 to December 2013. Inclusion criteria were patients under 22 years old who had VWD, low Von Willebrand factor (LVWF) or PFD, responded well to DDAVP and had surgery. Prophylactic IV DDAVP with or without aminocaproic acid was used perioperatively. The primary outcome was the incidence of postoperative bleeding in the first 24 hours (early bleeding) and between 24 hours and 10 days (late bleeding).

Results: Of 194 patients who underwent a DDAVP challenge, 58 had surgery. The mean age was 8.6 ± 4.4 years and 50% were female. 42 patients (72%) had Type 1 VWD, 5 (9%) had LVWF, 10 (17%) had a PFD and 1 (2%) had evidence for both Type 1 VWD and a PFD. These patients underwent 72 procedures. Postoperative aminocaproic acid was used inconsistently. There was no early postoperative bleeding for any patient and 3 patients (4%) had late bleeding, all after tonsillectomy with or without adenoidectomy. 27 procedures (38%) were a tonsillectomy with or without adenoidectomy and had a bleeding rate of 11%. None of our patients who had other procedures developed postoperative bleeding. Published bleeding rates for large series of untreated patients with known bleeding disorders were as high as 32%.

Conclusion: Patients with VWD and PFD who received prophylactic IV DDAVP had a lower rate of postoperative bleeding versus untreated patients with the same diagnoses. It is unclear if aminocaproic acid provides additional benefit.

SPEAKING TO THE “NEW NORMAL”: WOULD FAMILIES VALUE A DAY 100 TALK IN THE FIRST SIX MONTHS OF CANCER CARE?

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Background: The first six months of childhood cancer treatment may lead to changed illness understanding and altered communication needs among families compared with those at diagnosis, but currently, there is no framework to guide communication in this early treatment period.

Objectives: To elicit (1) lived illness experiences during the first 1-6 months, (2) the acceptability of engaging in a novel in-depth conversation with the primary pediatric oncologist, the “Day 100 Talk,” (D100) during this period, and (3) preferred topics and goals for D100.

Design/Method: We conducted semi-structured interviews with children aged ≥ 13 years and parents of all-aged children with non-relapsed cancer undergoing treatment for 4 weeks to < 7 months. Sampling, interviews, and constant comparative qualitative analysis were informed by grounded theory.

Results: Five of 10 (50%) adolescents and 6/11 (55%) parents participated in interviews. Five participants or children of participants had solid tumors, 3 had brain tumors, and 3 had hematologic malignancies. Mean treatment duration was 10 (+/-4) weeks. Emergent themes reflected a combination of relative normalcy during early treatment (“you have off weeks”; “they still fight”) and a “new normal,” composed of cancer care, new relationships, and altered daily lives. Participants speak of emerging “out of the woods” and getting their “sea legs” during this early treatment period, and so are able to engage with their care differently than at diagnosis. Frequently, one parent takes charge of the ill child’s care while the other maintains work and home life. This role division leads to different information needs for members of the same family. Overall, parents endorsed D100 (5/6, 83%) more than adolescents (3/5, 60%), though all adolescents endorsed the desire to discuss the future. Participants suggest D100 could serve to 1) reflect on progress; 2) consolidate illness understanding and create shared understanding between family members with different roles; 3) ensure the current treatment path is still “right,” and 4) manage transitions, such as from hospital-based to home-based care.

Conclusion: Families endorsed the D100 concept, which could serve to reflect on progress, deepen family illness understanding, revisit treatment decisions, and anticipate future transitions. Future work should further develop D100 by integrating oncology providers’ perspectives.

RARE BLEEDING DISORDERS IN OMANI CHILDREN: A SINGLE CENTRE EXPERIENCE

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Background: Rare bleeding disorders (RBDs) are autosomal recessive heterogeneous group of inherited coagulation factor deficiencies, with a prevalence ranging from 1:500,000 to 1:2,000,000. Remarkably, there is a paucity of data on RBDs from the Middle East. Despite education and social modernization, Oman still has a high prevalence of consanguineous marriage, reaching more than 50% of all registered marriages. RBDs are expected to be relatively high in Oman compared to western countries.

Objectives: The aim of the current work is to study the demographic characteristics, clinical presentations and management of RBDs in Omani pediatric patients.

Design/Method: Retrospective data analysis of all children diagnosed with inherited coagulation factor deficiencies in Pediatric Hematology Unit, Sultan Qaboos University Hospital, and Muscat, Oman from January 2009 till December 2015.

Results: Deficiencies of fibrinogen, FV, FVII, FX and FXIII were diagnosed in 19 pediatric patients (9 males and 10 females), accounting for 10.8 % (19/176) of all children with inherited coagulation factor deficiencies. Hypofibrinogenemia and FV deficiency were the commonest disorders diagnosed in 8 and 5 patients respectively. The age ranged from 3 days to 6 years and consanguineous marriages were found in 16/19 cases (84.2%). The clinical spectrum varied from mild mucocutaneous bleeding to serious sight-threatening intraocular hemorrhage in a neonate with afibrinogenemia. As an initial presentation, intracranial hemorrhage occurred in 6/19 cases (31.6%). Two patients; one with FV deficiency and another with FXIII deficiency suffered from global developmental delay due to severe intracranial hemorrhage in early infancy. As regards management, 4 patients with severe FV deficiency and one with severe FXIII are on fresh frozen plasma (FFP) prophylaxis. Other patients receive on-demand therapy.

Conclusion: In conclusion, children with RBDs constitute almost one tenth of cases of hereditary coagulation factor deficiencies in our centre. They have some unique features in terms of severity, clinical profile and the need for prophylaxis early in life. We recommend establishing a national/regional registry of RBDs in collaboration with other centres. This will serve to identify the epidemiology, clinical presentations, genotype-phenotype correlation and therapeutic options of such rare, yet significant disorders in this part of the world.

INVESTIGATION OF PROPRANOLOL PREMEDICATION TO REDUCE FDG UPTAKE IN BROWN ADIPOSE TISSUE ON PET SCANS OF PEDIATRIC ONCOLOGY PATIENTS

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Background: Positron Emission Tomography (PET) scans using 18F-fluorodeoxyglucose (FDG) are increasingly used for cancer staging and treatment response assessment. Physiologic uptake of FDG in brown adipose tissue (BAT) in the neck and chest is common in pediatric patients and can confound interpretation of PET scans, creating false positives by mimicking tumor or false negatives by obscuring malignant nodes. FDG uptake in BAT is mediated by adrenergic signaling and can be blocked by propranolol, as shown in previous studies of adult oncology patients.

Objectives: We prospectively assessed the safety of a single low dose of propranolol in fasting adolescent and young adult oncology patients undergoing FDG-PET imaging. We also retrospectively reviewed data from pediatric oncology patients who had undergone PET scans at our institution to identify features most likely associated with BAT uptake.

Design/Method: Propranolol 20 mg (0.1-0.4 mg/kg) was given one hour prior to FDG injection. Vital signs, blood glucose measurements, and symptom assessment were performed before and after scanning. Images were reviewed by a blinded radiologist. Charts were retrospectively reviewed from 76 additional patients to assess whether gender, age, body mass index (BMI), or season of year predicted FDG uptake in BAT.

Results: Nine patients received propranolol (median age 18 years, range 14-24). No clinically significant changes were observed in blood pressure, heart rate, or serum glucose following propranolol administration. No patient had observed or subjectively reported adverse events. Four patients with previous uptake in BAT had none following propranolol. In the retrospective review of 85 total patients (median age 15 years, range 7-29), BAT uptake was identified in 57% of patients. On multivariate analysis, lower BMI was the only factor associated with BAT uptake ($p=0.0087$).

Conclusion: Propranolol was convenient and safe in fasting pediatric oncology patients undergoing PET scans, and effectively eliminated BAT uptake in 4 patients who had this finding on previous scans. Lower BMI was the most important factor in predicting BAT uptake. Future studies could target patients with low BMI, and compare the efficacy of propranolol with other drugs like fentanyl which have been used to reduce BAT uptake.

**IMPACT OF GENETIC POLYMORPHISMS DETERMINING
LEUKOCYTE/NEUTROPHIL COUNT ON CHEMOTHERAPY TOXICITY IN
CHILDHOOD LEUKEMIA**

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Background: Neutropenia and infection are major dose-limiting side effects of chemotherapy. The risk of initial infection and subsequent complications are directly related to the depth and duration of neutropenia. Recent publications provided evidences that genetic variants in DARC gene, ORMDL3-GSDMA-CSF3 locus on chromosome 17q21, and CXCL2 gene influence total white blood cell (WBC) and neutrophil count irrespective of the treatment.

Objectives: Evaluate the association between polymorphisms capturing variability in these loci with chemotherapy complications in children treated for acute lymphoblastic leukemia. (ALL)

Design/Method: Retrospective study of children treated for ALL using DFCI protocol. 16 tagSNPs in DARC gene, 9 SNPs in ORMDL3-GSDMA-CSF3 locus and 2 SNPs in CXCL2 gene were analyzed. Chart review was then performed to evaluate episodes of neutropenia and infectious complications

Results: 300 Caucasian children of French-Canadian origin diagnosed with ALL at the CHU Sainte-Justine, Montreal, between January 1989 and July 2005. After correction for multiple testing, DARC SNP rs3027012 was associated with low absolute phagocyte count (APC<500 and <1000 cells/ μ L, $p=0.009$ and $p=0.0005$, respectively) and hospitalization due to neutropenia ($p=0.004$). We also observed an association among rs862996 (upstream DARC variant), chemotherapy cessation due to neutropenia ($p=0.004$) and APC< 500 cells/ μ L ($p=0.008$). SNPs in the ORMDL3-GSDMA-CSF3 locus were associated with hospitalization due to infection (rs3859192, $p=0.004$), and hospitalization due to infection and neutropenia (rs17609240, $p=0.003$, rs25645, $p=0.003$ and rs2227319, $p=0.005$).

Conclusion: This study identifies for the first time that loci modulating WBC and neutrophil count may play a role in the onset of chemotherapy complications and may thus serve as markers for adjustment or follow-up of the treatment of childhood ALL.

EXAMINING URINARY BIOMARKERS OF CISPLATIN NEPHROTOXICITY IN CHILDREN

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Background: Cisplatin, a chemotherapeutic agent used in the treatment of medulloblastoma, has the potential to cause nephrotoxicity. Monitoring for renal injury relies on changes in serum creatinine. This can be delayed and may not be observed until significant renal injury occurs. Urinary protein biomarkers may serve as a more sensitive method in detecting renal injury and are currently studied in numerous clinical settings.

Objectives: To evaluate changes in urinary biomarkers in response to cisplatin containing chemotherapy in children with medulloblastoma.

Design/Method: Urinary Creatinine and Biomarker Analysis: Samples were collected from pediatric patients with medulloblastoma treated with cisplatin (n=11). Samples were collected pre and post treatment cisplatin. Lab values were obtained for serum creatinine, magnesium, phosphorus, potassium, and GFR. Urinary creatinine levels were obtained using the Cayman Chemical Urine Creatinine assay. Millipore's Human Kidney Toxicity Panel 2, Human Kidney Injury Panel 1 and BioRad's Human Kidney Toxicity Panel 2 were run on the FlexMap 3D Suspension Array System. Proteins examined included: TIMP-1, KIM-1, TFF-3, Osteopontin, B2M, Albumin, NGAL, Cystatin C, and Clusterin. Assays were run per manufacturers' recommendations and protocols. Data Analysis: Data was analyzed using GraphPad Prism 6. A p-value of ≤ 0.05 was considered significant. All biomarker values were normalized to the urinary creatinine levels and expressed as ng of urinary biomarker/mg of creatinine. Biomarkers and lab values were analyzed by unpaired t-test by comparing pre and post treatment to determine differences between biomarker concentration and treatment.

Results: Trefoil factor 3 (TFF-3) was expressed at higher concentrations post cisplatin treatment when compared to pretreatment (p=0.0049). No significance was found in the other biomarkers. Additionally, serum phosphorus levels were decreased post cisplatin treatment (p=0.0268).

Conclusion: TFF-3 is a member of the trefoil factor peptide family and is secreted by epithelial cells of the urinary tract and the proximal and distal collecting ducts. In this study, children receiving cisplatin had significant changes in TFF-3 concentrations post cisplatin treatment. Serum creatinine did not change post cisplatin treatment. This suggests TFF-3 may be a sensitive biomarker of acute kidney injury secondary to cisplatin.

VORICONAZOLE DOSING IN CHILDREN YOUNGER THAN 3 YEARS UNDERGOING CANCER CHEMOTHERAPY OR HEMATOPOIETIC STEM CELL TRANSPLANTATION

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Background: Voriconazole dosing, pharmacokinetic (PK) and pharmacodynamics (PD) data are limited in children, especially those < 3 years. Various factors can impact PK and PD in infants and young children due to age-related changes in drug absorption, distribution, metabolism and elimination.

Objectives: The primary objective was to evaluate the proportion of patients who achieved a plasma trough concentration of ≥ 1 $\mu\text{g/mL}$ with the initial dosing of voriconazole for fungal prophylaxis or treatment in pediatric oncology and hematopoietic stem cell transplant (HSCT). The secondary objectives were to evaluate efficacy and side effects of voriconazole.

Design/Method: We reviewed data from 34 pediatric patients (< 3 years old) who received ≥ 5 consecutive days of voriconazole for either prophylaxis or treatment of invasive fungal infection (IFI) and had at least 1 measurement of voriconazole trough concentration between 2002 and 2015.

Results: The median age of patients was 1.6 years (range 0.2–2.9 years). Median weight was 10.2 kg (range 5.2–19.1 kg) and included 15 patients with an actual body weight (ABW) < 10 kg. Eleven of 34 (32%) patients had a voriconazole trough concentration of ≥ 1 $\mu\text{g/mL}$ (median 1.4 $\mu\text{g/mL}$; range 1–19 $\mu\text{g/mL}$) at the first measurement. The median voriconazole dosage referenced to ABW in these patients was 14 mg/kg/day (range 7.2–36 mg/kg/day). The 23 patients with concentration < 1 $\mu\text{g/mL}$ were younger in age (median 1.3 years; range 0.28–2.9 years; $P=0.016$) and had lower ABW (median 9.2 kg; range 5.8–15 kg; $P=0.06$). No patients experienced breakthrough IFI or any permanent side effects from voriconazole.

Conclusion: Using dosing recommendations for patients aged 2 to 12 years old resulted in sub-therapeutic plasma trough concentrations in 68% of patients < 3 years. Sub-therapeutic concentrations were more frequently seen in patients < 10 kg and < 1.4 years. Further work may be needed to develop dosing recommendation for voriconazole that can achieve a targeted therapeutic level with the first dose of voriconazole in patients < 3 years.

INTEGRATION OF TOBACCO CESSATION PROGRAMS IN COMMUNITY PRACTICES IN TENNESSEE

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Background: Background: Tobacco use increases the risk of lung and many other tobacco related cancers, with higher risk conferred by longer duration and more intensive tobacco use. Further, tobacco use is associated with other adverse health outcomes, such as cardiovascular disease, stroke, chronic obstructive pulmonary disease, and decreased physical fitness, all of which may result in shortened life span. More than 90% of smokers initiate tobacco use prior to the age of 18 years and more than 42.1 million adults currently smoke in the U.S. The rate of cigarette smoking remains higher than the national average in Tennessee. Starting in 2013 and using Tobacco Master Settlement funding, the Tennessee Department of Health initiated a goal to further integrate tobacco cessation interventions into community primary care clinics. However, several barriers arose to successful promotion and integration of community tobacco cessation.

Objectives: The objective of this study was to identify common barriers to integrating successful community practice-based tobacco prevention and cessation interventions and develop an action plan to facilitate successful program establishment.

Design/Method: Methods: Semi-structured, key informant interviews were conducted with seven Tennessee county department of health directors to assess facilitators and barriers to implementation of evidence-based tobacco cessation interventions within community primary care practices. Facilitators or barriers were organized into themes that included intra-personal factors, institutional factors, and community factors as defined by the socio-ecologic model.

Results: Results: The barriers elucidated included time constraints, documentation challenges, organizational culture, resource availability and allocation, leadership approval, and lack of partnerships. The barriers identified in this study highlighted the need for an organized action plan to facilitate integration of a tobacco cessation intervention. The action plan developed includes: 1) an effective program champion; 2) utilization of local data; 3) adequate staff resources; 4) community education; and 5) strategic planning with key stakeholders.

Conclusion: Conclusion: Leveraging strategies to offset common barriers to the integration of tobacco cessation interventions are essential to establish practical, evidence-based tobacco cessation and prevention programs into clinical practices.

IMMUNE FUNCTION AND MINIMAL RESIDUAL DISEASE IN PEDIATRIC ACUTE LYMPHOBLASTIC LEUKEMIA

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Background: Minimal residual disease (MRD) in pediatric ALL is prognostic for relapse and survival, but little is known about how patients' innate and adaptive immune function may relate to MRD status. Host defense is an important aspect of anti-tumor effect and greater understanding of this relationship may identify novel targets and strategies for immune-based leukemia treatment.

Objectives: To test the hypothesis that patients with ALL with positive MRD (MRD+) after induction will have significantly worse innate and adaptive immune function than patients with negative post-induction MRD (MRD-).

Design/Method: This prospective, longitudinal, observational study of patients with newly diagnosed pediatric ALL (ages 1-21) tested functional immune recovery on Day 29 of induction and on Day 1 of consolidation. Immune function testing on peripheral blood included: innate—monocyte MCH class II expression (HLA-DR), neutrophil CD88 expression, and monocyte and neutrophil phagocytosis (all by flow cytometry); and ex-vivo TNF α production in response to lipopolysaccharide stimulation; adaptive—quantification of CD4/8 T-cells, immunosuppressive regulatory T-cells (Tregs, as a percentage of CD4 cells), B-cells, and NK cells by flow cytometry.

Results: Fifteen (15) patients with ALL have been studied to date (n=9 NCI standard risk precursor-B cell, n=3 NCI high risk precursor-B cell, n=3 T-cell). Five out of fifteen patients (33%) were MRD+ at the end of Induction. MRD+ patients had a higher percentage of Tregs on Day 29 of induction versus MRD- patients (median 10.2% vs 5.3%, interquartile range 6.8-11.95% vs 4.65-6.15%, p=0.027). By Day 1 of consolidation, this difference was not seen. CD3, CD4, CD8, B-cell, and NK cell counts were similar between groups at both time points. There were no differences in innate immune function on Day 29 of Induction. On Day 1 of consolidation, patients with positive MRD had lower neutrophil counts by flow cytometry (967 [493.5-1080] vs 1321 [986.5-2016], p=0.0420).

Conclusion: We show that pediatric patients with ALL who are MRD+ post-induction have a higher percentage of circulating Tregs compared to MRD- patients, with impaired neutrophil recovery evident by day 1 of consolidation. Further studies are ongoing to quantify lymphocyte function in these patients, and these data may inform future immunotherapeutic approaches in this population.

EVALUATION OF HEART FUNCTION IN 125 PEDIATRIC PATIENTS UNDERGOING CHEMOTHERAPY WITH ANTHRACYCLINES IN A BRAZILIAN HOSPITAL

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Background: Anthracyclines, such as doxorubicin and idarubicin, remain an important class of chemotherapeutic agents. Unfortunately, their efficacy in treating cancer is limited by a cumulative dose-dependent cardiotoxicity, which can cause irreversible heart failure.

Objectives: Observe the echocardiographic changes in patients who used anthracyclines.

Design/Method: We performed a retrospective cohort study analyzing the echocardiograms of the patients, from the start of chemotherapy until 4 years of follow up, in children who received chemotherapy protocols with anthracyclines between January 2008 and December 2011, in the Pediatric Oncology Unit of the Hospital Pequeno Príncipe.

Results: The profile of the 125 patients was 56% male with a mean age of 104.4 ± 58.7 months at diagnosis, mean cumulative dose of 188.4 ± 86.4 mg/m². We found an incidence of 11.2% for heart dysfunction in the whole period. No significant difference was found between sex, type and dose of anthracycline between groups with and without cardiac dysfunction. The average age was higher in patients with cardiac dysfunction. In the analysis of echocardiographic parameters, the group receiving doses > 200 mg/m² showed a significantly lower extent of left ventricular diastolic diameter in the period between 24 and 48 months. Between 36 and 48 months this group also showed lower systolic diameter of the left ventricle. The other parameters were not statistically different.

Conclusion: The frequency of cardiac dysfunction was similar to the literature and is closely related to age at diagnosis. Changes in ventricular volumes occurs more frequently after 2 years in patients with higher dose (> 200 mg / m²).

DRUG SENSITIVITY AND RESISTANCE TESTING AS PART OF A PRECISION MEDICINE APPROACH FOR CHILDREN WITH LEUKEMIA

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Background: Despite major advancements in pediatric leukemia therapy, toxicities are still a concern and morbidity from chemotherapy regimens has been detrimental. Advances in genomic research as well as precision medicine have helped identify specific mutations that may be susceptible to targeted therapy in patients with leukemia. Overall, the use of targeted drug therapy is rising in the pediatric oncology field.

Objectives: To complement genomic analysis of leukemia patients, our laboratory is developing a drug sensitivity and resistance screening assay that would provide clinically relevant drug response data of the patient's leukemia cells.

Design/Method: As part of our lab's development of this assay, we first prepare pre-dosed library plates of clinically active drugs. Cells are added to these plates and treated for 72 hours at which time cell viability is determined. Preliminary work in our laboratory used a library of 56 anti-cancer and targeted agents, which were tested on 16 AML cell lines and 8 ALL cell lines. Biological replicates were performed for each cell line and drug response data in the form of IC50s and Area Under the Curve (AUC) were calculated. Hierarchical clustering was performed to determine similar responses between cell lines and drugs.

Results: Our results identified several cell lines that showed hypersensitivity to specific drugs. Among them, the AML cell line KG-1a showed sensitivity to three FGFR inhibitors including Ponatinib, which was previously reported. Validation of the screening results was done using a 10-concentration drug dose response assay.

Conclusion: Further testing will include expansion of our drug library and application to ex vivo patient samples. The results from these studies can lead to the establishment of a drug sensitivity and resistance assay that could provide specifically engineered therapies for each patient. This form of precision therapy would lead to diminished toxicities from systemic therapies as well as allow for increased cure rates.

PREDICTORS OF MORTALITY AMONG HAITIAN CHILDREN TREATED FOR CANCER AT A PEDIATRIC HOSPITAL FROM 2010 TO 2014

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Background: Pediatric cancers represent about 1% of all diagnosed cancers around the world [1]. Epidemiologic studies on childhood cancers in Haiti are to date absent.

Objectives: The principal objective of this study is to determine predictors of mortality of pediatric cancers managed at a Haitian pediatric hospital.

Design/Method: This is a cross-sectional study on the cases of pediatric cancers admitted at the oncology department of St Damien Hospital, in Port-au-Prince, Haiti, from 2010 to 2014. The charts of children diagnosed with any type of cancer were reviewed to collect data on key variables that could be predictors of mortality. The number of cases diagnosed and mortality due to cancer are evaluated for each year of the study period. Odds ratios and P-values with Mantel-Haenszel chi square test evaluated whether gender, age group, the region of origin (Department), cancer type, the type of treatment, the occurrence of relapse or a complication were significant predictors of mortality in this population.

Results: One hundred thirty-nine cases of pediatric cancers (seventy-seven males, sixty-two females), among them 71.22% living in Port-au-Prince, were admitted during the study period. Nineteen different types of cancers were diagnosed. The most common ones were Wilms tumor (30.93%), the leukemias (30.93%) and retinoblastoma (15.11%). 53.2% of the children with cancer were less than 5 years of age. The overall cure rate is at 74.1%, the relapse rate at 15.1% and the overall mortality rate at 25.9%. The mortality rate was significantly higher in children with blood cancers (Odds Ratio (OR)=2.21; P=0.042), with relapse (OR=127.5; P=0.000000) or with a complication (OR=5.51; P=0.0006).

Conclusion: Blood cancers, relapse and complications are the main predictors of mortality among children with cancer managed in St Damien Hospital during the study period. Pediatric cancer care needs to be significantly improved in order to reduce unfavorable outcomes, especially for blood cancers. [1] E. Ward et al, Childhood and Adolescent Cancer Statistics, 2014.

IMPROVED TREATMENT RESULTS WITH CLADRIBINE AND CYTARABINE BASED CHEMOTHERAPY IN 86 CASES OF HIGH RISK AND RELAPSED CHILDHOOD ACUTE MYELOID LEUKEMIA: A SINGLE CENTRE EXPERIENCE

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Background: Synergism between cytarabine and cladribine in acute myeloid leukemia (AML) has been well demonstrated.

Objectives: Current retrospective analysis aims to evaluate the efficacy and toxicity of cladribine and cytarabine in high risk AML, patients with primary refractory disease or early relapses.

Design/Method: Children with AML under 15 years of age who received at least one cycle of cladribine based chemotherapy between January 2008 and December 2015 were retrospectively analyzed. Each cycle consisted of cytarabine (500mg/m²) as 24hr infusion from Day-1 to Day-5 and cladribine (9mg/m²) as half hour infusion from Day-2 to Day-6. Patients who achieved partial remission received a second similar course; patients in complete remission received consolidation with combination of cytarabine +/- cladribine or 7+3 regimen.

Results: Eighty six patients were included (Median age 7 years, M:F-3:1). Molecular studies were available in 63/86 cases and cytogenetics in all. Twelve patients received cladribine post oral chemotherapy (Group-1), 18 patients for primary resistant disease post standard induction chemotherapy (Group-2), 35 received as consolidation in view of high risk disease (Group-3) and 21 as salvage following relapse (Group-4). CR was achieved in 36/51 patients (70%) after a single course of induction (8/12 in Group-1, 13/18 in Group-2 15/21 in Group-4). Among these, 31(61%) were MRD negative (7/12 in Group-1, 11/18 in Group-3, 13/21 in Group-4). Seven patients died during induction, eight had refractory disease. Febrile neutropenia and fungal pneumonia were the most common complications. All patients experienced WHO grade 4 neutropenia and thrombocytopenia. One fourth required ICU admission. Median follow-up period is 10 months. Overall survival (OS) is 69% at 1yr and 50% at 2yr. For the 47 patients (Group-1,3) who received cladribine and cytarabine as induction post oral chemotherapy or consolidation in view of high risk disease, OS is 79% at 1 year and 55% at 2 yr. For 39 patients (Group-2,4) who received cladribine and cytarabine as salvage for relapse or resistant disease, OS is 57% at 1 yr and 44% at 2 yr.

Conclusion: Our preliminary result suggests that cladribine and cytarabine is an effective salvage regimen for high risk, refractory or relapsed AML. It shows a high rate of complete remission with manageable toxicity.

ASSOCIATION BETWEEN HISPANIC ETHNICITY AND CHILDHOOD CANCER SURVIVAL IN TEXAS, 1995-2013

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Background: In 2014, 15,780 new cases of cancer occurred among children and adolescents in United States, and approximately 15% of those children were Hispanic. In prior research, Hispanic children with cancer have shown an increase risk of death compared to their White peers. However, data on the impact of Hispanic ethnicity on pediatric cancer outcomes is relatively scarce. The strongest evidence to date is in the field of pediatric leukemia (both acute lymphoblastic and acute myeloid leukemia) where Hispanic patients, compared to Whites, have lower survival.

Objectives: To evaluate the association of Hispanic ethnicity with mortality among children with all cancer types in Texas.

Design/Method: We conducted a retrospective analysis using 1995-2013 Texas Cancer Registry data, including all patients between 0 and 19 years of age diagnosed with a first primary malignancy. We examined differences between Hispanic and Non-Hispanic White patients in all-cause mortality. Differences in survival and 5-year survival rates were estimated using unadjusted Kaplan-Meier curves fitted separately by cancer type (leukemia, lymphoma, and solid tumors). For patients with all cancer types, multivariate Cox proportional hazard models controlled for patient age, sex, year of diagnosis, and cancer type and stage.

Results: A total of 18,687 patients were identified (8,659 Hispanic and 10,028 Non-Hispanic white). In all, 27% had leukemia, 13% had lymphoma, and 59% had a solid tumor. In unadjusted Kaplan-Meier analysis, Hispanics with leukemia ($p<.001$) and solid tumors ($p<.001$) had higher risk of death, compared to non-Hispanic Whites. For Hispanics vs. Whites, respectively, five-year survival was as follows: leukemia (37.5% vs. 50.5%), lymphoma (62.0% vs 66.0%) and solid tumors (31.7% vs 45.2%). For patients of all cancer types combined, Hispanics (vs. Whites) had higher mortality after adjusting for all covariates (adjusted hazard ratio (aHR): 1.30; 95% CI: 1.22-1.37).

Conclusion: Hispanic children with leukemia or solid tumors in Texas have higher risk of death, compared to Non-Hispanic Whites. Future research should seek to understand the reasons underlying this disparity and to develop interventions designed to improve survival among Hispanic children with cancer. Additional research will also explore the reasons behind the observed low survival rates.

ADMINISTRATION OF DEXRAZOXANE IMPROVES CARDIAC OUTCOMES IN CHILDREN AND YOUNG ADULT PATIENTS WITH AML WHILE MAINTAINING SURVIVAL OUTCOMES

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Background: Acute myeloid leukemia (AML) comprises 5% of pediatric cancers and reports 5-year event free survival (EFS) of approximately 50% and overall survival (OS) of 60-70% following intensive multi-agent chemotherapy (1). Anthracyclines are the cornerstone in treatment of AML; however, they are associated with both acute and late cardiac toxicities. Nearly 1 in 10 pediatric patients receiving anthracyclines may develop congestive heart failure (CHF) with higher incidences when cumulative doses exceed 300 mg/m² (3). Importantly, current AML treatment in children commonly includes anthracyclines doses that are in excess of those known to cause CHF.

Objectives: Children's Hospital of Wisconsin (CHW) previously adopted a standardized clinical practice of administering dexrazoxane prior to any non-liposomal anthracycline beginning in 2011. We are reporting the differences in cardiac and treatment outcomes in children and young adults with AML treated with and without dexrazoxane at CHW from 2008 to 2013.

Design/Method: A retrospective chart review of children ages 0 to 21 years who received chemotherapy for AML at CHW between January 1, 2008 and December 31, 2013 was performed. Data collected from the electronic medical record included such variables as: anthracycline administration, echocardiogram measurements and relapse status. Statistical analyses were conducted using SAS statistical software version 9.2 with two sided p value of ≤ 0.05 considered statistically significant. Data was expressed as frequency count and percentage for categorical variables.

Results: A total of 44 patients, median age 8.3, were included with 28 (64%) who received dexrazoxane and 16 (36%) who did not. There was no statistical difference in the EFS or OS. There was a significantly higher ejection fraction, lower shortening fraction, and higher left ventricular systolic volume in patients who received dexrazoxane.

Conclusion: In summary, utilization of dexrazoxane prior to anthracycline chemotherapy in pediatric patients with AML demonstrated no significant difference in either EFS or OS relative to our institutional historical controls and appears to improve cardiac function. While promising, further studies in this patient population are needed to confirm these findings.

BUILDING A NEW PROCESS: NURSING VERIFICATION OF PEDIATRIC ORAL CHEMOTHERAPY

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Background: While team-based safety checks ensure safe prescribing of parenteral chemotherapy, oral chemotherapy is usually prescribed by a single clinician. With the growing use of oral chemotherapy, processes including nurse-led patient and family education are needed to protect patients from prescription errors.

Objectives: Describe a process for oral chemotherapy prescription verification. Present process measures, including nursing time needed. Illustrate the benefits of an oral chemotherapy prescription verification process.

Design/Method: Nurses, prescribers, pharmacists and administrators developed a new process and checklist for nursing verification of oral chemotherapy prescriptions in Dana-Farber/Boston Children's Cancer and Blood Disorders Center oncology clinic. Prescriptions are verified independently against the treatment plan by two pediatric oncology nurses. The verification checklist includes drug, dosage (with any modifications), final dose, height and weight, laboratory values and patient instructions. When available, the prescription bottle is also verified. The process was implemented in patients in one disease center. Data was collected over a three-month pilot period.

Results: From 6/18/15-9/16/15, 56 prescription verifications occurred. Verification rate of on-site retail pharmacy filled prescriptions was 81% (55/68 prescriptions). By December 2015, mean time for verification was 12.4 minutes (SD 10.1) per nurse. Nurses identified problems outside of prescription verification, including missing prior authorizations and unclear treatment plans. Medication bottles were not routinely available for verification. One identified near miss would have resulted in an 80% under-dose of everolimus.

Conclusion: Prescription verification by nursing in a pediatric oncology clinic is feasible. While it was successful in identification of one medication error before it reached the patient, 19% of prescriptions were not verified. Since prescription bottles are usually obtained after a visit, verification of the actual bottles will require new workflows, such as additional clinic visits or uploading a picture via the patient portal. Involving the nurse in the review of oral chemotherapy not only identified a prescription error, but also highlighted issues within other aspects of patients' care, including a need for patient/family education and inconsistent documentation of the treatment plan. The inclusion of nursing in the review and management of oral chemotherapy has the potential to improve safety and outcomes for these patients.

RESPONSE TO VACCINATION IN CHILDHOOD CANCER SURVIVORS

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Background: Evidence-based guidelines do not exist for re-vaccination of childhood cancer survivors following chemotherapy.

Objectives: To prospectively determine the response rate following re-vaccination with age-appropriate immunizations in this cohort of patients.

Design/Method: We conducted a phase II, single center study of patients in remission following chemotherapy, excluding those who received an autologous or allogeneic HSCT. Immune recovery was defined by absolute CD3+4+ >200 cells/ μ L, T cell proliferative response to PHA > lower limit normal, and IgG >500mg/dl without supplementation of IVIG. Response to vaccine was defined as seroconversion to a positive titer.

Results: Seventy-five patients, 1.1 - 19.6 years (median, 9.2 years), 35 males, were enrolled at a median of 4.8 months (range, 3-20.5 months) post-chemotherapy. Patients had ALL (SR =7, HR =17); AML (n=6); Hodgkin Lymphoma (n=16); Non-Hodgkin Lymphoma (n=4); CNS tumor (n=17); retinoblastoma (n=3); germ cell tumor (n=3); embryonal rhabdomyosarcoma (n=1); and Wilms tumor (n=1). Thirty-six patients completed all planned vaccines and follow-up serologic testing, 19 completed at least 75%, 22 completed less than 75%; reasons for incomplete participation included relapse, poor compliance or death. Time to start vaccination ranged from 3 to 21 months (median, 3 months). At base-line, protective titers were absent for 10-25% patients for polio, tetanus, diphtheria, 30-60% MMR, varicella, hepatitis B, haemophilus influenzae B, >90% for meningococcal (A, C, W and Y), pneumococcal and pertussis. Seropositivity for tetanus, diphtheria, polio, haemophilus influenzae B, hepatitis B, and pneumococcal was >98% at the completion of the trial. The rate of seropositivity for the remaining pathogens were pertussis, 52%; meningococcal A, 94%, C, 58%, Y 61%, W 44%; measles, 69%; mumps, 73%; rubella, 82%; and varicella 72%. Primary disease type was not predictive of response.

Conclusion: This study confirms poor residual immunity to many vaccine preventable diseases in childhood survivors of cancer. Re-vaccination with age-appropriate vaccines and schedule may provide protective levels for many pathogens. However, some patients continue to be at risk for pertussis, meningococcal (C,W and Y), MMR and varicella.

WILL CHILDREN OF COLOR BE DENIED ACCESS TO THE BEST CANCER TREATMENTS?

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Background: The Children's Oncology Group (COG) has played a major role in improving survival in children with cancer. For most diagnoses, patients treated at pediatric oncology centers have much better outcomes, and children treated on standardized protocols do better than those who are not. The Project Every Child Protocol (APEC14B1) was recently launched by COG. This is a registry, eligibility screening, biology and outcome study that requires enrollment in order to participate in any COG treatment study. This requirement may lead to even fewer children of color being able to benefit from COG treatment protocols.

Objectives: The goal of this study was to quantify the number of refusals to enroll in the COG registry ACCRN07 by race and ethnicity.

Design/Method: We reviewed the database of oncology patients at Children's Hospitals and Clinics of Minnesota to find patients offered participation in COG study ACCRN07 between April 2008 and December 2015. Data was collected on race and ethnicity as well as refusal to enroll. Racial differences were evaluated using the Fisher exact probability test.

Results: A total of 921 patients were offered enrollment on ACCRN07. Information on race/ethnicity was available for 869 children. Of these, 64 families refused enrollment (7.4%). Only 33 of 716 white patients refused enrollment (4.6%). Refusal rates were much higher for patients of color (20.3%, $p < 0.0001$). Asian patients had the highest refusal rate (31.6%, $p < 0.0001$) followed by our black patients (21.2%, $p = 0.0002$). Bi-racial, Native American and Hispanic refusal rates were also higher, but only the refusal rate of our bi-racial patients reached statistical significance ($p = 0.009$).

Conclusion: The refusal rates to enroll in ACCRN07 were significantly higher for patients of color. This fact alone would not be of great concern if this did not immediately impact access to care and outcomes. The requirement to enroll on APEC14B1 will likely lead to even fewer children of color benefiting from COG treatment protocols. We would encourage COG to revisit the requirement for enrollment on Project Every Child Protocol (APEC14B1) as this will likely exacerbate the already inferior outcomes for our patients of color.

**RISK OF INTRATHECAL METHOTREXATE NEUROTOXICITY AND
SUBSEQUENT ISOLATED CENTRAL NERVOUS SYSTEM RELAPSE IN PEDIATRIC
PRE-B ACUTE LYMPHOBLASTIC LEUKEMIA**

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Background: About 5-10% of pediatric patients with acute lymphoblastic leukemia (ALL) develop neurotoxicity secondary to intrathecal (IT) methotrexate (MTX). It remains unclear if switching from IT MTX to IT cytarabine/hydrocortisone (Ara-C/HC) increases the risk of isolated central nervous system relapse (iCNSr) in these patients. Also, it is unknown if neurotoxicity itself is a risk factor for the development of iCNSr.

Objectives: To determine whether substitution of IT MTX with Ara-C/HC after an IT-related neurotoxic event increases risk for iCNSr. Additionally we sought to determine if IT-related neurotoxic events lead to increased iCNSr.

Design/Method: We performed a retrospective chart review of all pre-B ALL patients who completed treatment between January 1999 and December 2015 at Children's Hospital and Research Center Oakland. Patients who had CNS leukemia (CNS3) at diagnosis were excluded. We quantified those patients who had an IT-related neurotoxic event and compared results in this cohort with those without a neurotoxic event. We subsequently compared risk of iCNSr in those with neurotoxicity who continued on IT MTX with those who switched to IT Ara-C/HC.

Results: Of the 311 pre-B ALL patients treated during this time period, 31 (10%) had definitive neurotoxicity related to IT MTX. Patients who were classified as high-risk (HR) either at presentation or with post-induction risk stratification had a significantly higher risk of IT MTX neurotoxicity compared with standard-risk (SR) patients (17.5% vs. 4.9%, $p < 0.001$ by Fisher Exact test). In total 15 patients (4.8%) had iCNSr. There was no difference in risk of iCNSr between HR and SR patients. Patients with IT MTX neurotoxicity had a trend towards increased risk of iCNSr (12.9% vs. 3.9% in those without neurotoxicity, $p = 0.051$ by Fisher Exact test). Of the 31 patients with IT-related neurotoxicity, 21 switched to IT Ara-C/HC with three having iCNSr while the other 10 remained on IT methotrexate with one subsequently having an iCNSr (non-significant difference in iCNSr rate).

Conclusion: In pre-B ALL pediatric patients with IT MTX neurotoxicity, there was no increased rate of iCNSr with switching to IT Ara-C/HC. HR patients are at increased risk of IT MTX neurotoxicity and neurotoxicity itself may be a risk factor for subsequent iCNSr.

COSTS FOR SCREENING OF CHILDHOOD CANCER SURVIVORS

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Background: Childhood cancer survivors (CCS) bear a high burden of chronic disease. With over 350,000 CCS in the US, it is likely that their care has a large impact on health care spending. There has been little published on the costs of their care.

Objectives: To quantify the actual costs and reimbursements of screening for late-effects amongst CCS at a single institution, with screening recommendations following the Children's Oncology Group Guidelines.

Design/Method: A retrospective review of medical records from all patients seen in the Survivors Facing Forward program at the Cohen Children's Medical Center between 2010 and 2012 was performed. Demographic data, original cancer diagnosis, chemotherapy, radiation and surgery exposures were collected. All screening tests that were recommended by the survivorship program and subsequently completed were tabulated. Actual cost was defined as the estimated cost incurred by the hospital to perform the procedure and reimbursement was defined as the amount refunded to the hospital for the costs incurred. These were calculated per patient per visit using hospital and CPT dollar amounts provided by the hospital's finance department. A linear mixed model was used to examine each cost-related outcome, patient demographic and clinical characteristics, with a mixed models approach used to account for the hierarchical structure of the data.

Results: 286 patients (49.7% male) were seen 542 times during the three-year period (range: 1-5 visits). The average actual cost per patient per visit was \$449.21 and the average reimbursement per patient per visit was \$1838.32. The frequency of visits, alkylator use, cancer diagnosis, and radiation therapy were significantly associated with reimbursements. The frequency of visit, alkylator use, and radiation therapy were significantly associated with costs.

Conclusion: Overall, patients with greater exposures had greater costs associated with their screening, and in particular, patients with prior alkylator chemotherapy or radiation therapy treatment had the highest costs of screening. Of note, reimbursements exceeded costs by a wide margin. Further research is required to assess whether the direct provision of survivorship care is cost effective from an institutional, as well as a societal, perspective.

FEASIBILITY OF OUTPATIENT HIGH DOSE METHOTREXATE (HDMTX) INFUSIONS IN PEDIATRIC PATIENTS WITH B-LINEAGE ACUTE LYMPHOBLASTIC LEUKEMIA (ALL)

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Background: HDMTX given in four hospitalizations during interim maintenance for high risk pediatric B-lineage ALL significantly improves survival but increases resource utilization. Children remain hospitalized for IV hydration and blood/urine monitoring until MTX clearance parameters are reached. Improved supportive care, extended infusion center hours and pediatric home health expertise afford alternatives to prolonged hospital admissions potentially offering quality, cost-effective approaches positively impacting the delivery of care.

Objectives: To compare feasibility, safety and cost effectiveness of 24hour continuous 5 gm/m² HDMTX infusion as an outpatient vs inpatient in pediatric patients with ALL.

Design/Method: A convenience sample of patients with de novo ALL, ages 3-17years were randomly assigned to receive their first HDMTX infusion as an outpatient or inpatient, with their second infusion in the alternative setting. A pediatric home health company provided HDMTX infusion oversight, supportive needs and skilled nursing care. Data included billed charges, out of pocket expenses, MTX levels and time to clearance, change in creatinine, antiemetic usage and emetic episodes with each patient serving as their own control in a matched-pairs analysis of each comparison. Outpatient subjects tracked emesis, urine pH and antiemetic usage on a standardized form.

Results: Six outpatient and inpatient infusions were successfully completed. Comparing the outpatient to the inpatient HDMTX infusion in each patient, there was a significant reduction between out of pocket patient expenses (median (range) for a single infusion: \$19(8-300) vs \$231(40-600), p=0.01) and billable care charges (\$2,550(1,981-3,197) vs \$28,075(10,921-44,533), p=0.004). Safety measures were similar between outpatient and inpatient infusions, including time to MTX clearance (48hr(48-72) vs 66hr(48-110), p=0.18), change in serum creatinine from the start of HDMTX infusion to clearance (0.08mg/dl (0.0-0.12) vs 0.03mg/dl(-0.01-0.13), p=0.48) and number of emetic episodes (0(0-1) vs 0(0-3), p=0.46). Whereas the number of emetic episodes were similar there was a significant decrease in the number of doses of antiemetics in the outpatient setting (5(4-9) vs 18(4-29), p=0.02).

Conclusion: In this feasibility study, outpatient HDMTX administration was safe and cost effective in pediatric patients with B-lineage ALL and more tolerable as evidenced by a significant decrease in antiemetic use.

PERCEPTIONS OF CHILDHOOD CANCER IN PEDIATRIC ONCOLOGY IN KUMASI, GHANA

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Background: More than 80% of children with cancer live in low and middle-income countries (LMIC) where cure rates are significantly lower compared to high-income countries (HIC). In many Sub-Saharan African countries, misperceptions about cancer among patient caregivers may contribute to poorer survival due to delays in cancer diagnoses and abandonment of care.

Objectives: This study aims to identify attitudes and perceptions about childhood cancer care among caregivers of pediatric cancer patients in Kumasi, Ghana.

Design/Method: We administered a survey to 53 caregivers of pediatric oncology patients at Komfo Anokye Teaching Hospital in Kumasi, Ghana. Measures included the time from first symptoms to diagnosis, utilization of traditional healers, and questions about perceptions of childhood cancer.

Results: The average patient age was 8 years. Lymphoma (28%), Wilm's tumor (22%), and leukemia (18%) were the most common diagnoses among the children of the participants. The average time from symptom onset to cancer diagnosis was 10 weeks. Of all participants, 29% reported using a traditional healer to treat their child's initial symptoms. Those utilizing a healer did so for an average of 10 weeks before seeking a medical provider. Over half (60%) of participants reported using herbal remedies to treat their child's cancer. Prior to their child's diagnosis, 92% of participants were not aware that children could get cancer, 16% believed that cancer was contagious while 11% believed it was a curse or bewitchment.

Conclusion: Misconceptions exist among caregivers of childhood cancer patients in Kumasi, Ghana, which may impact treatment decisions. Many of the caregivers use traditional healers before presenting to a medical provider, which could cause diagnostic delays.

CHEMOTHERAPY-INDUCED PERIPHERAL NEUROPATHY IN CHILDREN AND ADOLESCENTS AFTER TREATMENT FOR NON-CNS CANCERS: SHORT-TERM RECOVERY AND BALANCE IMPACT

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Background: Chemotherapy-induced peripheral neuropathy (CIPN) can develop in children during cancer therapy, but little is known about its resolution and impact.

Objectives: The objective was to describe CIPN and balance deficits longitudinally in children during and just following treatment for non-CNS cancers. The impact of diagnosis and chemotherapy type on CIPN were also investigated.

Design/Method: Children (N=66, mean age 11.4 ± 3.5 years, 47% male) being treated for non-CNS cancer were assessed for Pediatric Modified Total Neuropathy Score (ped-mTNS) and balance (Bruininks-Oseretsky Test (BOT-2)) 3 to 6 months into treatment (based on diagnosis) and 3 and 6 month after completion of chemotherapy. Treatment was categorized by neurotoxic drug used (vincristine (V), V + Intrathecal Methotrexate (V+M), or V + Etoposide (V+E)).

Results: Ped-mTNS scores decreased over time for the entire group (9.4 ± 4.5 initial, 6.0 ± 4.5 3 mo, 4.2 ± 3.6 6 mo, $F=38.14$, $p<0.001$, effect size=0.6). After adjusting for age and sex, when compared to those with ALL (N=26), children with other solid tumors (OST) (n=15), but not lymphoma (N=25), had higher ped-mTNS scores during treatment (7.7 ± 3.1 ALL, 8.7 ± 4.6 Lymphoma, 11.8 ± 4.2 OST, $F=3.96$, $p=0.02$). 6-months post-treatment, both those with lymphoma and OST had higher ped-mTNS scores than those with ALL (2.3 ± 3.1 ALL, 5.7 ± 3.1 Lymphoma, 5.2 ± 3.1 OST, $F=8.38$, $p < 0.001$). Children treated with V+E (n=20), compared to V (n=15) or V+M (n=29), had the highest ped-mTNS scores during treatment (9.3 ± 1.0 V, 7.5 ± 0.7 V+M, 11.5 ± 0.9 V+E) and at 3 and 6 month follow-up. Over the same time period, balance scores improved (7.4 ± 3.3 initial, 9.1 ± 3.3 3 month, 10.3 ± 3.9 6 month, $F=11.75$, $p<0.001$, effect size=0.32) but never to population norms of 15.0 ± 5.0 . Neither diagnosis nor treatment were associated with balance recovery at 6 months.

Conclusion: While many children who experience CIPN from cancer treatment recover by 6 months post-treatment, those who are treated with vincristine + etoposide may have longer-term nerve dysfunction. All groups improved in balance over time, yet none achieve balance control comparable to population norms.

TELEMEDICINE AND ITS APPLICATION IN PEDIATRIC HEMATOLOGY ONCOLOGY

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Background: The use of telemedicine in the pediatric hematology oncology population is greatly underutilized despite technologic advances that have made telemedicine visits as effective as in-person visits. Telemedicine is a resource that has the ability to lower the health care costs and bridge a geographic disparity that many patients and families face with a child that requires subspecialty care. However, the willingness to utilize telemedicine comes from both physicians and families.

Objectives: Evaluate the cost and satisfaction of patients and families that could use telemedicine to deliver quality care to patients with hematology or oncology diagnoses that live in underserved areas.

Design/Method: This is a cross-sectional study. Two subject groups aged 0-21 years old, with a Hematologic or Oncologic diagnosis that live >70 miles from Children's Mercy Hospital in Kansas City Missouri were evaluated in this study. The experimental group consisted of subjects who follow up at outreach clinics and have telemedicine capabilities. The control group are subjects who do not have outreach clinic options and must travel to Kansas City. A total of 32 patients per group were evaluated. The experimental group answered a cost analysis and a telemedicine satisfaction questionnaire following their telemedicine visit. Whereas the control group answered the same cost analysis and a utilization of telemedicine survey.

Results: Study results are preliminary, and anticipated closure is February 2016. At this point in the study, the experimental group is noted: to have saved hundreds of dollars in out-of-pocket expenses, families have been able to miss less school and work, a majority thought the telemedicine visit was as good as an in-person visit, and a majority would be willing to utilize telemedicine with subsequent visits in comparison to the control group. Additionally, a majority of the control group would be willing to utilize telemedicine and they believe it would allow their family to save money, and miss less school and work.

Conclusion: To our knowledge, this is the first cost-analysis and satisfaction survey evaluating the use of telemedicine in the pediatric hematology oncology population. Preliminary results favor future research investment in telemedicine to care for a subspecialized patient population in underserved communities.

SYMPTOMATIC HYPERAMMONEMIA WITH ERWINIA CHRYSANTHEMI IN PEDIATRIC LEUKEMIA PATIENTS

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Background: Asparaginase is a pillar of pediatric leukemia therapy with multiple sources, each with a well-established toxicity profile. In recent years, increasing amounts of asparaginase derived from the bacterium *Erwinia chrysanthemi* have been used. We encountered a series of symptomatic hyperammonemia in pediatric patients following *Erwinia* administration.

Objectives: We sought to characterize the incidence of symptomatic hyperammonemia in pediatric leukemia patients receiving asparaginase derived from *Erwinia* as a portion of their therapy. In addition, we sought to identify clinically relevant associations of ammonia and asparaginase levels.

Design/Method: A retrospective review revealed 45 consecutive patients receiving *Erwinia* at Children's Hospitals and Clinics of Minnesota from July 2014 to August 2015. Laboratory evaluations were analyzed with SPSS software version X. Hyperammonemia was defined as ammonia greater than 50 $\mu\text{mol/L}$ and symptomatic hyperammonemia was defined as refractory nausea, vomiting, fatigue, malaise or coma that temporally correlated with elevated ammonia levels, without other identified etiology.

Results: 7 of 45 patients (16%), were found to have symptomatic hyperammonemia. Ammonia levels drawn as troughs prior to *Erwinia* dosing ranged from 17-358 $\mu\text{mol/L}$, (N=103, median: 133 $\mu\text{mol/L}$, Std dev 92, normal <50 $\mu\text{mol/L}$). Asparaginase levels drawn at the same time ranged from 0-1.29 IU/mL (N=39, median: 0.32 IU/mL, Std. dev: 0.32, therapeutic level >0.1 IU/mL). Ammonia and asparaginase levels drawn simultaneously were correlated with statistical significance ($R^2=0.32$, $p < 0.001$). 38 of 39 (97.4%) measured asparaginase levels were therapeutic (i.e. >0.1 IU/mL). All patients with trough ammonia greater than 100 $\mu\text{mol/L}$ had corresponding therapeutic asparaginase activity.

Conclusion: Ammonia is an expected product of *Erwinia* metabolism and symptomatic hyperammonemia has been previously reported as a rare occurrence, yet our findings indicate an increased incidence. Additionally, our data demonstrate a correlation between ammonia and asparaginase activity levels following *Erwinia* dosing. Furthermore, nearly all asparaginase activity levels were therapeutic despite dose reduction in some cases. Thus, this series provides sufficient evidence for further investigation to determine which patients require interventions to prevent symptomatic hyperammonemia, which patients may have ammonia levels used as an asparaginase activity surrogate and which patients may achieve equivalent efficacy with abridged dosing.

EXPANDED ACCESS PROGRAMS REQUIRE MORE THAN COMPASSION: CHALLENGES IN PEDIATRIC ONCOLOGY

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Background: Expanded access, also known as compassionate use, programs provide an opportunity for select patients to access investigational drugs, biologics or medical devices outside a clinical trial. A successful expanded access application requires the treating physician to obtain agreement from the pharmaceutical company developing the investigational agent, authorization by the Food and Drug Administration (FDA), and authorization by the hospital's Institutional Review Board. These poorly understood and difficult to execute steps, especially in pediatric cancer cases, present barriers to obtaining access to investigational drugs via expanded access programs.

Objectives: To create an intervention to help pediatric providers make more informed decisions regarding expanded access based on analysis of available resources and assessment of pediatric oncologists' experiences and challenges with expanded access applications.

Design/Method: Analysis of current regulatory framework and review of literature focusing on the pediatric oncology expanded access process and physician experiences. A survey was developed to assess pediatric oncologists' experience and knowledge about the expanded access application process.

Results: The FDA is in the process of simplifying the approval application form for expanded access and there is currently a bill under consideration by the U.S. Congress to reform expanded access programs. However, there remains a lack of data on physicians' experiences and barriers affecting use of expanded access programs. In addition, there is a paucity of support for physicians to guide them through the process. Finally, there are no data on the numbers and outcomes of expanded access applications by pediatric oncology patients. We will distribute a 30-question survey to pediatric oncologists to identify their experiences and challenges, and uncover gaps in knowledge about expanded access approval. Data will be presented at the ASPHO annual meeting.

Conclusion: There are limited resources to guide pediatric oncologists who seek expanded access to investigational agents. Educational resources for providers and patients to help them navigate the process are needed.

ASSOCIATION BETWEEN FLT3-ITD ALLELIC RATIO AND MINIMAL RESIDUAL DISEASE IN PEDIATRIC ACUTE MYELOID LEUKEMIA

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Background: FLT3-ITD mutation is an adverse prognostic feature in acute myeloid leukemia (AML). Therapy is intensified for FLT3-ITD-positive AML with an allelic ratio (AR) >0.4 or for minimal residual disease (MRD) $\geq 0.1\%$ after remission induction (two courses of ADE). However, it is not established whether AR and MRD are interrelated risk factors.

Objectives: The primary aim was to determine whether FLT3-ITD AR is an independent prognostic factor.

Design/Method: We compared data of 46 patients with FLT3-ITD-positive AML according to AR values. Patients were enrolled on the St. Jude Children's Research Hospital AML02 or AML08 protocols. The remission induction regimen was comprised of two cycles of cytarabine plus etoposide and daunomycin (ADE). Consolidation therapy consisted of chemotherapy with or without sorafenib and/or transplantation.

Results: Comparisons of patients with AR ≤ 0.4 (n=14) versus AR >0.4 (n=32) showed no significant difference in median age (12.5 years vs. 12.7 years, $p=0.56$), white blood cell count ($65.3 \times 10^9/L$ vs. $143.6 \times 10^9/L$, $p=0.13$), normal karyotype (85.7% vs. 93.7%, $p=0.57$) or MRD $\geq 0.1\%$ after two courses of ADE (38.5% vs. 44.4%, $p=1$). The 4-year event-free survival (EFS) estimates for cases with MRD $\geq 0.1\%$ after two courses of ADE were 20.1% (95% CI, 7.5%-54.4%) compared with 54.1% (95% CI, 36.5%-80.1%) for cases with MRD $<0.1\%$, ($p=0.04$). Conversely, the 4-year EFS estimates for cases AR >0.4 were not significantly different from those with AR ≤ 0.4 (43.2% vs. 59.9%; $p=0.38$). When data on AR is integrated with those of MRD after two courses of ADE, the 4-year EFS estimates for cases with both MRD $<0.1\%$ and AR ≤ 0.4 were not significantly different from those with both MRD $<0.1\%$ and AR >0.4 (60.0% vs. 51.3%, $p=0.62$).

Conclusion: FLT3-ITD AR >0.4 may not contribute prognostic information when patients have negative MRD after two courses of ADE chemotherapy. This observation must be confirmed in a larger cohort of patients with FLT3-ITD-positive AML.

FEASIBILITY OF CRYOTHERAPY IN PEDIATRIC ONCOLOGY

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Background: Mucositis is a significant cause of morbidity and treatment delay in pediatric patients receiving chemotherapy. Evidence suggests a role for cryotherapy in adult patients for mucositis prevention, but it has not been fully studied as a preventative treatment in children.

Objectives: To study the feasibility of cryotherapy in pediatric cancer patients.

Design/Method: Participants were patients on active chemotherapy, from 5-21 years old. Samples of ice chips, ice water, and three ice pop flavors in the form of ice pellets or full ice pops were offered. Participant preferences were determined by survey, with standard taste test protocols. Participants then used their preferred preparation for up to sixty minutes. At 30 and 60 minutes, FACES scale was used to measure oral pain. At the completion of participation, parents (or patients 18 years and older) completed a survey regarding challenges during cryotherapy and estimated total time of cryotherapy use.

Results: Twenty-four patients were invited to participate; nine consented. Common reasons for non-participation included feeling ill on day of invitation, and reluctance to spend additional time in clinic. Participating patients were 78% (n=7) male and 22% (n=2) female. Ages ranged from 5-20 years, with a mean of 12.1y. Fifty-five percent (n=5) of participants preferred flavored ice preparations. Patients utilized cryotherapy for a range of 4 to 60 minutes, with a median time of 30 minutes, with a trend toward longer use in older patients. Mean pain score (out of 10) was 0.9 at 30 minutes and 2 at 60 minutes. Common challenges included patient distraction and discomfort due to temperature.

Conclusion: Among pediatric cancer patients, cryotherapy appears to be well-tolerated for short periods of time, and shows the greatest feasibility in older children and adolescents. It will likely show the most benefit in mitigating mucositis caused by agents with relatively short half-lives and predictable peaks in concentration. Additionally, children and their caregivers may be more amenable to cryotherapy if it were being attempted for a possible therapeutic purpose, rather than a feasibility study. Data collection is ongoing in order to elucidate more specific subgroups for which it is most feasible. (Chen, Journal of Oncology Pharmacy Practice, 2015).

CHEMOTHERAPY EFFECTS ON HEIGHT VELOCITY OF PEDIATRIC CANCER SURVIVORS

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Background: BACKGROUND: Over the past several decades there have been significant advancements in the management of pediatric malignancies and a resultant increase in survival rates and average life expectancy. As such, there is a heightened awareness of previously under-appreciated long-term treatment-related outcomes, or late effects. The endocrine system, and particularly the growth hormone axis, is particularly vulnerable to the deleterious effects of current treatment modalities. The presence or absence of growth hormone deficiency and the attainment of final adult height have become the principal measures of interest in current medical literature focusing on height-related late effects. It has been well documented that cranial or craniospinal irradiation has a negative impact on height and that concurrent chemotherapy may intensify the growth deterring effects of radiation. However, the effect of chemotherapy alone on the growth hormone axis and final adult height in the absence of confounding variables such as radiation exposure and/or the presence of a CNS tumor is less well understood.

Objectives: OBJECTIVE: To investigate the effect of chemotherapy on the growth velocity of pediatric cancer survivors at various stages off therapy.

Design/Method: DESIGN/METHOD: This study is a retrospective chart review of 71 patients from the oncology long-term follow-up clinic registry at Nationwide Children's Hospital from 1/1/2008 – 4/1/2013 who received chemotherapy without radiation and who did not have a primary brain tumor diagnosis.

Results: RESULTS: Over the first 5 years off therapy, the percentages of patients with growth velocities at or below the third percentile for their specific age and gender were 14.08%, 18.31%, 26.76%, 22.54%, and 24.56%, respectively. The association of specific cancer types and chemotherapeutic agents on delayed growth velocity will be discussed.

Conclusion: CONCLUSION: Chemotherapy alone can lead to delayed growth velocity in pediatric cancer survivors. Pediatric oncologists and general practitioners should have a low threshold for further work-up including bone age radiographs, growth hormone levels, and placement of an Endocrinology referral when growth delay is noted in this patient population.

GINGIVAL HYPERPLASIA AND GINGIVITIS PHENOTYPE IN A PTEN PATIENT COHORT

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Background: The phenotype associated with PTEN hamartoma syndrome (PHTS) in pediatric patients is variable, and may include only macrocephaly and one other feature of PHTS. Mucocutaneous findings are pathognomonic for PHTS, including oral papillomatosis on the gingiva, though it may not appear until adolescence or early adulthood. Often, dentists are the first to refer patients for evaluation based on oral papillomatosis, and case reports show adults are being referred by dentists for PTEN evaluation. Individuals with PTEN gene mutations are at risk for several health problems, including vascular anomalies and malignancies of the breast, thyroid, and endometrium, and should be followed by appropriate specialists for recommended surveillance protocols. Early identification of at-risk individuals is of the utmost importance to prevent or treat these symptoms.

Objectives: Determine gingival hyperplasia and gingivitis phenotype in cohort of five pediatric patients with PHTS, followed in the Vascular Anomalies Clinic at Texas Children's Cancer Center.

Design/Method: Five pediatric patients with confirmed PTEN molecular diagnoses followed in the Vascular Anomalies Clinic at Texas Children's Cancer Center were noted to have a gingival hyperplasia phenotype. The patients were either referred to the Dental Division at Texas Children's Hospital for evaluation, or records from their primary dentist were requested and reviewed.

Results: Five of five pediatric patients in the cohort of patients with confirmed PTEN molecular diagnosis have gingival hyperplasia, with dental records confirming moderate to severe gingivitis in three patients. Two dental record reviews are pending.

Conclusion: Gingival hyperplasia and gingivitis may be an early indicator of the oral findings associated with PHTS. Pediatric clinical providers, including dentists, seeing patients with macrocephaly, gingival hyperplasia, and gingivitis should consider referral for PHTS evaluation. These may also be indicators to aid in identifying at-risk relatives that may be too young to have yet developed papillomatosis. Pediatric patients with confirmed PHTS should be referred to and followed by dentists for gingival hyperplasia and gingivitis surveillance and treatment.

APOLIPOPROTEIN E (APOE) GENOTYPE AND NEUROCOGNITIVE OUTCOMES IN SURVIVORS OF PEDIATRIC LEUKEMIA

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Background: Many survivors of childhood acute lymphoblastic leukemia (ALL) exhibit deficits in neurocognitive function following treatment. Despite generally uniform treatment protocols, individual neurocognitive outcomes are not predictable. One potential genetic risk factor for neurocognitive late effects is the apolipoprotein (APOE) e4 allele. This allele has been most strongly associated with increased risk for dementia and also has been implicated as a risk factor for cognitive deficits following various neurological stressors. Central nervous system (CNS)-directed chemotherapy, as utilized in childhood ALL treatment, may be considered a similar insult to the brain.

Objectives: To evaluate the association between APOE genotype and neuropsychological functioning following treatment for childhood ALL.

Design/Method: Participants were survivors of childhood ALL, treated with chemotherapy only, currently 8 to 18 years of age. During a routine clinic visit, blood was obtained for APOE genotyping, and participants completed a brief neuropsychological assessment battery to evaluate attention, processing speed, memory, and executive function. Analysis of covariance (ANCOVA) and multiple analysis of covariance (MANCOVA) were used to detect significant differences in neurocognitive performance variables between groups defined by APOE status while controlling for age, gender, education, and socioeconomic status.

Results: Fifty-seven patients were enrolled (57.8% male; 51.9% Caucasian; mean age 12.82 years). The average age at time of ALL diagnosis was 5 years, with an average time to completion of treatment of 5 years. Fifteen participants (26.3%) were found to carry the APOE e4 allele. Preliminary results indicate that pediatric ALL survivors who carry the APOE e4 allele have no significant difference in attention, processing speed, memory, or executive function when compared to non-carriers of the e4 allele (all $p > 0.05$).

Conclusion: In previous studies, the effect of APOE genotype on neurocognitive outcome in children has been mixed (1). Our pilot sample found no significant difference in neurocognitive functioning between carriers and non-carriers of the APOE e4 allele. A larger sample size is needed to evaluate for subtle neurocognitive differences between the two groups; thus, enrollment is ongoing. Longitudinal follow-up is required to investigate whether e4 carrier status influences neurocognitive outcome for survivors of pediatric ALL in adulthood.1. Blackman, *Dev Med Child Neurol*, 2005.

A RETROSPECTIVE CHART REVIEW OF DOSE-ESCALATION HYDROXYUREA THERAPY IN INFANTS AND YOUNG CHILDREN WITH SICKLE CELL DISEASE

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Background: The BABY HUG clinical trial of hydroxyurea in infants and young children with sickle cell disease (SCD) established the safety and clinical benefit of hydroxyurea therapy in this age group. The study did not establish, however, if escalation to maximum tolerated dose (MTD) could be safely and effectively accomplished in this age group.

Objectives: We sought to determine the safety and effectiveness of dose-escalation hydroxyurea therapy in children with SCD under age two years.

Design/Method: We conducted a retrospective chart review of children with HbSS or HbS β 0 Thalassemia under the age of two years started on hydroxyurea therapy between 2013 and 2016 at the Texas Children's Hematology Center. We determined the laboratory response to dose-escalation therapy as well as any clinical or laboratory adverse events associated with hydroxyurea therapy.

Results: We identified 29 patients ranging from 5 to 21 months in age (mean of 12.9 ± 4.2 and median of 13 months) initiated on hydroxyurea therapy in the study period. MTD was reached in 19 of 29 patients during the study period, with the remainder having had their dose escalated but not having reached MTD. The mean and median MTD were 22.7 ± 6.3 mg/kg and 20.5 mg/kg respectively. MTD dose correlated strongly with baseline absolute reticulocyte count (ARC) and absolute neutrophil count (ANC), but less so with baseline creatinine or body mass index. All patients had significant increases in hemoglobin concentration and %HbF and declines in ARC and ANC, with the magnitude of increases in [Hb] and %HbF being greater than those seen in the BABY HUG cohort on hydroxyurea. There were no clinically significant adverse events attributable exclusively to hydroxyurea over 413 patient-months of therapy. There were six episodes of neutropenia, nine of reticulocytopenia, and four of thrombocytopenia, all associated with intercurrent illnesses and all self-limited.

Conclusion: Hydroxyurea therapy with dose escalation to MTD appears to be safe in infants and young children in a standard clinical setting and results in more significant increases in hemoglobin concentration and %HbF than were seen with fixed dosing in the BABY HUG study.

OBESITY IN PEDIATRIC PATIENTS WITH ACUTE LYMPHOBLASTIC LEUKEMIA INCREASES THE RISK OF ADVERSE EVENTS DURING PRE-MAINTENANCE CHEMOTHERAPY

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Background: Comorbid obesity is correlated with more adverse events (AE) in children with acute myelogenous leukemia and in patients with acute lymphoblastic leukemia (ALL) during maintenance therapy. Less is known about AEs in obese patients with ALL during intense pre-maintenance chemotherapy.

Objectives: To evaluate the relationship between obesity (BMI \geq 95th %-ile) and AEs during pre-maintenance chemotherapy in pediatric patients with ALL.

Design/Method: The charts of children aged 2-22 years who completed pre-maintenance chemotherapy for pre-B and T-cell ALL at our institution between 2006-12 were evaluated for infections, hypertension (necessitating medication), hyperglycemia (necessitating insulin), pancreatitis, PICU admissions, sepsis, febrile neutropenia admissions (FN), thrombosis, hepatotoxicity, and nephrotoxicity. Patients with BMI <10th %-ile, pre-existing medical conditions, trisomy 21, or relapsed disease were excluded. Univariate analysis with Chi-Squared and Fisher exact tests compared proportions of obese versus non-obese patients experiencing AEs. Further univariate analysis examined the effects of age and NCI risk status on AEs, followed by multivariate analysis to evaluate independent predictors.

Results: 155 of 232 patients with ALL were eligible. 40 (25.8%) were obese and 115 (74.2%) non-obese. Groups were similar in ALL type, age, demographics, NCI risk status, and early response to treatment. AEs occurring significantly more frequently in obese patients included treatment-requiring hypertension (17.5% vs. 6.9%, RR 2.1, 95% Confidence Interval [95% CI] 1.0-4.25, $p=0.05$), insulin-requiring hyperglycemia (25.0% vs. 11.3%, RR 2.2, 95% CI 1.05-4.64, $p=0.04$), admission-requiring infections (62.5% vs. 42.6%, RR 1.5, 95% CI 1.08-2.07, $p=0.03$) and FN admissions (77.5% vs. 53.9%, RR 1.4, 95% CI 1.13-1.82, $p<0.01$). Accounting for age >10 years and NCI risk status, obesity was an independent risk factor for treatment-requiring hypertension (OR 3.535, 95% CI 1.05-11.87, $p=0.04$), insulin-requiring hyperglycemia (OR 3.915, 95% CI 1.38-11.03, $p=0.01$), and admission-requiring infections (OR 2.109, 95% CI 0.99-4.46, $p=0.05$). Obesity's effect on FN admissions was not confounded by age or risk status. Age and NCI risk status were independent risk factors for hypertension, hyperglycemia, and infections.

Conclusion: During pre-maintenance chemotherapy for ALL, obesity is an independent risk factor for the development of hypertension, hyperglycemia, infection, and FN admissions. This research provides implications for the development of preventive and supportive care guidelines in this population of patients with ALL.

RESTRICTIVE CARDIOMYOPATHY IS ASSOCIATED WITH NEPHROPATHY IN SICKLE CELL ANEMIA

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Background: Cardiopulmonary and renal complications are major causes of morbidity and mortality in sickle cell anemia (SCA). Recently, we have observed that SCA is characterized by a unique cardiomyopathy, with features of both restrictive physiology (diastolic dysfunction, disproportionate left atrial (LA) enlargement and normal systolic function) and an anemia-related hyperdynamic state with ventricular enlargement. Restrictive physiology could lead to secondary elevation in tricuspid regurgitant jet velocity (TRV) and exercise intolerance, independent of pulmonary artery hypertension. Albuminuria is an early manifestation of sickle nephropathy. Albuminuria has been correlated with echocardiography-estimated pulmonary hypertension using TRV as a surrogate measure. Whether the sickle cardiomyopathy correlates with nephropathy is unknown.

Objectives: Assess the relationship between sickle cardiomyopathy and albuminuria in SCA.

Design/Method: Echocardiograms were performed in individuals with SCA (SS and S β 0-thalassemia) participating in a clinical trial of losartan for sickle nephropathy. We analyzed baseline (pre-losartan) results and correlated the cardiac phenotype with urine albumin-to-creatinine ratio (UACR), 6-minute walk distance (6MWD) and hematological markers. Albuminuria was defined as UACR \geq 30 mg/g.

Results: Thirty-six SCA patients were included (mean age 24.1y; 53% female). Fifteen had normal UACR (mean \pm SEM 9.2 \pm 1.5 mg/g) while 21 patients had albuminuria (UACR 373 \pm 87 mg/g). Patients with albuminuria had worse diastolic function indicated by the early-to-late ratio of mitral inflow velocities, E/A (1.81 \pm 0.1 vs 2.3 \pm 0.1, P=0.018), and septal annular velocities, e'/a' (1.5 \pm 0.2 vs 2.4 \pm 0.2, P<0.001), and significantly larger LA volumes (57.2 \pm 3.1 vs 38.9 \pm 3.7 ml, P<0.001). Systolic function was normal and similar in both groups (shortening fraction 36.9 \pm 2% vs 36.7 \pm 1.5%, P=0.94). Patients with albuminuria had significantly lower hemoglobin (8.3 \pm 0.3 vs 9.2 \pm 0.3 g/dL, P=0.04); however, there was no difference in TRV, LV mass, LV diameter or reticulocyte count between groups. 6MWD correlated significantly with the diastolic measures E/A and septal e'/a' (P=0.013 and P=0.015, respectively). Patients with albuminuria had significantly shorter 6MWD (1182 \pm 78 vs 1472 \pm 86 ft, P=0.018).

Conclusion: The restrictive physiology of sickle cardiomyopathy, irrespective of elevated TRV, is associated with albuminuria, a marker of sickle nephropathy. Common mechanisms may underlie both complications. Albuminuria should be studied as a predictor of cardiomyopathy in SCA.

PILOT STUDY TO DETERMINE INCIDENCE OF VITAMIN D DEFICIENCY IN NEWLY DIAGNOSED PEDIATRIC PATIENTS WITH ACUTE LYMPHOBLASTIC LEUKEMIA AND THEIR SIBLINGS

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Background: Vitamin D is a significant topic of interest in patients with Acute Lymphoblastic Leukemia (ALL), particularly in long-term survivors who have been shown to have decreased bone density. However, there has been a lack of investigation into vitamin D levels at diagnosis and during treatment for leukemia.

Objectives: The primary aim of this single institution prospective pilot study was to evaluate vitamin D levels at time of diagnosis in patients with ALL and their closest in age sibling. The secondary aim was to determine the efficacy of vitamin D supplementation in increasing serum levels of vitamin D in patients with ALL.

Design/Method: Vitamin D levels [measured as 25-hydroxyvitamin D (25-(OH)-D)] were obtained from patients with ALL and matched sibling controls at diagnosis. In addition blood was drawn from patients at 3 month intervals for a total of 4 blood draws. Patients with levels less than 30 were given vitamin D supplementation as per the Institute of Medicine recommendations.

Results: The study included 16 patients with newly diagnosed ALL, and 16 siblings controls, average ages 9.5 and 10.6, respectively. There was no significant difference in the vitamin D level of patients and siblings at diagnosis ($p = 0.215$). At diagnosis, 37.5% of patients had sufficient, 43.8% had insufficient and 18.8% had deficient serum vitamin D levels. There was a decrease in vitamin D levels between diagnosis and the second blood draw ($p = 0.001$). There continued to be differences between the diagnosis and vitamin D levels ($p = 0.026$) during maintenance, with the latter being higher. In the patients getting supplementation, the second vitamin D serum levels were lower in 70% of patients compared with 88% of patients without supplementation.

Conclusion: This exploratory pilot study suggests that treatment for ALL is associated with a significant decrease in vitamin D levels even in the face of supplementation. Diagnosis of leukemia in of itself does not appear to have an effect on vitamin D levels. Given these findings it will be important to perform a larger multi-institutional study to further evaluate levels of vitamin D during treatment, effects of increased supplementation on serum levels and long-term bone health.

AN OBSERVATIONAL DESCRIPTION OF THE PRESENTING FINDINGS AND CLINICAL CHARACTERISTICS OF CHILDREN WITH SICKLE CELL DISEASE IN HAITI

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Background: Sickle cell disease (SCD) is globally distributed and its prevalence is greatest in populations of African descent. The population of Haiti is derived mainly from West Africa and it has been estimated that greater than 1 in 200 Haitian live births are affected with SCD. Despite this high prevalence no universal screening programs exist in Haiti and few studies describe the presentation or clinical characteristics of children with the disease.

Objectives: Describe the presenting findings and clinical characteristics of Haitian children with SCD.

Design/Method: This study is a retrospective chart review of patients cared for at St. Damien Hospital in Tabarre, Haiti. For each child, we recorded age at diagnosis, method of diagnosis, presenting symptoms, number of hospital admissions, transfusions, acute chest (ACS) and vaso-occlusive (VOC) episodes, and laboratory data from the most recent encounter.

Results: We reviewed 453 patient charts containing both inpatient and outpatient encounters. Electrophoresis data were available for 72% of patients and among these the genotype distribution was 87% Hgb SS and 13% Hgb SC. Median age at diagnosis was 7.7y (1.25y-18y). The most common presenting symptoms were fever (57.6%), anemia (49.7%), and pain (48%). We counted 907 total hospital admissions in the cohort, with a mean of 2 (0-25) per patient. Sixty-three percent of children required at least one transfusion in their lifetime with a mean of 1.9 (0-19) per patient. Mean number of episodes of VOC and ACS were 1.1 (0-13) and 0.5 (0-10), respectively. Hepatomegaly and splenomegaly were each documented in 5% of the patients. Mean hemoglobin concentration was 8.0g/dL (1.9-14.1). Mean WBC count was 15.9 x 10⁹/L (1.4-83.6). Mean platelet count was 395 x10⁹/L (0.5-1264).

Conclusion: The clinical features of Haitian children with sickle cell disease are similar to those in African countries. Most patients present with a morbid encounter. This study provides valuable data describing the presentation and clinical characteristics of children with SCD in Haiti which may be useful when considering initiation of newborn screening and comprehensive care models in this setting.

NEUROCOGNITIVE PERFORMANCE IN ADULT SURVIVORS OF PEDIATRIC ACUTE LYMPHOBLASTIC LEUKEMIA MAY RELATE TO DECREASED BRAIN VOLUME AND CELL DENSITY AS MEASURED BY QUANTITATIVE SODIUM MR IMAGING AT 9.4 TESLA

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Background: Many adult survivors (AS) of pediatric acute lymphoblastic leukemia (ALL) suffer from unexplained neurocognitive (NC) deficits. ^{23}Na magnetic resonance (MR) imaging measures brain volume (BV) and tissue sodium concentration (TSC). Elevated TSC reflects decreased cell volume fraction (CVF), a measure of brain cell density. The biological mechanism for why some AS have NC changes has never been studied.

Objectives: BV, regional TSC and NC performance were measured to investigate if NC performance was related to changes in neuroimaging. ALL and its treatment with intrathecal and systemic chemotherapy \pm radiation were hypothesized to lower NC performance by decreasing BV and possibly CVF.

Design/Method: Adult patients with a diagnosis of ALL during childhood and off all anti-cancer therapy at least two years were recruited and signed informed consent for both imaging and NC testing. Quantitative ^{23}Na MR imaging at 9.4T provided TSC maps from which regional TSC and BV values were measured. Mean BV values and linear correlations between regional TSC values and BV values were performed for the AS group. Validated NC assessments were performed on the AS group. Relationships between NC scores, regional TSC and BV were examined by Pearson correlation.

Results: Ten AS (60% female, mean age 25.4 years) were enrolled. BV was decreased ($P < 0.015$) from age-matched controls and significant inverse linear correlations existed between BV and regional TSC for frontal ($p < 0.011$) & parietal ($p < 0.004$) lobes, basal ganglia ($p < 0.001$) and thalami ($p < 0.001$) but not for temporal ($p > 0.05$) or occipital ($p > 0.05$) lobes (OL) in AS. NC performance was not related to BV. There was a suggestion of increasing NC performance with increasing OL TSC, most prominent in processing speed ($p < 0.020$).

Conclusion: Results of this exploratory study showed ALL and its treatment during childhood results in smaller cerebral volume and this decrease is correlated with regional increases in TSC, reflecting decreases in CVF in fronto-parietal and deep gray matter regions. Preliminary results also suggest a possible relationship between OL TSC and processing speed but the etiology of this relationship is unclear. Both small sample size and lack of consistent regional correlation likely reflects the wide variations in NC performance found. Future larger studies are warranted.

PROCESS MAP ANALYSIS INCREASES HYDROXYUREA UTILIZATION

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Background: The National Heart, Lung, and Blood Institute strongly recommends that infants (greater 9 months of age), children, and adolescents with sickle cell anemia begin hydroxyurea (HU) regardless of clinical severity. Proven benefits include fewer episodes of pain, the acute chest syndrome, blood transfusions, and hospitalizations. Nonetheless, identifiable barriers prevent eligible sickle cell patients from being treated with HU, and fewer than 25% of eligible patients in the United States are currently on the therapy.

Objectives: Map the process from HU eligibility to utilization at effective dosing. Develop and implement a process map based tool to increase HU utilization in a pediatric sickle cell disease clinic.

Design/Method: We identified children in our practice who were eligible for HU. We then mapped the process from patient identification to HU utilization. A HU utilization pathway was created to address access to HU, confirm patient eligibility, identify patient-specific barriers, and guide clinical and laboratory follow up, with the intention of moving patients along the pathway towards the goal of maximum HU dosing. This report period lasted for 5 months after implementation of our tool.

Results: Sixty-three patients >9 months of age and with hemoglobin SS and not on chronic transfusions were identified in our practice (39 males, 24 females; mean age 10.1y). Utilization barriers included 1) lack of HU discussion between provider and patient, 2) poor follow-up to clinic appointments, 3) fear of side effects, 4) parental refusal, and 5) persistent non-compliance. Using the pathway, HU utilization increased from 60% (38/63) to 74.6% (47/63). Of the patients already on HU at study outset but not at maximum dose, 47.4% (9/19) patients had an increase towards maximum. The increase in patients at maximum dose was from 51.3% (20/39) to 71.8% (28/39).

Conclusion: The use of a process map that prioritizes patient/physician interaction and identification and addressing of specific barriers can efficiently increase HU utilization.

PARENTAL KNOWLEDGE AND PROVIDER COMMUNICATION ABOUT WEIGHT AND PHYSICAL ACTIVITY IN PEDIATRIC CANCER SURVIVORS

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Background: Childhood cancer survivors experience increased risk of obesity, physical inactivity, and related chronic diseases. Little is known about parental knowledge and provider education on these topics.

Objectives: To evaluate knowledge and communication about weight status, physical activity, and chronic disease risk among parents of childhood cancer survivors and their oncology providers.

Design/Method: To date, parents of 67 children who concluded therapy for cancer (median age: 11 years, range 5-18; median off-therapy time: 31 months, range 6-162; 55.2% male) completed a survey of five-point Likert statements about weight, exercise, chronic disease risk, and communication regarding these topics with their oncology provider. Parents reported whether their child was at, under, or above their appropriate weight, and their accuracy was assessed based on the child's BMI percentile. Parents documented exercise goals and actual practices for their child.

Results: Most parents reported that their oncology provider discussed with them, at least half of the time, their child's anthropometrics (87%), exercise (81%), and chronic disease risk (84%). However, parents misidentified weight status in 30% of children who were obese (15%), 57% of children who were overweight (21%), 10% of children who were normal weight (61%), and 100% of children who were underweight (3%). Identification of how much their child should exercise (median 3.5 hrs./wk., range 1-10.5) and how much their child exercises (median 2.7 hrs./wk., range 0-21) were significantly less than the CDC's recommendation of 7 hours per week ($p < 0.001$); 83.6% of all participants and 95.8% of participants who were overweight/obese did not meet the CDC goal. Many parents reported that their provider rarely or never offered specific exercise recommendations (36%), helped them establish exercise goals (48%), or followed-up on exercise progress (33%). Thirty-six percent of parents disagreed that their child has increased risk of chronic diseases.

Conclusion: While parents of childhood cancer survivors report frequent communication about weight, physical activity, and chronic disease risk with their oncology provider, parental knowledge of these topics is inadequate. Other approaches to improve knowledge and elicit behavior change are needed.

PATIENT REPORTED OUTCOMES AND ADHERENCE TO HYDROXYUREA IN ADOLESCENTS AND YOUNG ADULTS WITH SICKLE CELL DISEASE: A FEASIBILITY STUDY

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Background: SCD-related complications result in significant declines in health-related quality of life and other patient-reported outcomes (PROs). However, PROs are not routinely monitored in the SCD-clinic setting. Hydroxyurea reduces complications, decreases hospitalizations and improves PROs in SCD patients. Yet hydroxyurea adherence remains suboptimal, especially among adolescents and young adults (AYA) with SCD. No previous studies have addressed the relationship between hydroxyurea adherence and PROs.

Objectives: 1) To assess the feasibility of evaluating PROs and hydroxyurea adherence in AYA with SCD in the outpatient setting, and 2) To explore the relationship between PROs and hydroxyurea adherence.

Design/Method: A cross-sectional survey was administered on electronic tablets to 34 AYA (12-22 years old, all genotypes) on steady state hydroxyurea in our SCD clinic from January through December 2015. PROs were assessed by Patient Reported Outcomes Measurement Information System (PROMIS) – Computerized Adaptive Testing (CAT), and hydroxyurea adherence was assessed using the Modified Morisky Adherence Scale-8.

Results: At survey time, participants (52% male, 89% Black, 89% Hb SS, mean 15±3.3 years) had taken hydroxyurea at a mean dose of 32.5±4.9 mg/kg/day for an average of 15±8.6 months, most commonly for recurrent pain. All patients approached agreed to participate and successfully completed all assessments during their clinic visits, meeting our feasibility criterion of a ≥85% completion rate. The average time to complete PROMIS-CAT was 61±30 seconds/instrument. Participants with low hydroxyurea adherence, compared to moderate/high adherence, had significantly worse mean fatigue (54.4 vs. 33.5, p<0.001) and depression (48.4 vs. 34.4, p=0.04) scores. Participants with fetal hemoglobin (Hb F) <10%, compared to ≥10%, had significantly worse mean fatigue (60 vs. 47.4, p=0.03) and peer relationship (58.5 vs. 45.7, p=0.006) scores. Mean PROs scores did not correlate with mean Hb, Hb F, hydroxyurea dose or duration.

Conclusion: PROs assessment in the clinic setting is feasible and can be incorporated as part of routine care. Patients with low hydroxyurea adherence or lower Hb F levels had significantly worse fatigue, depression and peer relationships. Real-time tracking of PROs over time, in relationship to pain and other SCD-related complications, may represent a useful strategy for improving hydroxyurea adherence in AYA with SCD.

ADRENAL SUPPRESSION IN PEDIATRIC PATIENTS DURING MAINTENANCE TREATMENT FOR ACUTE LYMPHOBLASTIC LEUKEMIA

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Background: Adrenal suppression (AS) can be found following the use of corticosteroids, such as during the treatment for acute lymphoblastic leukemia (ALL). Research has shown that AS is present in the early phases of treatment for ALL, but its prevalence and duration is not fully understood, especially in later phases of treatment such as Maintenance. Patients with AS may have non-specific, or no symptoms, until they are challenged with stress such as infection or surgery. A patient with AS is at risk of adrenal crisis in times of stress; this can mean hypoglycemia, hypotension, critical illness, and is associated with significant morbidity and mortality. As treatment for ALL improves, there is a need to reduce the risks of the treatment itself, such as adrenal crisis. There is no standard protocol to monitor for AS in ALL, despite its potential serious effects and proven presence at least in the early phases of treatment.

Objectives: To identify if AS is present in patients during Maintenance treatment for ALL.

Design/Method: All cases of ALL treated at the Children's Hospital of Eastern Ontario (CHEO) from 2000 to 2014 were retrospectively reviewed for AS. Patient characteristics, clinical features, laboratory data, treatment, adverse events and outcomes were examined.

Results: Between 2000 and 2014, 176 patients were diagnosed with ALL at CHEO. Prompted by clinical suspicion, 24 had testing done to investigate for AS. Fourteen of those patients had cortisol levels and symptoms of AS requiring further management. Four had AS identified for the first time during Maintenance. Many more patients had documented symptoms that could be attributed to AS, but never had adrenal testing done.

Conclusion: AS is identified in children being treated for ALL, including during the Maintenance phase of therapy. AS may be present in greater numbers of children, but no routine testing protocol exists to identify these patients. This study supports the need to conduct further research to determine the prevalence and duration of AS in ALL with the goal of developing a standard screening protocol. Effective screening could lead to early identification, improved management, and reduced morbidity and mortality from AS in ALL.

SICKLE CELL ANEMIA MICE DEVELOP A UNIQUE CARDIOMYOPATHY CHARACTERIZED BY A PROGRESSIVE RESTRICTIVE PHYSIOLOGY AND ABNORMAL ELECTROPHYSIOLOGY THAT PREDISPOSES TO SUDDEN DEATH

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Background: Sickle cell anemia (SCA) is a common monogenic disorder associated with significant morbidity and mortality and a high incidence of unexplained sudden death in young adults. Currently, cardiopulmonary complications are the leading cause of mortality in SCA. Elevated tricuspid regurgitant-jet velocity, pulmonary hypertension, diastolic and autonomic dysfunction have all been described, but a unifying pathophysiology and mechanism explaining the poor prognosis and propensity to sudden death has been elusive.

Objectives: To define the progression of cardiac pathology in SCA and determine the pathophysiology that underlies the diverse reported cardiopulmonary phenotypes including sudden death.

Design/Method: Mouse models of SCA and iron-deficient anemia mice underwent a longitudinal comprehensive cardiac analysis, combining state-of-the-art cardiac imaging (cardiac MRI and echocardiography), electrocardiography, histopathology and molecular analysis to determine the basis of cardiac dysfunction.

Results: SCA mice showed anemia-induced hyperdynamic physiology, with gradual additional development of restrictive physiology. There was a progressive increase in the left atrial diameter and diastolic dysfunction despite normal systolic function. This restrictive physiology was noticeably absent in chronic iron-deficiency anemia mice. In SCA mice, this was associated with increased extracellular volume by cardiac-MRI and resulted from microscopic myocardial fibrosis. Mitochondrial ultrastructural changes were consistent with severe hypoxia/ischemia/oxidative stress, and significantly shortened sarcomere diastolic lengths were noted. Transcriptionally, genes involving angiogenesis, extracellular-matrix, circadian-rhythm, lipid metabolism and oxidative stress/hypoxia were upregulated and ion-channel transport and fatty-acid metabolism genes were downregulated. A functional interaction network analysis suggested lowered expression of genes essential for normal cardiac conduction. Indeed, prolonged QTc, with remarkably increased prolongations occurring pre-mortem, arrhythmias and ischemic changes were observed prior to sudden death.

Conclusion: Collectively, SCA mice developed a distinct sickle cardiomyopathy with restrictive physiology from cumulative cardiomyocyte hypoxia/ischemia-induced fibrosis, resulting in an arrhythmogenic myocardium. Sudden cardiac death is common in restrictive cardiomyopathies and prolonged QT syndromes. This comprehensive longitudinal analysis and our finding of this cardiomyopathy in this preclinical SCA mouse model may be the unifying cardiac pathophysiology of the previously reported diverse cardiac phenotypes, which also explains the

sudden death seen in this disease. Furthermore, it will also open new avenues for early diagnostics and targeted therapies for human SCA-related cardiac disease.

OLDER AGE AND VINCRISTINE THERAPY ARE ASSOCIATED WITH INCREASED RISK OF NEUROPATHIC PAIN IN PEDIATRIC ONCOLOGY PATIENTS

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Background: Neuropathic pain is a known complication of cancer therapy and worsens quality of life. Poor understanding of patient and treatment-related risk factors for neuropathic pain limits development of targeted screening and prevention strategies to decrease morbidity of therapy.

Objectives: In pediatric oncology patients: 1) Determine prevalence of neuropathic pain and 2) Investigate risk factors for neuropathic pain.

Design/Method: We conducted a retrospective cohort study of newly diagnosed or relapsed pediatric oncology patients between 11/2/2012 and 5/7/2015. Neuropathic pain was defined a priori as documentation of one or more of the following in the medical record: 1) "neuropathic pain"; 2) "pain" in a nerve distribution; 3) "pain" + qualitative neuropathic pain descriptor (i.e., numb, burning); 4) "pain" + initiation of neuropathic pain medication. Demographic variables were compared using Mann-Whitney test for continuous variables and Chi-square test for categorical variables. Multivariable logistic regression (forward stepwise selection method and $\alpha=0.10$) was performed to find the best set of predictive factors for the diagnosis of neuropathic pain.

Results: Charts were reviewed for 162 patients. Median (IQR) age at cancer diagnosis was 7.5 (3.2, 13.8) years and 45% were female. Diagnoses included 55% leukemia/lymphoma, 32% solid tumors and 13% central nervous system tumors. Twenty-eight percent (95% CI 21-35%) of patients met our definition of neuropathic pain. Age was not significantly different between those with and without neuropathic pain ($p=0.110$), but was significantly lower in those treated with vincristine (median age 5.8 vs. 12.7 years, $p=0.004$). Older age (OR 1.10, 95% CI 1.03-1.17) and vincristine therapy (OR 8.65, 95% CI 2.88-26.02) were associated with increased odds of neuropathic pain diagnosis and radiation therapy (OR 0.11, 95% CI 0.03-0.40) was associated with decreased odds of neuropathic pain diagnosis. Gender, ethnicity, intrathecal chemotherapy and surgery had no significant impact on neuropathic pain diagnosis.

Conclusion: Neuropathic pain is diagnosed in over a quarter of children with cancer. Older age and vincristine therapy are associated with increased risk for diagnosis of neuropathic pain. Improved prevention, diagnostic and treatment modification strategies are needed to reduce the burden of neuropathic pain from cancer treatment.

FEVER MANAGEMENT PRACTICES AMONG SICKLE CELL DISEASE PROGRAMS IN LOW AND MIDDLE-INCOME COUNTRIES

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Background: Under-5 mortality for children with sickle cell disease (SCD) in low and middle-income countries (LMIC) is high, with the majority of deaths likely related to infectious complications. In the United States, dramatic decreases in childhood mortality for SCD over the past 40 years have been aided by interventions to reduce mortality associated with infections. In LMIC, these interventions (i.e. penicillin prophylaxis, rapid investigation and treatment of febrile illness, and vaccination) may not be consistently available.

Objectives: To determine provider practices in LMIC regarding prevention of infectious complications in patients with SCD.

Design/Method: A survey of English and French-speaking providers at SCD programs in LMIC. The survey was available online and offline, distributed via email distribution lists, at applicable meetings, and by referral.

Results: Providers from 13 LMIC returned 27 interpretable surveys, including 23 from malaria-endemic areas. Newborn screening is associated with 34% (n=10/27) of programs. Pneumococcal conjugate vaccine is available at 66% (n=14/25) of programs. Penicillin prophylaxis is prescribed to some or all patients by 65% (n=17/26) of respondents. Malaria prophylaxis is prescribed by 83% (n=19/23) in malarial-endemic areas. Forty-eight percent of programs (n=14/27) have written fever management protocols. To patients with SCD presenting with fever, 21% (n=5/24) of respondents 'always' give antibiotics, although 54% (n=13/24) give antibiotics 'almost always'. First line antibiotics are given orally by 27% (n=7/26); 77% (n=20/26) would consider oral antibiotics in some circumstances. The preferred first line antibiotic is ceftriaxone for 9/19 giving IV/IM antibiotics and amoxicillin-clavulanate for 4/7 giving oral antibiotics. At programs in malaria-endemic areas, 79% (n=18/23) 'always' or 'almost always' give antimalarials to febrile patients. Forty-six percent (n=12/26) of respondents report that a majority of febrile patients receive antibiotics prior to presentation. In malaria-endemic areas, 74% (n=17/23) report that a majority receive antimalarials prior to presentation.

Conclusion: There is considerable practice variation around management of infection prophylaxis and fever in patients with SCD in LMIC. In a majority of responding programs, oral antibiotics are acceptable for use in some febrile patients with SCD. Results of this survey will inform a consensus-based protocol for fever management in SCD in LMIC.

INCREASED INCIDENCE OF INTRACRANIAL HYPERTENSION IN ALL MAINTENANCE THERAPY

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Background: Intracranial hypertension (IH) is characterized by elevated cerebrospinal fluid (CSF) pressure, defined as an opening pressure greater than 25 mmHg, in the context of normal CSF composition and normal neuroimaging studies. IH is an uncommon condition particularly in childhood, presenting in 0.9 per 100,000 children annually (1). Untreated IH can cause significant debilitation, particularly chronic headaches, and lead to papilledema and visual failure.

Objectives: The aim of this study was to determine the incidence of IH in pediatric patients in maintenance therapy for acute lymphoblastic leukemia (ALL).

Design/Method: This study was conducted at Wolfson Children's Hospital in Jacksonville, Florida, United States. Opening pressure was measured during routinely scheduled lumbar puncture under general anesthesia for intrathecal chemotherapy administration during maintenance therapy for ALL. IH was defined as opening pressure greater than 25 mmHg. In patients with IH, measurements were repeated up to 2 additional times during routine lumbar punctures.

Results: Twenty seven patients between the ages of 4 and 15 were enrolled. Opening pressure was measured 43 times. Intracranial hypertension was found 25 times in 18 patients. The overall incidence of IH was 63%. All participants with the exception of one were asymptomatic at the time of diagnosis of IH. The patient with symptomatic IH was treated successfully with acetazolamide. The incidence of IH was not statistically significant based on gender, age groups, and leukemia risk type. Additionally, the number of prior lumbar punctures/intrathecal chemotherapy administration was not associated with development of IH.

Conclusion: Our results indicate that there is a significantly higher incidence of IH in patients undergoing maintenance therapy for ALL. This suggests that ALL treatment may be associated with the development of IH. Given this high incidence, IH should be strongly considered in any child being treated for ALL who has persistent headaches or visual disturbances. Further studies are needed to determine when IH develops in ALL patients. Treating physicians should consider measuring opening pressures routinely with all intrathecal chemotherapy administration to identify patients with IH before they become symptomatic which may prevent significant symptoms and irreversible damage such as optic atrophy leading to blindness. (1) Vartzelis, Ped Blood & Cancer, 2009

IMPACT OF HYDROXYUREA THERAPY ON ALBUMINURIA AMONG CHILDREN WITH SICKLE CELL DISEASE

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Background: Nephropathy is a chronic complication of sickle cell disease (SCD) that begins in childhood and leads to ESRD in 12% of adults with HbSS, thus early identification and treatment is critical to prevent irreversible renal damage. Early sickle nephropathy is characterized by hyperfiltration and microalbuminuria; therefore, urine albumin/creatinine ratio (ACR) is an effective screening tool for detection of early nephropathy.

Objectives: To investigate the effect of Hydroxyurea (HU) therapy on urine ACR levels among children with Sickle cell Anemia SCA (HbSS and S β 0 thalassemia).

Design/Method: A retrospective review of all SCA patients' ages 5-21 years who started HU therapy between 2011 and 2013 at Children's Healthcare of Atlanta was conducted. Patients were included if they had urine ACR measured prior to and \geq 6 months after starting HU; patients were excluded if they were on chronic transfusions, ACE-inhibitor/ ARB medications or other diseases causing renal damage.

Results: 79 patients with SCA met eligibility criteria (Mean age = 10.4 \pm 3.9 yrs., Pre-HU hemoglobin 8.3 \pm 1.1 g/dl). Follow up ACR data was available in 51 (65%) patients at 2 years and 28 (35%) patients at only 1 year post HU. 20 (25%) had albuminuria (ACR >30 mg/g) prior to initiation of HU. Patients with albuminuria pre-HU had lower baseline hemoglobin compared to patients with no albuminuria (7.6 \pm 1.2 vs. 8.5 \pm 1 P-value: 0.004). The frequency of patients with albuminuria decreased at 1 year to 21% (N=17/79) and to 13% (N=7/51) at 2 years of HU therapy. Median urine ACR levels declined at 1 year (11.4 \pm 24 vs. 9 \pm 21 mg/g p-value: 0.24) and 2 years (11.4 \pm 24 vs. 7 \pm 15 mg/g P-value: 0.02) of HU therapy. Among patients with abnormal urine ACR pre HU (N=20), the frequency of patients with albuminuria decreased to 64% (N=12/20) at 1 year and 36% (N=5/14) after 2 years of HU therapy. In patients with albuminuria pre HU, there was a significant decline in median urine ACR levels both after 1 (95 \pm 103 vs. 33 \pm 58 p-value: 0.005) and 2 years (23 \pm 39, P-value: 0.02) of HU.

Conclusion: HU therapy leads to reduction in urine ACR levels over time, especially among SCA patients with abnormal urine ACR levels.

GENETIC RISK FACTORS FOR CHEMOTHERAPY INDUCED ACRAL ERYTHEMA IN CHILDREN

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Background: Chemotherapy induced acral erythema (CIAE) is an uncommon side effect of high-dose cytotoxic chemotherapy in children. Prior case reports of CIAE in pediatrics have been limited, and the predisposing factors to CIAE remain unknown.

Objectives: To identify characteristics and genetic risk factors of CIAE in children.

Design/Method: Adverse events databases for 9 front-line treatment protocols were reviewed to identify cases of CIAE following either high-dose methotrexate or cytarabine, which were confirmed by chart review. Controls comprised up to 449 patients treated on front-line protocols who received either high-dose methotrexate or cytarabine. Germline DNA was genotyped and a two stage genome-wide association study (GWAS) treating CIAE as a categorical outcome measure was performed. In stage 1, we performed a GWAS of the non-acute lymphoblastic leukemia (ALL) cases compared to controls; in stage 2, we included all diagnoses, and adjusted for ancestry and chemotherapy.

Results: 21 patients experienced a total of 38 episodes of CIAE with symptoms lasting a mean of 5.8 days. Hands and feet were both involved in 71% of initial episodes. CIAE occurred following the administration of cytarabine [22 events in 13 patients (mature B-cell lymphoma in 7 patients, acute myeloid leukemia in 6 patients)] and methotrexate [14 events in 9 patients (ALL in 2 patients; osteosarcoma in 4 patients; and mature B-cell lymphoma in 3 patients, all 3 of whom also had CIAE following cytarabine)]. Administration of both agents together occurred prior to 2 events in 2 patients (both with mature B-cell lymphomas). Parenteral opioids were required for symptom control in 28.6% of patients. No genetic variants reached the genome-wide association threshold of $P < 5 \times 10^{-8}$. The top identified variant was intronic in MSRA (rs17708090, $P = 1.09 \times 10^{-5}$, OR 7.7), with a risk allele frequency of 27.5% in cases and 9.4% in controls. Additionally, the intronic variant rs13214952 in MTHFD1L was also associated with an increased risk of CIAE ($P = 4.25 \times 10^{-5}$, OR 5.7), with 90% of patients developing CIAE following methotrexate carrying the risk allele.

Conclusion: CIAE is a rare toxicity in children receiving high-dose methotrexate or cytarabine. Genetic variants in folate metabolism and oxidative stress response genes may predispose to the development of CIAE.

ASSOCIATION BETWEEN EARLY BIOMARKERS AND TRANSCRANIAL DOPPLER VELOCITIES IN SICKLE CELL DISEASE

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Background: Patients with Sickle cell anemia (SCA) have an 11% risk of overt stroke and up to 30% risk of silent infarction during their lifetime. Routine screening with Transcranial Doppler ultrasound (TCD) allows for selecting patients with the highest risk and providing chronic transfusions to decrease their risk of stroke by 90 %. Abnormal velocities on TCD are associated not only with an increased risk for stroke, but also with poor cognitive performance and irreversible changes on magnetic resonance imaging (MRI) in a subset of patients. Even in the absence of MRI abnormalities patients with SCA can experience neurocognitive problems and decline in performance over time. Early laboratory predictors of TCD velocities would allow identification of patients at risk during the first years of life to introduce appropriate treatment modalities and educational support.

Objectives: To study the linear correlations of early biomarkers with TCD velocities at different age intervals.

Design/Method: We performed a retrospective chart review of patients with SCA and Sbeta0thalassemia followed at Marian Anderson Center at St. Christopher's Hospital for Children in Philadelphia. We identified 132 consecutive patients who meet inclusion criteria. Pearson correlations were calculated to explore linear associations of steady state biomarkers of anemia, hemolysis and inflammation with patients' maximum left middle cerebral artery (MCA) velocities at different age intervals (2 to 6 years, 6 to 11 years, and older than 11 years).

Results: In the 2 to 6 year age group, there was a positive linear correlation of TCD velocities of the left MCA with lactate dehydrogenase (n=51, r=0.341, p=0.014), reticulocyte count (n=92, r=0.314, p=0.002) and bilirubin (n=71, p=0.037 p= 0.037), white blood cell count (n=94, r=0.249, p= 0.015) and a negative linear correlation with hemoglobin (n=94, r=0.317, p=0.002). In the 6-11 year age group the only significant correlation was lactate dehydrogenase (n=29, r=0.452, p=0.014) and no correlation of laboratory biomarkers in the older than 11 age group.

Conclusion: Decreased hemoglobin, increased white blood cell count, increased bilirubin and increased lactate dehydrogenase from the first few years of life correlate with increased MCA velocities in the 2 to 6 year age group and may help to identify high risk patients.

PRESCRIBED DOSES OF MAINTENANCE ORAL CHEMOTHERAPY IN THE TREATMENT OF ACUTE LYMPHOBLASTIC LEUKEMIA VARIES BY PATIENT RACE

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Background: Antimetabolite dose intensity and compliance during maintenance therapy for ALL are associated with improved event free survival. The focus on racial disparities in ALL has been on poor compliance with 6-mercaptopurine (6MP) as indicated by high ANC as a surrogate marker. Less is known about the influence of benign ethnic neutropenia (BEN) on prescribed 6MP/methotrexate (MTX) dosing.

Objectives: We evaluated whether prescribed doses of 6MP and/or MTX varies by patient race during maintenance therapy for ALL.

Design/Method: A single institution retrospective study of prescribed 6MP and MTX dose during monthly visits for the first 6 cycles of maintenance therapy was done in children treated for ALL on Children's Oncology Group studies for B- and T-ALL. The initial and average ANC, weighted average dose of 6MP and MTX prescribed per visit, and the number of visits where prescribed doses were less than 90% of goal were abstracted. Descriptive statistics were dichotomized by race in univariate analysis.

Results: Among 99 patients eligible, 17% were black and 83% were non-black. There were no differences in key demographic, risk characteristics or TPMT status by race. The median ANC at study entry was 1.43 thou/uL and did not differ by race (1.36 vs 1.58, $p=0.67$), but the average ANC over the course of therapy was greater in non-blacks (2.00 vs 1.63, $p=0.07$). The median weighted dose of 6MP and MTX prescribed over all courses was 63 mg/m²/dose and 16.6 mg/m², respectively ($p=0.40$; $p=0.43$) and did not differ by race. Interestingly, the number of visits with prescribed MTX doses less than 90% of expected was 51% in blacks and 45% in non-blacks ($p=0.04$). No difference was present with respect to 6MP.

Conclusion: Despite the 15% incidence of BEN in black children, the ANC of patients at entry of maintenance did not differ by race in our population. The lack of significant differences in prescribed 6MP/MTX may be a reflection of the small number of black patients in our study. Black children did have significantly more visits with less than 90% of expected MTX prescribed prompting the need for further analysis of factors influencing prescribed antimetabolite dose intensity.

HEALTH LITERACY IN ADOLESCENTS WITH SICKLE CELL DISEASE

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Background: Health literacy is defined as “the degree to which individuals have the capacity to obtain, process, and understand basic health information and services needed to make appropriate health decisions”. There is a paucity of literature regarding health literacy in adolescents and specifically no published data describing the state of health literacy in adolescents with sickle cell disease (SCD).

Objectives: The purpose of this study was to evaluate health literacy in a cohort of 75 adolescents with SCD.

Design/Method: This cross-sectional, descriptive correlational study included assessment of demographic measures and evaluation of data resulting from completion of the REALM-Teen and Newest Vital Sign (NVS) instruments by 75 Black, non-Hispanic adolescents with SCD followed at Children’s Medical Center (CMC) in Dallas, Texas. Convenience sampling was utilized. Inclusion criteria were a diagnosis of one of the four primary genotypes of SCD and age 10-19 years. UT Austin and UT Southwestern Institutional Review Boards approved the study.

Results: Thirty-seven males and 38 females were recruited for the study. Their mean age was 14.7 years (SD=2.2; range 8.1). Their grade level ranged from 4 to 12 (mean 8.7; SD=2.2). The following SCD genotypes were represented: SS (81.3%); SC (14.7%); S β + (2.7%) and S β 0 (1.3%). Scores on the REALM-Teen ranged from 12 to 66 (mean 53.7; SD=12.8). Scores on the NVS ranged from 0 to 6 (mean 2.37; SD=1.33). These health literacy scores were lower using both the REALM-Teen and the NVS instruments when compared to scores in healthy adolescent and adult controls. However, the mean REALM-Teen score of this sample was slightly higher than Black controls from the validation study. Current grade level and health literacy scores showed a moderately high positive correlation ($r = .52, p < .01$). Health literacy scores were also significantly positively correlated with age ($r = .49, p < .01$) and income ($r = .37, p < .01$).

Conclusion: Health literacy in adolescents with SCD appears to be suboptimal. Future research should include identifying facilitators and barriers to health literacy levels in a larger cohort of adolescents with SCD. Ratzan, S. C., & Parker, R. M., National Library of Medicine Current Bibliographies in Medicine: Health Literacy, 2000.

SIGNIFICANCE OF DAY 29 BONE MARROW IN PATIENTS WITH M1 AT DAY 8/15 BONE MARROW IN ACUTE LYMPHOBLASTIC LEUKEMIA IN ABSENCE OF MRD

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Background: ALL is most common malignancy in Children. All treatment protocols include multiple bone marrow examination to check treatment response including minimal residual disease (MRD). In our country we are following these protocols even in absence of MRD facility.

Objectives: Acute lymphoblastic leukemia (ALL) is most common hematological malignancy among pediatric population. Different protocols like UKALL and COG are used for management and all protocols suggest bone marrow biopsy at day 8 or 15 and then at day 29 during induction phase. On day 29 Minimum residual disease (MDR) status is usually advised. Developing countries where facility of MDR is not available patients of ALL are being treated according to these protocols and bone marrow biopsies are advised on both day 8/15 and day 29. Our hypothesis is “if day 8/15 bone marrow is in remission there is no significance of day 29 bone marrow in absence of MRD facility”

Design/Method: All patients of ALL admitted from Jan 2008 to Dec 2013 and survived during induction were included. Induction therapy according to standard arm of UKALL 2003 was given. Bone marrow biopsy was done on day 8 or 15 depending upon regimen and day 29 in all patients. MDR was not available.

Results: Total 282 patients were included. Male to female ratio was 2:1. Age range from 7 month to 17 year. Seventeen (6%) patients were >10 yrs. and 265(94%) were < 10 year. 30 (10.6%) patients had T cell ALL and 252(89.4) had Pre B ALL. Seventeen (6%) patients had M2 bone marrow and 13(4.6%) had M3 bone marrow on day 8/15 but none of them had residual leukemia on day 29. 252(89.3%) patients had bone marrow in remission on day 8/15 and none of them had evidence of residual leukemia on day 29 bone marrow

Conclusion: In absence of MRD facility there is no significance of day 29 bone marrow if day 8/15 bone marrow is in remission.

A SURVEY OF SICKLE CELL PATIENTS TRANSITIONED TO ADULT CARE FROM TEXAS CHILDREN'S HEMATOLOGY CENTER BETWEEN JANUARY 1999 AND JANUARY 2014

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Background: An estimated 93-98% of sickle cell disease (SCD) patients now reach adulthood in high resource countries. Studies show that this growing cohort of young adult SCD patients aged 18-26 years old experiences a marked rise in medical complications and early mortality, coinciding with decreased use of life-prolonging therapies and increased use of emergency care.

Objectives: We surveyed SCD patients who previously transitioned to adult care to determine: 1) If they currently had an adult SCD provider, 2) If they continued their pre-transition therapies, and 3) Their perception of the transition process.

Design/Method: 441 SCD patients transitioned from pediatric care at Texas Children's Hematology Center (TCHC) between 01/1999 and 01/2014. We contacted these patients at their last known address and phone number to request completion of a 23 question survey assessing patient demographics, post-transition medical outcomes, and personal experiences.

Results: 48 surveys were completed. 17 patients (35.4%) lack a provider, with top reasons being lack of insurance/funding (44%) and "can't find a physician" (38%). Patients without an adult physician within 6 months of transition were less likely to have a physician currently ($p < 0.017$). 83.3% of patients on hydroxyurea as pediatric patients (15/18) continued hydroxyurea therapy after transition. Subjects reported difficulties with finding knowledgeable adult providers, medical insurance, and inadequate transition preparation. Examples of qualitative results include comments such as the following: "The adult doctors are not aware of the disease... They have to call the pediatricians." While another said, "[It was] hard finding a physician in the two years after TCHC [because of insurance loss]... my health worsened because I wasn't getting the medication that I needed." When asked, 94% of patients wanted a dedicated SCD transition clinic. 12 patients were identified as deceased from all causes.

Conclusion: This survey shows that the first 6 months after transition is a critical period in identifying a sickle cell healthcare provider, supporting the need for a dedicated transition clinic to facilitate transition for SCD patients. It also quantitatively and qualitatively demonstrates that lack of sickle cell focused healthcare providers for adults is a barrier to successful transition.

STUDY OF THE EFFECT OF AGE ON TOXICITY DURING TREATMENT OF HIGH RISK ACUTE LYMPHOBLASTIC LEUKEMIA (HRALL)

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Background: Adolescents and young adults (AYAO) may experience greater toxicity than younger patients, treated for HR-ALL, with greater vulnerability to steroids and asparaginase which are commonly included in the induction phase of therapy. The relative role of age when ethnicity and body mass index (BMI) are taken into account has not been addressed.

Objectives: We sought to determine the impact of age on the number and/or maximum grade of chemotherapy-related toxicities during induction while controlling for BMI, ethnicity, and gender.

Design/Method: Consecutive non-Down Syndrome patients with HR ALL aged >1 and < 22 years at diagnosis, treated on or as per the Children's Oncology Group protocols AALL0232/AALL1131, over the past 10 years, were identified through the pediatric oncology registry at Children's Health. A retrospective chart review was conducted and all toxicities graded using the CTCAEv4 system. Patient characteristics were summarized by quartile of age at diagnosis. Unadjusted trends between toxicity outcomes and age were tested using the Jonckheere-Terpstra nonparametric method. Trends between toxicity outcomes and age adjusted for BMI, ethnicity, and gender were tested using Poisson regression models.

Results: The 158 patients experienced 69 distinct toxicities. Common toxicities included febrile neutropenia (FN), sepsis, hypertension, and hyperglycemia. There were 4 deaths during induction (ages > 13 at diagnosis). We omitted FN in analyses since patients did not have an infection. Unadjusted trends between age at diagnosis and both maximum grade of toxicity and number of grade 3-5 toxicities are significant with $p=0.011$ and 0.009 , respectively. However, multiple regression analysis indicates that when the relationships between age at diagnosis and toxicity are adjusted for BMI, ethnicity, and gender, the relationships are no longer significant.

Conclusion: Age was not a significant risk factor for a higher number or greater severity of chemotherapy-related toxicity when adjusted for BMI, ethnicity, and gender. This research will allow for better supportive care measures and counseling of patients and their parents with respect to the risks associated with ALL therapy.

THE DEVELOPMENT AND VALIDATION OF A COMPUTABLE PHENOTYPE FOR PATIENTS WITH SICKLE CELL DISEASE

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Background: Utilizing an electronic medical record (EMR) offers a unique opportunity to study large cohorts of patients over time. However, the ability to identify and follow these cohorts relies on the use of a valid computable phenotype consisting of a defined set of data elements in the form of a computable query to an EMR data warehouse. Although such computable phenotypes have previously identified patient populations with various conditions, a computable phenotype has not yet been developed to identify patients with sickle cell disease (SCD).

Objectives: To develop a computable phenotype identifying our patient population with SCD using an algorithm approach and to validate and refine the computable phenotype as a means of improving its accuracy.

Design/Method: This retrospective study utilized our computable phenotype to search our EMR data warehouse. Eligible patients included those ages 0-18 years, diagnosed with a qualifying SCD ICD-9 code, and being followed by the SCD clinic at the Children's Hospital of Wisconsin. The computable phenotype was developed as a series of queries to the data warehouse aimed at identifying our patient population with SCD. These queries included patients with a qualifying diagnosis of SCD who also had two outpatient visits at least 30 days apart or one hospitalization in the EMR. Validation studies using medical record numbers from the clinical program database were run against the results of the queries.

Results: The computable phenotype identified 352 patients. Of these patients, 350 were confirmed to meet the inclusion criteria. Two patients identified by the computable phenotype were incorrectly identified as having SCD. The computable phenotype failed to identify 2 patients meeting inclusion criteria. Overall, the computable phenotype accurately identified 350 of 354 (98.9%) patients known to fit the inclusion criteria.

Conclusion: The advent of EMRs provides a unique opportunity to track and follow known cohorts of patients with a given disease and is a rich resource for future clinical trials. The computable phenotype developed in this study allows for rapid and accurate identification of pediatric patients with SCD and provides a distinct advantage over administrative claims methods.

HYPERLEUKOCYTOSIS IN PEDIATRIC ACUTE LYMPHOBLASTIC LEUKEMIA (ALL): DOES IT MAKE A DIFFERENCE?

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Background: Hyperleukocytosis is defined as a peripheral leukocyte count of $\geq 100 \times 10^9/L$. This problem is seen in 5-20% of newly diagnosed cases causing hyperviscosity, culminating in early morbidity and mortality in these patients.

Objectives: To review factors predicting clinical and outcomes of Hyperleukocytosis

Design/Method: We performed a retrospective review of 455 A.L.L patients, diagnosed and treated at our institute between 2005 and 2014. Data on 58 patients with hyperleukocytosis is being compared with 397 non hyperleukocytic patients, with reference to their clinical characteristics and outcome.

Results: Median age at diagnosis for hyperleukocytic patients was 6.62 years (min: 1.07-max: 13.78) compare to 4.5 years (min: 1.01- max: 14.75) in non-hyperleukocytic group with 38(65.5%) and 233(58.7%) males in each group respectively. Median WBC (109) in hyperleukocytic was 213(min: 102-max: 923) vs 8.9(min: 0.68-max: 100) in others. Amongst hyperleukocytic at day 14 BM, 47(81%) were M-1, 3(5.2%) M-2 and 8 (13.8%) M-3 compare to 358(93%) M-1, 18(4.7%) M-2 and 10(2.6%) M-3 in the other group (P= 0.001). There were 43(74%) CNS1, 9(15.5%) CNS2 and 6(10.3%) CNS3 in hyperleukocytic patients vs 334 (84%) CNS1, 56(14%) CNS2 and 6(1.5%) CNS3 in others (P= 0.003). Hyperleukocytic group had 25(43%) B-cell, 29(50%) T-cell and 4(7%) Biphenotype vs 354 (89%) B-cell, 24 (6%) T-cell and 19(4.8%) Biphenotypic in others (P= <0.001). 16(40%) patients in hyperleukocytic group had abnormal cytogenetics compare to 117 (38%) in others. Amongst hyperleukocytic 2(4.3%) were positive for MLL against 11(3.5%) in others whereas Trisomies 4, 10 or 17 was positive in 1(5%) in hyperleukocytic vs 57 patients (43.8%) in non hyperleukocytic (P= <0.001). 12 patients (21%) died in hyperleukocytic group with a five year overall survival of 77.3% compare to 26 deaths (6.5%) in non hyperleukocytic with a five year overall survival of 92.4% (P=<0.001) whereas 15(26%) relapsed in hyperleukocytic and 48 patients(12%) in non hyperleukocytic with a five year event free survival of 68.8% and 83.6% respectively (P=<0.001).

Conclusion: Our results show that hyperleukocytosis in ALL is associated with T-cell ALL, less frequent favorable cytogenetics, slow early responder, CNS3, and poor outcome with more frequent deaths and relapses which is comparable with published data.

PSYCHOMETRIC EVALUATION OF THE MODIFIED FACES PAIN SCALE REVISED (MODIFIED FPS-R) IN CHILDREN AND ADOLESCENTS WITH SICKLE CELL DISEASE (SCD)

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Multinational

Background: The modified Faces Pain Scale Revised (Modified FPS-R) is a patient-reported outcome measure with established content validity, that is used to assess pain intensity in children and adolescents, 7 to <18 years of age, with sickle cell disease (SCD). A daily evaluation of pain can provide important insight on the clinical consequences of SCD that is not obtained from occasional inpatient or outpatient healthcare visits.

Objectives: To evaluate the psychometric properties (validity, reliability and responsiveness) of the Modified FPS-R in pediatric patients with SCD.

Design/Method: This evaluation was conducted in the context of a randomized, multinational clinical study in pediatric patients with SCD, 7 to <18 years of age. Symptom intensity was reported in a daily diary during the 2 week screening period/prior to randomization starting at Visit 0 through Month 9. The Modified FPS-R asks patients to consider their pain related to SCD, and report their worst pain over the course of a day. Mean monthly scores were calculated based on the number below the chosen face selected by the patient (“0”=“no pain”, “10”=“worst pain possible”). Intra-class correlation coefficient (ICC) was used for test-retest reliability between Month 1 and Month 2. Pearson correlation between monthly mean intensity of sickle-cell-related pain and analgesic use and narcotic use was conducted to assess convergent validity. Responsiveness was assessed with correlations of calculated changes from baseline corresponding to changes in analgesic use and change in activity score from Month 1 to Month 9.

Results: ICC was 0.77 (n= 42) indicating agreement among stable patients; moderate associations were shown between the Modified FPS-R and analgesic use (r=0.39) and narcotic use (r=0.44); and moderate-to-large associations were observed between the Modified FPS-R and change in analgesic use 0.39 (p<0.001) and activity scores 0.92 (p<0.001).

Conclusion: Results of the quantitative analyses support use of the Modified FPS-R in children and adolescents aged 7 to <18 years with SCD. The instrument has sufficient reliability, validity, and responsiveness to measure pain in clinical studies and will provide valuable insight when measured on a daily basis. This study was sponsored by Daiichi Sankyo, Ltd and Eli Lilly and Company.

OUTCOME OF RELAPSED AND NON-RELAPSED PATIENTS IN PEDIATRIC ACUTE LYMPHOBLASTIC LEUKEMIA (ALL): TEN YEAR'S EXPERIENCE AT KING FAISAL SPECIALIST HOSPITAL AND RESEARCH CENTER, RIYADH, SAUDI ARABIA

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Background: ALL treatment is often marred by a relapse in about 10- 20% patients, which is the main cause of treatment failure in most cases, more so in high risk patients.

Objectives: Review factors that predict relapse in ALL.

Design/Method: Retrospective review of 455 ALL patients (63 relapsed vs 392 non-relapsed), diagnosed and treated at our institute (2005-2014).

Results: Median age at diagnosis for both groups was 4.8 years with ranges (min: 1.1-max: 13.8) & (min: 1.1- max: 14.8) for relapsed and non- relapsed respectively. 12 (19%) were more than 10 years in relapsed whereas 55(14%) in other group. There were 44 (70%) males in relapsed and 227(58%) males in others. Median WBC (109) in relapsed group was 11.9(min: 0.68-max: 886) vs 11.2(min: 1.0-max: 923) in non-relapsed. 41(77%) patients in relapsed and 225(69.4%) in non-relapsed had DNA < than 1.16. Amongst relapse patients, at day 14 BM, 53(84%) were M-1, 6(9.5%) M-2 and 1 (1.6%) M-3 compare to 352(90%) M-1, 15(3.8%) M-2 and 17(4.3%) M-3 the in other group. There were 50(79.3%) CNS1, 10(15.8%) CNS2 and 3(4.7%) CNS3 in relapsed patients vs 327 (83.4%) CNS1, 55(14%) CNS2 and 9(2.3%) CNS3 in others .Relapsed group had 49(77%) B-cell, 7(11%) T-cell and 7(11%) Biphenotype vs 330 (84%) B-cell, 46 (11.7%) T-cell and 16(4%) Biphenotypic in others. 23(36.5%) patients in relapsed group had abnormal cytogenetics compare to 110 (28%) in others. Amongst relapsed 1(1.58%) was positive for MLL against 12(3%) in others whereas Trisomies 4, 10 or 17 was positive in 2(3%) in relapsed vs 56 patients (14.2%) in non-relapsed .26 patients (41.2%) died in relapsed group with a five year overall survival of 56.8% compare to 12deaths (3%) in non-relapsed with a five year overall survival of 97%(P<0.001) and a five year event free survival of 11.1% and 97% respectively (P<0.001).

Conclusion: Our results show that a relapse in ALL is associated with poor outcome which is comparable with published data and there is a trend in increase relapse rate in Biphenotypic leukemia, male gender, abnormal cytogenetics and DNA index less than 1.16.

USE OF TELEMEDICINE TO IMPROVE ACCESS TO CLINICAL SERVICES AND TREATMENT FOR CHILDREN WITH SICKLE CELL DISEASE

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Background: Patients with sickle cell disease (SCD) who live at long distances from their specialty care center can have difficulty with clinic visit compliance. The Children's Hospital of Pittsburgh (CHP) and the New York Mid-Atlantic Consortium for Genetics and Newborn Screening Services (NYMAC), a federally funded regional collaborative, recognized the need for families and providers to improve access to clinical services for these patients.

Objectives: To continue to provide service utilizing telemedicine for pediatric patients with SCD. To host onsite telemedicine training to illustrate how Telehealth can improve accessibility to care, increase workforce capacity, and identify barriers to its implementation at CHP for pediatric hematologists in the NYMAC region (DC, DE, MD, NJ, NY, PA, VA, and WV).

Design/Method: Telemedicine infrastructure was established in a satellite clinic at both Erie and Johnstown in Western Pennsylvania for monthly telemedicine sessions. CHP Staff and CHP SCD providers completed the telemedicine training. Patient satisfaction surveys were administered following the telemedicine visit. Pediatric hematologists in the NYMAC region were invited to participate in an onsite training program at CHP.

Results: Nine pediatric patients were seen at the Erie clinic which yielded 73 completed telemedicine visits. Two pediatric patients were seen at the Johnstown clinic, yielding 7 completed telemedicine visits. Improvements with clinic access, hydroxyurea adherence, and patient satisfaction were noted as positive results of Telemedicine. The pilot at CHP in 2013 resulted in an increased proportion of patients receiving four annual clinic visits to 90%, as well as access to genetic counseling for SCD families. The proportion of patients receiving hydroxyurea increased to 50%. SCD telemedicine services saved patients/families crucial time and resources.

Conclusion: Telemedicine is potentially a cost effective model of delivering and improving SCD services. An onsite telemedicine training program has been established for pediatric hematologists and allied health professionals. CHP and NYMAC continue to promote awareness and education for SCD telemedicine service as well as identify barriers to and strategies for implementation of telemedicine services in the region.

INDUCTION PHASE REMISSION RATE AND MORTALITY AMONG CHILDREN TREATED FOR ACUTE LYMPHOBLASTIC LEUKEMIA AT MUHIMBILI NATIONAL HOSPITAL IN DAR ES SALAAM-TANZANIA EAST AFRICA

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Background: Treatment response is considered the most important prognostic indicator for Pediatric Acute lymphoblastic Leukemia (ALL). Also induction phase therapy carries the highest mortality risk for children with acute lymphoblastic leukemia due to disease complications and treatment related toxicity. This audit reviewed treatment response at day 28 and mortality characteristics for children treated for acute lymphoblastic leukemia at completion of induction therapy.

Objectives: To evaluate the end of induction morphological remission status and mortality among children treated for acute lymphoblastic leukemia at Muhimbili National Hospital (MNH) in Dar es Salaam Tanzania.

Design/Method: Retrospective chart review was conducted to evaluate the remission status and mortality characteristics at the end of induction therapy among pediatric leukemic patients treated from 1st January 2013 to 31st December 2014. Charts were reviewed to look for clinical characteristics of the disease, bone marrow morphological remission status and mortality characteristics at day 28 of the (MNH ALL protocol – locally revised from the UKALL2003) induction phase therapy.

Results: Acute leukemia accounted for 16.66% (156/629) of all children treated. Out of which 105 patients had acute lymphoblastic leukemia (ALL) and 86.62% (92/105) had files reviewed. At the end of induction therapy, 70.65% (65/92) of the patients were alive, 63.03%(41/65) got treated on an intermediate-risk regimen and 36.93%(24/65) on the low risk regimen. At the end of induction therapy 31.7% (13/41) of the patients on the intermediate risk regimen and 33.3%(8/24) on low risk regimen were confirmed to be in morphological remission respectively. For the remainder of the patients, 40.07% (28/65) bone marrow samples were not taken on day 28 or the results were reported as inconclusive. By day 28, 29.35%(27/92) of the patients died before the end of induction therapy and the causes of death included anemia and bleeding, febrile neutropenia and tumor lysis syndrome.

Conclusion: The results of this audit highlight the need to improve our documentation and attention to protocol requirements. Induction phase mortality was unacceptably high underscoring the need for efforts to improve early access to treatment and improvements of supportive care for patients presenting with high disease burden and experiencing high treatment related toxicity rates.

A PHASE I PHARMACOKINETIC AND SAFETY STUDY OF INTRAVENOUS L-CITRULLINE IN STEADY STATE SICKLE CELL DISEASE

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Background: Perturbations in the arginine pathway with hemolysis associated nitric oxide (NO) depletion plays a central role in the pathogenesis of vaso-occlusion in sickle cell disease (SCD). Multiple studies have shown that citrulline is an effective NO booster, even during conditions of inflammation and acute arginase-induced arginine deficiency, characteristic of SCD.

Objectives: To assess the safety and pharmacokinetic profile of intravenous (IV) L-citrulline in steady-state SCD (ClinicalTrials #NCT02314689).

Design/Method: Each cohort of participants received an IV bolus of 20mg/kg of L-citrulline over five minutes with dose increments of 10 mg/kg until a target citrulline level of 80 to 100 $\mu\text{mol/L}$, a level known to elevate NO based on previous studies. Plasma samples were collected at certain time points for pharmacokinetic studies. Adverse events were followed according to the NCI Common Terminology Criteria for Adverse Events (CTCAE).

Results: In the first cohort of four participants, the intravenous bolus infusion of 20mg/kg of L-citrulline yielded a mean peak level of 259 $\mu\text{mol/L}$ and trough level in the range of 20-40 $\mu\text{mol/L}$ 4 hours after the infusion. The average rate of citrulline appearance, Rapp, was 11.1 $\mu\text{mol/hr/kg}$ (+/- 2.8 SD) and the average constant for citrulline removal, Krem was 1.06 (+/- 0.19 SD). The mean clearance was 0.52L/hr/kg with a volume of distribution of 0.50L/kg. All subjects had a significant rise in their arginine level within one hour of receiving the bolus IV citrulline (mean increment of 182%). One subject transiently dropped the diastolic blood pressure by >20% within 30 minutes of study drug with no intervention needed. There were no other reported side effects. Further analysis using a simulated dosing scheme shows that a 20 mg/kg bolus dose of IV citrulline followed by a continuous infusion of 7 mg/kg/hour is needed to maintain the target citrulline concentration.

Conclusion: Bolus intravenous L-citrulline is safe and well tolerated in patients with SCD but has a rapid clearance. Further studies are needed to evaluate the pharmacokinetic and safety profile of continuous dose IV citrulline in SCD, including its effect on NO production as a potential novel therapeutic option for sickle cell pain crisis.

CAN PEDIATRIC RISK OF MORTALITY SCORE (PRISM III) BE USED EFFECTIVELY IN INITIAL EVALUATION AND FOLLOWING UP OF CRITICALLY ILL CANCER PATIENTS ADMITTED TO PEDIATRIC ONCOLOGY INTENSIVE CARE UNIT (POICU)? A PROSPECTIVE STUDY IN A TERTIARY CANCER CENTER IN EGYPT

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Background: Pediatric cancer is a rare disease but, it's one of the leading causes of children's death. Intensification of treatment lead to significant improvement in cancer outcomes and also to significant complications. Admission to Pediatric Oncology Intensive Care Unit (POICU) is a costly event. Pediatric risk of mortality score (PRISM III) is a physiologically based predictor for outcome of critically ill patients.

Objectives: Assessment of the efficacy of PRISM III in predicting the risk of mortality in patients with cancer admitted to POICU, following them up during POICU stay, assessing the relationship between PRISM III and length of stay in POICU and assessing the effect of other factors as type of malignancy, septic shock, number of organ failures and type of intervention used on mortality risk in POICU

Design/Method: A prospective study conducted from 1\1\2014 to 1\1\2015 in four-bedded POICU, Pediatric Oncology Department, South Egypt Cancer Institute (SECI), Assiut University. The study population consisted of pediatric cancer patients admitted to POICU from Pediatric Oncology Department.

Results: One hundred twenty three pediatric cancer patients were admitted to POICU. Median age was 5 years (1-15).Male: Female ratio was 2:1.Death rate was 20%.Patients with hematological malignancies and lymphomas represented 75%.Sepsis and respiratory failure were the main indications of admission. Median length of stay was 5 days (2-24).First PRISM III (within the 1st 24 hours of admission) mean was 19 (0-61).First PRISM III correlated significantly with outcome ($p=0.000$), indication of admission ($p=0.000$).First PRISM III correlated weakly positive with length of stay ($r=0.2$ $p=0.024$).PRISM III was done serially every 3 days during POICU admission. At discharge, Mean PRISM III for survivors was 5 (0-25) $p=0.000$ Mean PRISM III for non survivors was 40 (19-61) $p=0.004$. Outcome also correlated with number of organ failures ($p=0.000$), indication of admission ($p=0.03$), stage of treatment ($p=0.001$) and intervention used (inotropes ($p=0.000$), ventilation ($p=0.000$), oxygen therapy ($p=0.015$)).

Conclusion: PRISM III can be used in predicting risk of mortality and following up patients with cancer admitted to POICU. Cancer related risk factors as indication of admission, stage of treatment and number of organ failures should be considered.

ESTABLISHING A ROLE FOR ASTHMA MANAGEMENT AS ADJUVANT THERAPY FOR VASO-OCCLUSIVE CRISIS

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Background: Asthma is a common comorbid condition in patients with sickle cell disease. It has been well reported that patients with sickle cell and asthma have increased risk of morbidity and mortality, especially in regards to acute chest syndrome. Limited research, however, has been done to establish the role of asthma in vaso-occlusive crisis.

Objectives: The study was designed to clinically assess the hypothesis that patients with sickle cell disease and asthma have increased severity and frequency of vaso-occlusive crisis secondary to increased impairment in oxygen exchange and associated sickling.

Design/Method: Following development of a comprehensive institutional database, 68 of 223 patients were identified with sickle cell disease and comorbid asthma ages 6 to 12 years of age. An additional 43 patients were identified as phenotypic and age-matched controls. Rates of emergency department visits and hospitalizations, frequency of vaso-occlusive crises, association with respiratory symptoms, and use of asthma controller medications were retrospectively analyzed over a 5 year period. Data collection and interpretation were accompanied by review of existing literature.

Results: Over the study period, patients with sickle cell and asthma had an increased frequency of acute chest presentations and other respiratory symptoms, as previously established. Of note, a similar increase was seen in pain presentations (4.14 compared to 1.5 hospital encounters per patient). While results did not definitively show causation between respiratory symptoms and onset of vaso-occlusive crises, the data suggest a direct correlation. Additionally, a statistically significant association between use of asthma controller medications and patients presenting with pain was identified ($p < 0.05$).

Conclusion: Asthma management may have a role in the treatment of sickle cell vaso-occlusive crisis as evidenced by more frequent pain presentations in patients with asthma, as well as, a correlation in those patients on controller therapy. Further study of the use of asthma management is in progress with the intent to improve pain management and decrease hospital encounters and hospital length of stay.

ABSOLUTE LYMPHOCYTE COUNT RECOVERY AT THE END OF INDUCTION PREDICTS SURVIVAL IN ACUTE LYMPHOBLASTIC LEUKEMIA IN GUATEMALA

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Background: The 5-year event free survival (EFS) of children with acute lymphoblastic leukemia (ALL) treated in high-income countries (HIC) is 80 - 85%. Cure rates are much lower in low-income countries (LIC). Lack of technology to perform accurate risk-classification contributes to this disparity. The assessment of the absolute lymphocyte count (ALC) recovery at the end of induction has been reported as a significant independent predictor of ALL survival in HIC.

Objectives: to determine if early recovery of absolute lymphocyte count ALC is an independent prognostic factor for patients with acute lymphoblastic leukemia (ALL) receiving standardized therapy in Guatemala, a low income country (LIC).

Design/Method: Retrospective review of patient's age 0 – 18 year with ALL, treated at Unidad Nacional de Oncologia Pediatrica (UNOP) in Guatemala, between May 2007 and May 2011.

Results: 389 eligible patients were included, 349 were evaluable: 274 were < 10 years of age, and 295 had < 50,000 WBC at the time of diagnosis. 232 had negative CNS, 105 positive CNS and 51 no data available. The majority of patients had pre- B ALL. There was not ability to do cytogenetic analysis. The ALC recovery at day 8 (ALC-8), 15 (ALC-15) and 33 (ALC-33) were assessed. ALC-15 and ALC-33 were significant discriminators of prognosis. Patients with an ALC-15 <350 cells/ μ L (n= had a 3-year EFS of 45% (P=0.002) vs. 66% with an ALC-15 >350 cells/ μ L (P=0.0415). Three-year EFS for patients with ALC-33 <350 cells/ μ L was 30% vs. 68% for patients with an ALC-33 > 350cells/ml (P=0.0024).

Conclusion: ALC <350 cells/ μ L during induction predicts poor prognosis in Guatemalan children with ALL. ALC-15 and ALC-33 \geq or \leq 350cells/ μ L differentiates survival groups by a difference of 21% and 38%, respectively. This finding implies that a patient with an ALC-15 and ALC-33 <350 cells/ μ L has a 68% higher probability of recurrence compared with a patient with an ALC-15 and ALC-33 > 350cells/ μ L. In LIC the ALC recovery at the end of induction may be used as a surrogate of MRD to allow post-induction risk stratification for ALL. This finding needs to be confirmed prospectively in current ALL therapy in Guatemala.

FLOW CYTOMETRY OF RED CELL BOUND IMMUNOGLOBULIN TO EVALUATE ALLOANTIBODY FORMATION IN SICKLE CELL DISEASE

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Background: Blood transfusions are essential in the treatment and prevention of Sickle Cell Disease (SCD)-related morbidity and mortality. Standard ABO/Rh cross matching attempts to prevent acute hemolytic transfusion reactions, but does not address alloantibody formation. The risk of developing alloantibodies after a single transfusion is 2%, but may be as high as 8-13% in patients receiving multiple or chronic transfusions.

Objectives: To evaluate the use of flow cytometry (FC) to detect red cell bound immunoglobulin in patients with SCD.

Design/Method: An IRB-approved, prospective cohort study was performed. All patients with SCD of any genotype between 0-21 years were eligible, with no exclusion criteria. Baseline testing included serologic tests, direct antiglobulin testing (DAT) by FC and tube and Gel techniques; repeated every six months, on acute admission and two weeks after discharge. FC and Gel testing was performed using de-identified, blind samples. Clinical data including SCD genotype, number of transfusions, alloantibody history, and medications were collected.

Results: Twenty-nine patients have been enrolled; 38% (11/29) were male; average age 14 years (range 1-19) with 76% (22/29) SCD-SS, 10% (3/29) SCD-SC, and 14% (4/29) SCD-SB0/+. Transfusion history included 14% (4/29) chronic transfusions; 72% (21/29) at least one transfusion; 14% (4/29) no previous transfusion. Standard serologic tests were positive in one patient with concordant gel and FC results. Eight patients had negative serologic, tube, gel and FC results. Thirteen patients had negative serologic, tube and gel tests, but positive FC results. Four patients had negative serologic tests but positive tube or gel tests with concordant FC results. One patient had insufficient sample. Seven patients had multiple samples; four progressed from IgM to IgG on FC with negative serologic tests. One patient became IgM and IgG positive and subsequently developed clinical evidence of a delayed hemolytic transfusion reaction although serologic testing remained negative and maintained positive red cell bound IgG on subsequent FC testing. The patients whose samples were negative in all tests had no signs of clinical transfusion reaction.

Conclusion: We present a novel method used to evaluate red cell destruction in patients with SCD. Further investigation correlating FC results with alloantibody formation is needed.

RELATIVE FREQUENCY AND SURVIVAL OF DIFFERENT IMMUNOPHENOTYPES OF ACUTE LYMPHOBLASTIC LEUKEMIA IN PEDIATRIC PATIENTS ADMITTED AT MUHIMBILI NATIONAL HOSPITAL, TANZANIA

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Background: Internationally, the proportion of Acute Lymphoblastic Leukemia (ALL) diagnosed of T-lineage is around 10-15%. Some studies suggest that T-cell ALL may be more common in non-Caucasian populations. There have been no published series of ALL with immunophenotyping in sub-Saharan Africa. Muhimbili National Hospital (MNH) has the only comprehensive pediatric oncology service center in Tanzania and flow cytometry has been recently established in clinical use.

Objectives: To determine the relative frequencies and overall survival of different immunophenotypes amongst new diagnoses of ALL at MNH.

Design/Method: Retrospective cohort study of children aged 0-20 years diagnosed with ALL at MNH June 2012-June 2015. The majority of flow cytometry was done at MNH using a Becton Dickinson FACSCalibur with remote review by medical scientists and hematologists Our Lady's Children's Hospital Crumlin, Ireland. If the FACSCalibur was unavailable or results were equivocal, samples were shipped to Ireland for flow cytometry (in TransFix solution(tm)) or for histopathology. All of the patients were treated with a modified UKALL protocol. Survival was analyzed using Kaplan Meier method and compared using Log-rank test. Medians were compared using the Mann-Whitney test.

Results: We identified 151 patients with ALL or suspected ALL, Charts were available for 95% (144/151). Of those with a known immunophenotype 31.1% (n=32/103) had T-cell ALL, 64.1% had pre-B cell ALL (n=66/102) and 4.9% (n=5/103) had other immunophenotypes including mixed lineage, Burkitt and NK cell. Twenty-four had an unknown immunophenotype of ALL and 17 died with a working diagnosis of acute leukemia before definitive diagnosis of ALL was made. Patients with T-cell ALL had worse overall survival compared to pre-B cell ALL (Kaplan-Meier log rank $p=0.045$), were older (median 10 vs 5 years; $p=0.08$) and had higher white cell counts at diagnosis (median $146 \times 10^9/L$ vs $26 \times 10^9/L$; $p<0.001$).

Conclusion: In this cohort of East African pediatric patients with ALL we have found that, in contrast to published series, the proportion of T-ALL is over double that seen on the large consortium trials in the US and Europe. This may reflect biologic differences in ALL in this population. As expected, the patients with T-cell ALL have worse survival and higher risk features.

EVALUATION OF AN ORAL MORPHINE PROTOCOL FOR TREATMENT OF ACUTE PAIN CRISIS IN SICKLE CELL PATIENTS IN THE OUTPATIENT SETTING

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Background: Sickle cell vaso-occlusive crisis (VOC) is one of the most frequent causes of emergency visit and admission in children with this condition.

Objectives: To evaluate whether the implementation of an oral morphine protocol has led to improved care of sickle cell disease (SCD), translated by a reduced hospitalization rate, an increased oral administration rate and faster opiate administration time, comparing cohorts of patients presenting to the emergency department (ED) and hematology outpatient clinic (HOC) with VOC pre and post implementation.

Design/Method: Retrospective chart review of patients with SCD followed at CHU Ste-Justine. Patients with a VOC diagnosis during the study periods were selected in each department's database. The primary outcome was to evaluate the hospitalization rate. The rate of oral administration and the opiate administration time were also calculated. We estimated that 35 patients per arm would be sufficiently powered to detect at least a 30% rate reduction of admissions, with a power of 80% and a significance of 0.05.

Results: Over the two periods, a total of 105 patients were included from the ED and 62 patients from the HOC. Both departments showed a reduction in hospitalization rate: a difference of 48% (95% CI 32, 61) in ED and 38% (95% CI 13, 57) in HOC. Both showed an increase in the rate of oral administration: a difference of 36% (95% CI 19, 50) in ED and 33% (95% CI 8, 53) in HOC. There was a non-significant difference of 10 min (95% CI -10, 25) in the opiate administration time in ED, as opposed to HOC where a significant difference of -45 min (95% CI -71, -6) was found, with both presenting median times over the recommended 60 minutes post implementation. Both settings showed an increase in the percentage of patients without IVs; a difference of 17% (95% CI 4, 30) in ED and 55% (95% CI 72, 31) in HOC.

Conclusion: This study validates the use of our oral morphine protocol for the treatment of VOC, by showing a significant reduction in hospitalization rates. Although delays remain in our opiate administration time, our protocol decreased the number of IV procedures.

THE ROLE OF IMMUNOPHENOTYPING AND CYTOGENETICS IN ACUTE MYELOID LEUKEMIA PROGNOSIS: 10 YEARS PROFILE IN A PAEDIATRIC BRAZILIAN HOSPITAL

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Background: The aid of immunophenotyping and cytogenetics became essential complement to the study of AML, because the prognosis is directly related to patient risk stratification, as well as the established treatment.

Objectives: Identify the phenotypes that were related to greater or lesser survival of patients and evaluate the response to induction treatment correlated with cytogenetic and phenotypic profile.

Design/Method: Conducted review of medical records of children with AML diagnosed and treated in the Pequeno Principe Hospital between January 1, 2002 to December 31, 2012.

Results: Evaluated 67 children, included 50 (34 children were treated according to BFM-98 protocol, 3 St. Jude AML protocol 02, the 2-BFM 87, BFM 2004 and 1st BFM-83). 27 boys. The age ranged from three days to 17 years, median of 6.98 years. Initially 50% with less than 10,000 leukocytes in the peripheral blood; 2% were between 50,001 and 100,000; 4% commas of 100,001 cells. The most common subtypes were AML AML M3 and M5, each representing 28%. According to cytogenetic analysis, 49% AML with recurrent abnormalities, and of these 56% were promyelocytic AML, 8.6 % were leukemia with translocation t (1; 22) (p13; q13) and 8.6% were leukemia with t (8; 21) (q22; q21). The group of this sample with better prognosis was the one with Down syndrome. 24 % of the amount of patients had search for DRM positive after induction (> 0.1 %), the survival rate in this sample over a period of 35 months was 39 %. The relapse rate was 70% for the positive DRM, while children with negative DRM had 39.39% of recurrence. The main reason of death was disease progression (53.8 %). Overall survival at 35 months of 57.45 %

Conclusion: Patients with cytogenetic alterations of good prognosis and / or negative DRM presence after induction had higher survival.

INCIDENTAL UNRUPTURED INTRACRANIAL ANEURYSMS IN SELECTED POPULATION OF SICKLE CELL DISEASE: AN INSTITUTIONAL EXPERIENCE

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Background: Cerebrovascular disease is a severe complication of sickle cell disease (SCD) affecting 25-30% of patients¹. The most common cerebrovascular events in SCD patients are ischemic, however there is an increase in hemorrhages in the 3rd decade of life attributed to Moyamoya disease². Ruptured intracranial aneurysms (IAs) are thought to be responsible for 2% of intracranial hemorrhages in SCD. The incidence and prevalence of IAs remain unknown in SCD.

Objectives: To assess the prevalence of IAs in a cohort of SCD patients who had not suffered stroke or been identified with an abnormal transcranial doppler (TCD).

Design/Method: Retrospective review of the SCD database to identify patients meeting the objective who underwent brain magnetic resonance imaging (MRI) and angiography (MRA) screening for headache or other non-stroke indication. Time period included patients scanned from 2010-2015. Demographic information collected included age (at scan), gender, genotypes, IAs, the indication for imaging, and management. All included patients didn't report history of stroke or abnormal TCD.

Results: Forty-three patients average age 18.20 years (SD= 7.43) were included. Five of forty-three patients (11.6%) imaged by MRI/MRA were found to have incidental unruptured IAs. Four patients (80%) had HbSS and one patient had HbSbeta+. All patients were asymptomatic. Multiple aneurysms were seen in 3/5 patients (75%). IAs were located at both the anterior and posterior cerebral circulation territory. 4/5 (80%) patients were managed conservatively with follow up scans. 1 patient was taken to the OR for aneurysm coiling and resection of an arterio-venous malformation.

Conclusion: The 11.6% prevalence of unruptured IAs in this cohort is much higher than the 3.2% reported prevalence of IAs in the general population³. SCD patients with IAs are likely at increased risk for hemorrhagic stroke or subarachnoid hemorrhage as they age. None of the patients included in this cohort had a history of abnormal TCD. Larger prospective studies are needed to accurately identify the prevalence, outcomes and optimal management of unruptured IAs in SCD. Additionally, maintaining a high index of suspicion for IAs in SCD patients with neurologic symptoms is necessary. This study is limited due to a small sample size of selected population.

COMPLEMENTARY AND ALTERNATIVE MEDICINE USE IN CANADIAN PEDIATRIC ONCOLOGY PATIENTS

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Background: Complementary and alternative medicine (CAM) includes therapies, practices and remedies that are not part of conventional medicine. The use of CAM is increasing among the Canadian pediatric population, but the incidence within pediatric oncology is not known.

Objectives: To determine the incidence of CAM use within a Canadian pediatric oncology population.

Design/Method: A questionnaire was developed and completed by parents/guardians of pediatric oncology patients (aged 0 to 18 years old) at the Children's Hospital of Eastern Ontario from January 2015 to July 2015. The questionnaire on CAM included reasons for use or non-use, types practiced, frequency of use, unwanted side effects, satisfaction of therapy, amount spent and supervision. Demographic characteristics, including ethnicity, marital status, level of education and profession were also collected.

Results: Of the 62 respondents, 61% of parents reported using CAM during their child's cancer treatment. Of those not using CAM therapies, the most common reason to not use CAM was that CAM "may interfere with the medicinal therapies my child is on" and that CAM "is not scientifically based" (n=25%). Of those that used CAM therapies, the most commonly used modality was prayers/faith (n=35%). Females ($\mu=61.0\%$) and males ($\mu=61.9\%$) were equally likely to use CAM. Ethnicity played a role in CAM use, as 100% of those that identified as European or Aboriginal used CAM, whereas approximately half of those that identified as Canadian ($\mu=57.4\%$), French ($\mu=50.0\%$), Asian ($\mu=60.0\%$) and African ($\mu=50.0\%$) used CAM. Parents who identified as married were least likely to use CAM ($\mu=59.8\%$) and those that were widowed were most likely to use CAM ($\mu=100.0\%$). Parents who completed a university degree were least likely to use CAM ($\mu=53.25\%$) and those who attained a college degree were most likely to use CAM ($\mu=70.0\%$). Only 57% of patients discussed their CAM use with a physician.

Conclusion: Sixty-one percent of pediatric oncology patients are using CAM therapies. Only 57% informed physicians of CAM use, emphasizing the importance of physicians and nurses consulting patients on CAM use to monitor for any side effects or interactions with cancer therapies.

PEDIATRIC PRESCRIBER PRACTICES OF HYDROXYUREA IN SICKLE CELL DISEASE

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Background: Hydroxyurea (HU) has been shown to be efficacious in individuals with sickle cell disease (SCD). Drug labeling gives prescribing guidance for use in adults, but use in children is based on expert consensus and not randomized trials. This leads to variation in HU initiation, counseling, monitoring, and discontinuation.

Objectives: To describe prescribing practices of HU for children with SCD, and identify areas for improvement.

Design/Method: We conducted an online survey of HU prescribing practices among providers in the New England Pediatric Sickle Cell Consortium caring for approximately 1000 children with SCD, from September-October 2013.

Results: We had responses from 13 providers from 10 New England institutions. Six providers estimated that they had > 50% of eligible patients on HU. HU initiation indications used by >70% of respondents included: all patients with hemoglobin SS and SB0-thalassemia, conditional TCD velocities, ≥ 3 pain episodes/year, multiple hospitalizations, and parental request. All providers felt HU was safe for children >2 years old, 7/11 offered it in children <2 years. Respondents reported that patient or family declining was the most common reason for not initiating HU; reasons given included the increased frequency of office visits, difficulty of daily medications, fear of side effects, concerns for dependency, and loss of fertility. Other reasons for ineligibility included hepatic or renal dysfunction, splenic sequestration, neutropenia, high baseline hemoglobin, and history of poor adherence. 90% of prescribers either provided or referred patients for counseling about birth control, 7/12 performed urine pregnancy tests routinely, and 33% of providers required documentation of birth control in females. Respondents typically started HU at 15-20 mg/kg/d, but maintenance doses varied widely, from 15 to 35mg/kg/d. Lab monitoring was done every 2-4 weeks during escalation, and every 2-3 months with stable dosing. Adherence was most commonly monitored by self-report and inferred by lab values. The top three indications to discontinue HU included missed visits, poor adherence or neutropenia.

Conclusion: There is significant variation in HU prescribing practices, even within a regional consortium. Protocolized guidelines and more study into pediatric use of hydroxyurea is needed to optimize prescribing practices and its impact in sickle cell disease.

QUALITY IMPROVEMENT AND EDUCATIONAL INTERVENTION TO IMPROVE PEDIATRIC RESIDENTS' MANAGEMENT OF PATIENTS' WITH ABNORMAL UTERINE BLEEDING

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Background: Abnormal uterine bleeding (AUB) is a frequent gynecologic complaint in adolescents. Despite this, research on management strategies for AUB is limited and there is often variation in acute care.

Objectives: Our objective was to improve pediatric residents' knowledge and confidence in the management of AUB in the emergent setting by implementing a local consensus algorithm and an electronic health record (EHR) order set with concomitant education.

Design/Method: We used a multidisciplinary approach involving the departments of emergency medicine, adolescent medicine, and hematology/oncology to create and implement an algorithm for the emergent management of AUB, along with an accompanying EHR order set to facilitate testing and treatment. Education on AUB management, the algorithm and EHR order set were provided to pediatric residents via didactics in-person and electronic mail. Resident knowledge (2 scenarios, 7 questions) and confidence in AUB management was assessed pre and post-intervention (algorithm/EHR order set implementation and didactics) with electronic surveys. χ^2 statistics were used to compare groups.

Results: The pre- and post- intervention surveys were completed by 48 and 30 residents, respectively. Knowledge in AUB management improved post-intervention ($p < 0.01$). Residents reported lacking confidence in AUB management less often post-intervention (36% versus 13%; $p = 0.03$).

Conclusion: Implementation of an algorithm and EHR order set may be an effective method to improve residents' knowledge in the management of AUB in the emergent setting. In the future, we hope to assess the association between our implementation and clinical outcomes.

EARLY INITIATION OF INHALED CORTICOSTEROIDS FOR THE PREVENTION AND TREATMENT OF ACUTE CHEST SYNDROME DOES NOT REDUCE ITS MORBIDITY IN PEDIATRIC PATIENTS WITH SICKLE CELL DISEASE

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Background: Acute chest syndrome (ACS) is the leading cause of mortality in patients with sickle cell disease (SCD). Treatment is multimodal and includes anti-inflammatories like corticosteroids. While systemic corticosteroids may decrease length of hospital stay for ACS, the risk of readmission for vaso-occlusive crises (VOC) has limited their use. Inhaled corticosteroids (ICS) may be a safe alternative, but efficacy is currently unknown.

Objectives: To investigate the effects of initiation of ICS at the time of hospital admission in reducing ACS morbidity.

Design/Method: A case control study compared SCD patients with a discharge diagnosis of ACS who received ICS (cases) at admission to those who did not (controls). History of asthma and severity of ACS (unilateral infiltrate vs. bilateral) were collected. Outcome measures included transfusion and oxygen requirement, rate of PICU transfer, intubation, or BiPAP initiation, and need for readmission. Statistical analyses included Pearson chi-square and student t-tests.

Results: One hundred twenty SCD patients (55 controls, 65 cases) were included in this study. A significantly higher proportion of controls had bilateral infiltrates (40% vs. 20% of cases, $p=0.03$), but fewer had asthma (12.7% vs. 52.3% of cases, $p<0.001$). Twelve cases (18.3%) and 9 controls (16.3%) were transferred to the PICU ($p=0.80$). While a lower proportion of cases required intubation (8.3% vs. 33.3% of controls, $p=0.15$), more cases required BiPAP (15.3% vs. 5.4%, $p=0.02$). Transfusion rates ($p=0.10$), oxygen requirement ($p=0.09$), and readmission rates ($p=0.41$) did not differ between groups.

Conclusion: More controls had bilateral infiltrates in this study, suggesting more severe ACS, yet initiation of ICS in cases did not significantly decrease morbidity despite having less severe disease. More cases were diagnosed with asthma which may be why they were treated with ICS on admission despite less severe ACS. Overall, initiation of ICS did not decrease ACS morbidity as measured by the need for transfusion, oxygen supplementation, or PICU intervention. While systemic steroids increase the risk of readmission for VOC, cases were not more likely to be readmitted after the use of ICS. Despite a plausible pathogenic mechanism to reduce airway hyperreactivity, our study did not demonstrate a significant benefit of ICS in the treatment of ACS.

HELPING PARENTS LIVE WITH THE HOLE IN THEIR HEART: THE ROLE OF HEALTH CARE PROVIDERS AND INSTITUTIONS IN BEREAVED PARENTS' GRIEF JOURNEYS

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Background: Bereaved parents experience significant psychosocial and health sequelae, suggesting that this population may benefit from ongoing extension of support and resources throughout the grief journey. The interaction of healthcare providers (HCPs) and hospital staff with patients and families at the end of a child's life and after death profoundly affects the parental grief experience, offering a unique opportunity for the medical community to positively impact the bereavement experience.

Objectives: To explore the role of the health care team and the institution in the grief journeys of parents who lost a child to cancer.

Design/Method: Eleven bereaved parents participated in 2 focus groups. Responses to each of the 3 main prompts were coded and analyzed independently using semantic content analysis techniques.

Results: Four main concepts were identified within the parental narratives, including the importance of strong and ongoing relationships between HCPs and bereaved families, the importance of high quality communication between HCPs and families, the effect of negative experiences between HCPs and families on parental grief, and the importance of the institution's role in the grief journeys of bereaved parents.

Conclusion: Bereaved parents consistently identify the critical role played by HCPs and medical institutions throughout the grief journey. Key components of bereavement support identified by parents should serve to guide the actions of HCPs as well as provide a template for the development of a comprehensive bereavement program within an institution.

A PHASE I TRIAL OF ZILEUTON IN SICKLE CELL DISEASE

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Background: Sickle cell disease (SCD) is associated with airway hyper-reactivity (AHR), and with augmented inflammation and leukotriene production, known mediators of AHR. Zileuton is a specific inhibitor of 5-lipoxygenase, a key enzyme in the leukotriene synthetic pathway, and is licensed for asthma. However, its safety/pharmacokinetics is not investigated in patients with SCD, where liver and renal functions are often compromised. We hypothesized that zileuton will be safe in patients with SCD, with pharmacokinetics similar to asthma

Objectives: The primary objective was to determine safety, tolerability and pharmacokinetics of twice daily administration of ZL (Zyflo CR) in patients with SCD.

Design/Method: We employed a 3x3 dose escalation/de-escalation design of twice daily zileuton for 6 weeks. Nine patients 7-30 years of age with SCD at steady state, who were not on hydroxyurea or chronic transfusions, were enrolled. Pharmacokinetics was performed after the first dose, using a Bayesian model. Total zileuton exposure was defined by the area under the concentration-time curve between zero and 24h (AUC_{0-24h}) normalized by dose

Results: Zileuton was well tolerated at doses of 2400mg/day and 3000mg/day. No significant changes in any clinical or laboratory safety parameters occurred. Adverse events were limited to grade-1/2, the most common being pain and hypertension. Pharmacokinetic parameters of zileuton were [mean, (CV %)]: plasma clearance (CL/F) 0.53 L/h/kg (36.4%); volume of distribution (V/F) 1.12 L/Kg (32%); absorption rate constant (K_a) 0.12 1/h (82.2%); elimination phase half-life (t_{1/2}) 1.52 h (24.4%); AUC_{0-24h} (per 1200 mg) 52.61 µg·h/ml (45.7%). The population CL/F estimate of 0.51 L/h/kg in the NONMEM analysis was consistent with MWPharm results (0.53 L/h/kg). Variability was smaller when CL/F and V/F were normalized to body mass, suggesting that differences in body weight helped to explain some variability. The coefficient of determination (R²) between body weight and CL/F was 0.44 (P < 0.1), and the R² between body weight and V/F was 0.40 (P < 0.1).

Conclusion: This phase-1 trial demonstrates that zileuton was safe, well tolerated by patients with SCD although there was significant inter-individual pharmacokinetic variability; and warrants a future phase 2/3 trial to study its efficacy in reducing AHR and associated pulmonary morbidity in SCD.

PARENT'S PERSPECTIVES ON THE END OF LIFE CARE OF THEIR CANCER CHILD-INDIAN PERSPECTIVE

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Background: Parents report that end of life decisions are the most difficult treatment related decisions that they face during their child cancer experience. Research into the parent's perspective of the quality of end of life care of their cancer children are scarce, particularly in developing countries like India.

Objectives: This study aimed to identify the symptoms (medical/social/emotional) that most concerned parents during the last days of their child's life and to identify the strategies parents found to be helpful during this period.

Design/Method: Parents who lost their child to cancer, treated in our institution were interviewed with a validated prepared questionnaire.

Results: 50 % of them were able to understand the concept of palliation vs curative option while 20 % could not understand at all. 80% of them were able to come in terms with palliative mode of treatment while 20 % could not. Only 40 % of them opted for alternative medicine and 70 % of them accepted that it worsened the symptoms. 60 % of them wanted their child to be at the hospital during the period of death and 40 % opted home to be the place of death. When questioned about what made them to opt for aggressive therapy towards the end of life, 60% reported that they hoped for a miracle, while 30 % wanted to do everything possible to reduce the suffering. Retrospectively, 70% of them felt that what they did was right as they wanted to help the child in all possible ways. Towards death, dullness (30%), irritability (30%) and withdrawn from surroundings (10%) were the most common symptoms encountered. 30 % of the children had fear to be alone. 50% of the children had the fear of death. Pain, fatigue, loss of appetite, were the main distressful symptoms that these child suffered from parent's perspective.

Conclusion: In developing countries, with scarce financial resources and the increasing magnitude of competing problems, little resources are left for hospice and palliative care services. However, the human factor should not be underestimated, and as end of life of care is far more than medical treatments and pain killers. Greater attention should be paid to symptom control and overall well-being of the child on end of life care.

EFFECTS OF SICKLE CELL DISEASE ON CAREER AND EDUCATIONAL PROSPECTS: TOWARD THE SOCIAL VALUE OF A CURE

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Background: Sickle cell disease (SCD) is a chronic disorder with lifelong effects. Complications include: pain crises, chronic fatigue, organ damage, infections, acute chest syndrome and stroke. Research shows that health related quality of life suffers along with daily activities. Stem cell transplant is an option for eligible patients. Cure by transplant can markedly improve quality of life, but how patients perceive this benefit is not clear.

Objectives: The goal of this study was to explore self-reports of the effects of SCD on work or school along with common themes regarding participants' perspectives on life without SCD. The hypotheses were that patients (1) perceive greater disability of SCD as they age, and (2) recognize that transplant could relieve them of that disability.

Design/Method: Mixed methods surveys were administered in person to patients seen at the UI Health Comprehensive Sickle Cell Center hospital, pediatric clinic, or adolescent transition clinic. Participant ages ranged from 10 to 40+. Exclusion criteria were: respiratory or contact isolation or extreme pain. Qualitative responses were examined using thematic analysis.

Results: Themes identified by all ages about the effect of SCD on work and school included "Disability," "School absence," and "Motivation to disprove odds." Thematic analysis identified that patients would live their lives differently if cured: "More energy to improve myself," "New educational goals", "Career aspirations." The potential that stem cell transplant would relieve their disability was recognized by nearly all subjects. Older age correlated significantly ($P < 0.02$) with responses that as relieving their disability, and almost universally the patients would pursue more in their career or education if cured.

Conclusion: Advances in transplantation for SCD can achieve cure for adults and often reduces disability from pain. Heightened perception of benefits by adults supports the important role of adult SCD transplant programs. This survey is the first to examine perception of disability among the factors that patients consider in their decision about stem cell transplant for sickle cell. Further, few studies include both adolescent and adult sickle cell patients in a single survey, and this opens the door on age-related differences in perception of stem cell transplantation.

FORWARD OBSERVATION TO IMPROVE HEALTH OF CHILDREN AND AYA WITH METASTATIC, UNRESECTABLE, OR RARE GENETIC CANCER: HOW WE PARTNER WITH CAREGIVERS TO REDUCE LEARNED HELPLESSNESS AND FACILITATE OUTPATIENT CARE

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Background: Families and caregivers of pediatric oncology patients can get overwhelmed when coping with the multitude of tasks required to maintain health, much less improve health.

Although Children's Hospitals are loving and caring environments, there is no place like home.

Objectives: Our goal in 2015 was to transform care delivery of a largely inpatient focused solid tumor chemotherapy team into one that could provide outpatient forward observation. This involved: a) facilitating outpatient chemotherapy, b) anticipating and preventing side effects, c) improving nutrition, d) providing resources to enable families and caregivers to take more active roles, and d) encouraging a "forward observer" mind set.

Design/Method: Tools used to facilitate and foster forward observation and more active participation in improving health included: 1- improved EMR notes using the Snipping Tool to embed calendars, images, and photos into EMR notes for better team communication, 2- web resources (lotsahelpinghands.org; chemocare.org or ASPHO chemo; disease oriented groups such as ACOR for osteosarcoma or Ewing sarcoma), 3- provision of calendars for families, pharmacy, and infusion nurses, 4- one-page summaries of care (including contact information, previous treatments) which provide the relevant clinical details to facilitate meaningful discussions during clinic visits and improved anticipation of plans and tasks, 5- flash drives containing articles+ nutrition info, images, calendars+ roadmaps, and summaries for caregivers, 6- advance directives information, 7-after-visit-summaries, and 8-creating things to look forward to (make-a-wish, college scholarships).

Results: We provide most chemotherapy regimens safely in the outpatient clinic including VAC, VDC, IE, HDMTX with fewer readmissions. Forward observation as a mindset for improving health of patients with metastatic medullary thyroid carcinoma, clear cell sarcoma, neuroectodermal tumor, rhabdomyosarcoma, Ewing's sarcoma, osteosarcoma, and desmoplastic round cell tumor resulted providing successful outpatient care. Snipping Tool use in EPIC has made our notes more informative "at-a-glance". Many of our children and AYA seem to have improved performance status, excellent QOL, and superlative coping skills that positively affect family dynamics and outcomes.

Conclusion: Instead of "expecting the worst", we have adopted a forward observer mind set to actively create an environment to "hope and prepare for the best"- and now routinely exceed expectations.

CLINICAL, GENETIC AND BIOLOGICAL CHARACTERISTICS OF HbS_OMAN: A SEVERE UNREVEALED FORM OF SICKLE CELL DISEASE

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Background: Hemoglobin SOman results from double mutations in the β globin chain; the classic β S mutation (β 6 Glu→Val), and a second mutation in the same chain (β 121 Glu→Lys) identical to that of HbOArab. In the literature only 6 carriers have been described. HbS-Oman carriers can have severe clinical presentation matching sickle cell disease with frequent vaso-occlusive crises, acute chest syndrome and even cerebrovascular accidents.

Objectives: Study the clinical phenotype, genotype and cell biology of both carriers of HbSOman and compound heterozygotes HbS-SOman.

Design/Method: A cross sectional study that includes all identified carriers of HbSOman and compound heterozygotes. Demographic and clinical phenotype data were collected, including family pedigrees that were tracked to the same grandmother indicating a founder effect. Hematological parameters and HPLC were performed. β -globin chain haplotypes were done using RFLP. Next generation Exom sequencing for α -globin gene non-deletional mutations, β -gene mutations and other genetic modifiers including AHSP, BCL11a, KLF1, TAL1 and GATA1 was performed. Deletional α -thalassemia mutations were identified using α -gene scan. Samples were processed for non-electrolytic hemolysis test, K⁺ efflux by using radioactive tracer studies.

Results: We identified 53 carriers, 27 males and 26 females and 6 HbS-SOman patients, 4 males and 2 females, age range between 2-75 years. Hemoglobin range was 7.5-14.7 g/dl (11.9±1.6), and SOman 9.5-25.3% (15.9±3.7) for carriers, while Hb ranged from 3.2-7.8 g/dl (5.2±2.4) and SOman 6-24.6% (11.6±6.6) for compound heterozygotes. Clinical severity index correlated with the SOman percent in the carriers with a cut-off value of 14% and with decreased production of α -chains due to deletional or non-deletional mutations; however, there were no such correlations in the compound heterozygotes who presented in early infancy with severe transfusion-dependence. Other genetic modifiers seem to have no effect. Activation of a deoxygenation-induced Cl⁻-independent K⁺ flux, i.e. Psickle-like permeability, a lack of Gardos channel activity and minimal activity of potassium chloride co-transporter was found in SOman carriers.

Conclusion: HbSOman is a severe form of SCD; carriers can be severely symptomatic and compound heterozygotes present as thalassemia major with early transfusion dependence. Alpha thalassemia mutation is the main genetic modifier in carriers. SOman cells have increased sickling and hemolytic characteristics.

MENTAL HEALTH SCREENING TOOLS FOR ADOLESCENTS WITH CHRONIC HEMATOLOGICAL DISORDERS: EVALUATION OF THE PEDIATRIC SYMPTOM CHECKLISTS

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Background: The Pediatric Symptom Checklist (PSC-P) is a well validated questionnaire completed by a caregiver in about 5 minutes to screen children and adolescents for psychosocial difficulties. The Pediatric Symptoms Checklist-Youth (PSC-Y) is a less extensively studied parallel version of the PSC designed for self-report by youth ages 11 years and up. Neither the PSC-P nor the PSC-Y has been studied in adolescents with chronic hematological disorders.

Objectives: This study examined using the PSC-P or PSC-Y to screen adolescents with sickle cell disease or chronic idiopathic thrombocytopenic purpura (ITP) for psychosocial problems that may require more evaluation and/or intervention.

Design/Method: Subjects were patients who routinely visited a comprehensive sickle cell or pediatric hematology clinic (ITP). Any parent/caregiver-patient dyad (age eligibility 11-19) was invited to participate. Consenting caregivers completed the PSC-P and CBCL (Achenbach Child Behavior Checklist), and corresponding adolescents completed the PSC-Y and YSR (Achenbach Youth Self Report). Total number of evaluable pairs was 19 (10 female; 8 Hemoglobin (Hb) SC disease, 5 Hb SS disease, 1 Hb S/ β thalassemia, and 5 chronic ITP). The agreement between parallel forms was analyzed descriptively. Correlation coefficients were calculated for each pair of instruments (the PSC-P and CBCL and the PSC-Y and YSR.)

Results: Patients age ranged from 11 to 19 years with a mean of 15.2 (\pm 2.2). We regarded CBCL and YSR as the reference instruments. Of the four patients who exceeded the CBCL threshold score indicating psychosocial risk (T-score >65), 100% also exceeded the PSC-P threshold (>28 points). PSC-P percent agreement with the CBCL was 84.2% (n=16). PSC-Y agreement with the YSR was 68.4% (n=13). Each instrument detected risk when it was not detected in the parallel instrument.

Conclusion: Our results suggest that the PSC-Y may have limitations to screen sickle cell disease or chronic ITP patients for psychosocial problems, though this conclusion is very tentative due to the very small sample size. In contrast, the PSC-P may be a reasonable alternative to the CBCL that should be explored further.

SPLENECTOMY TO OPTIMIZE HEMOGLOBIN S CONTROL IN CHILDREN WITH SICKLE CELL DISEASE ON CHRONIC TRANSFUSION THERAPY FOR STROKE PREVENTION

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Background: Consensus guidelines recommend chronic transfusion therapy (CTT) for stroke prevention in patients with sickle cell disease (SCD) who have a history of overt stroke or abnormal transcranial Doppler (TCD) velocities, typically with the goal of maintaining baseline hemoglobin (Hb) S <30%. Observational studies report considerable variation in Hb S% in children on CTT, but outside of alloimmunization, reasons for such variability have not been well-studied.

Objectives: We report the possibility of chronic splenic sequestration as a cause of poor Hb S control in 3 patients with SCD on CTT for stroke prevention and suggest consideration of splenectomy to optimize transfusion parameters in select high-risk children.

Design/Method: Patients were ages 7-9 years with Hb SS disease managed with chronic, partial-exchange PRBC transfusions every 3-4 weeks following a standardized institutional protocol with poor Hb S control. Indications for CTT were prior stroke (2) and abnormal TCD (1). Surveillance magnetic resonance angiography showed progressive CNS vasculopathy. Spleens measured 9.5-13.5 cms. There was no evidence of alloimmunization. After careful consideration, these patients underwent laparoscopic splenectomy. Mean hematologic parameters were compared by paired t-tests 6 months pre and post splenectomy.

Results: Prior to splenectomy, mean pre-transfusion Hb was 7.4 gm/dL, reticulocyte count 20.7%, and Hb S 56%. Post splenectomy Hb was 9.5 gm/dL, reticulocyte count 3%, and Hb S 17%. Following splenectomy, there was a mean reduction in Hb S of 39.77% (95% CI 34.3-45.3, p<0.001). With a mean follow-up of 19 months, there were no perioperative or infectious complications. One patient appeared to have reduced iron burden with a mean reduction in baseline serum ferritin of 1,500 ng/mL, perhaps in part because his transfusions were spaced out due to improved Hb S control.

Conclusion: This data suggest splenic sequestration may cause shortened red cell survival resulting in suboptimal Hb S control and increased risk of incident or recurrent stroke. Splenectomy may be a reasonable therapeutic option for select high-risk patients. Additional research is warranted into the causes of variable Hb S control in patients with SCD on CTT so that therapeutic options can be refined to reduce the risk of overt stroke.

IMPROVING TIME TO ANTIBIOTIC ADMINISTRATION FOR BMT INPATIENTS WITH FIRST FEVER

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Background: Timely antibiotic administration in febrile neutropenic patients has been associated with improved outcomes. Analysis of our inpatient BMT unit revealed only 50% of patients with new onset fever received antibiotics within 60 minutes. The aim of this project was to increase the percentage of febrile BMT inpatients receiving antibiotics within 60 minutes, from 50% to 75% by October of 2015 using the Model for Improvement.

Objectives: 1. Recognize the importance of timely antibiotic administration in immunocompromised patients 2. Identify potential barriers to timely antibiotic administration 3. Demonstrate the importance of establishing a standardized process for provider notification, antibiotic order entry and administration

Design/Method: Through Pareto analysis and Failure mode effects analysis (FMEA), we identified variables and underlying causes associated with delays. Pareto analysis revealed: orders placed by the providers, delays in pharmacy processing, delays in order placement, and delays in notification of new onset fever were associated with 80% of failures. FMEA revealed insufficient awareness of pharmacy, nursing, and providers of new onset fever; no standardized ordering process; and lack of provider and nursing accountability as likely causes of timely antibiotic delivery failures. From these findings, we created key drivers and through small tests of change developed a standardized process consisting of: 1) bedside nurse notifying ordering provider, charge nurse, and safety coach of a febrile patient, 2) a standardized order set specifically used for inpatients with their first fever, 3) pharmacy notification of a newly febrile patient via a STAT sticker printing off when antibiotics were entered via the order set. We monitored compliance with the process via a software monitoring system called VigiLanz.

Results: After implementing an antibiotic order set and developing a process in which the bedside nurse notified both the charge nurse and safety coach of a febrile patient, we saw an increase in the percentage of patients receiving antibiotics within sixty minutes of documented fever from a median of 55% to 80%. Our median time for antibiotic administration decreased from about 60 minutes to 45 minutes.

Conclusion: Implementation of a standardized process for provider notification and order entry has resulted in improved times to antibiotic administration in our patients.

UTILISATION OF ROMIPLOSTIN IN SICKLE CELL DISEASE IS SAFE

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Background: Romiplostin, a thrombopoietin analog, is an approved second-line therapy for immune thrombocytopenia (ITP). Its safety in patients with sickle cell disease and secondary thrombocytopenia is however unknown.

Objectives: Describe the use of romiplostin in a patient with sickle cell disease.

Design/Method: Single case report.

Results: A 16 year old female with Hb SS sickle cell disease (SCD) and systemic lupus erythematosus (SLE) developed secondary ITP in July 2014 (platelet count of $11 \times 10^9/L$). She was already on Prednisone 1 mg/kg for her SLE and therefore, was treated with intravenous immunoglobulins (IVIg) 1 g/kg x 2 doses with partial response. A month later, she received two cycles of Rituximab 375 mg/m² with good response. In January 2015, the platelet count went back to $12 \times 10^9/L$ and she received a third course of Rituximab with no sustainable response. It was then decided to introduce Romiplostin in February at a starting dose of 2 mcg/kg and was increased to a maximal dose of 5 mcg/kg. Within a month, she had normalized her platelet count (from 9 to $444 \times 10^9/L$). Romiplostin was then titrated as per standard recommendation to maintain platelet count between 50 and $200 \times 10^9/L$. Although platelet count remained stable, ofatumumab was further given one month later to avoid relapse of the other immune manifestation of SLE. Given sustained normal platelet count, romiplostin was gradually weaned and ceased in September 2015. The medication was well tolerated and the patient did not experienced any side-effects nor any pain crisis.

Conclusion: To our knowledge, this is the first report of utilization of Romiplostin in a patient with SCD. The medication was efficacious and well tolerated. In particular, no increase in pain crisis was noted. In contrast to GCSF, romiplostin might safely be used in SCD.

OUTCOMES OF PEDIATRIC HEMATOLOGY/ONCOLOGY INPATIENTS THAT DEVELOP A BLOODSTREAM INFECTION

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Background: Bloodstream infections (BSI) are serious complications in children receiving chemotherapy and undergoing stem cell transplantation (SCT). The outcomes of pediatric hematology/oncology/SCT (PHO) patients that develop a BSI are unknown.

Objectives: The objective of this project is to determine the outcomes of hospitalized PHO patients who develop a BSI.

Design/Method: In conjunction with the Children's Hospital Association Childhood Cancer Blood Disorders Network, 22 PHO centers prospectively tracked and categorized BSIs according to NHSN criteria in hospitalized PHO patients with a central line. BSI included central-line associated blood stream infections (CLABS), secondary BSI, and single positive blood cultures (SPBC). Chart review of BSI from November 2011 thru April 2015 was performed to identify specific patient, disease, treatment and outcome data.

Results: Demographic and outcome data of 386 of 2000 individual BSIs have been collected thus far including 295 CLABSIs, 47 secondary BSIs, and 44 SPBC. The majority of patients were male (60%) with a median age of 9.9 years (IQR: 3.2-15.9). 284 patients (74%) PHO patients had an underlying malignancy, with AML (n=135) and ALL (n=91) being the most common, 22% (n=85) had an underlying immune deficiency syndrome. In patients with malignancy, 36% (n=101) had uncontrolled disease at time of infection. 153 patients (40%) underwent SCT prior to the BSI, 85% were allogeneic transplants. 38% of SCT patients with a BSI had grade 2-4 GVHD at day 100. 140 patients (36%) were on prophylactic/treatment antibiotics and 249 patients (65%) were on prophylactic antifungals at time of infection. 33 patients (9%) died within 30 days of developing a BSI. In those that died within 30 days, 6 had a "do not resuscitate" directive in place at the time of the BSI. 70 patients (18%) were admitted to the intensive care within 48 hours of the BSI and stayed a median of 4 days (IQR:2-11). The CVC was removed within 7 days in 53 patients (14%).

Conclusion: This is the first multicenter study to evaluate the demographics and outcomes of PHO patients that develop a BSI. These data help support high risk of poor outcomes following a BSI, and enforce BSI prevention measures.

SICKLE CELL ANEMIA NEONATAL SCREENING AND CARE INITIATIVE IN MALAWI: PROGRAM DEVELOPMENT AND LOCAL CAPACITY BUILDING IN DETECTION AND PREVENTIVE SERVICES

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Background: Of the 225,000 children born annually with sickle cell anemia (SCA) in Sub-Saharan Africa, 50-90% die before adulthood due to under-diagnosis and insufficiently implementing simple preventive interventions. Severe infections and fulminant sepsis can kill these youth in less than 12 hours. In Malawi SCA incidence is unknown; newborn screening programs are non-existent. Devising a sustainable initiative to detect, screen, and treat SCA is urgent in Blantyre, Malawi's second largest city of greater than 1 million residents, to address unmet SCA public health and medical needs.

Objectives: To develop and implement a population-based SCA newborn screening and neonatal infection prevention program in Blantyre, Malawi to set the foundation for sustainable longitudinal care.

Design/Method: The University of California Los Angeles, the Pediatrics Department at Blantyre's Queen Elizabeth Central Hospital, and a UK Malawi based charity, Friends of Sick Children in Malawi initiated a collaborative effort in September 2015 to build local SCA screening capacity for 1,500 Blantyre children age 0 to 12 months. Three screening methods (RFLP, cellulose acetate, and gel electrophoresis) were tested to determine the most accurate and feasible method. A local research nurse conducted SCA education, mapped residences and conducted home visits, built population level trust, and promoted long-term SCA infection prevention adherence. Newborns testing positive were enrolled in SCA clinic for infection prevention, chiefly penicillin prophylaxis and vaccines.

Results: In August - September 2015, nearly 50 Blantyre nurses, doctors, lab technicians, and community health workers were educated about SCA diagnosis detection, screening, and preventive care. An SCA registry was created; enrollment protocols were devised. From September to December 2015, 107 children age 0 to 12 months were screened for SCA. Preliminary results reveal at least 5 positive; full confirmatory testing is still underway.

Conclusion: Instituting early detection of SCA in a large Malawi city appears feasible using a multi-institutional collaborative that builds local SCA public health and medical care capacity. Longitudinal data is needed to assess how well screening and infection prevention can reduce morbidity and mortality in children under age 1, and to inform the cost and value of service expansion throughout Malawi.

NATIONAL AND INTERNATIONAL INTERVENTIONS TO ACHIEVE HPV VACCINE UPTAKE: A SYSTEMATIC REVIEW

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Background: The HPV vaccine is a safe and effective cancer prevention method that is underused in the United States. Despite increased understanding of barriers to vaccination, rates remain low. Globally, developed and developing nations have achieved high rates of vaccination.

Objectives: Identification of effective strategies is necessary to optimize uptake of the HPV vaccine. This study is a systematic review of the literature for national and international interventions that have successfully increased HPV vaccine uptake.

Design/Method: We conducted searches using a standardized protocol in 3 electronic databases: PubMed, Scopus and Embase. We identified interventions designed to increase HPV vaccine uptake among adolescents 11-26 years old. All study designs were acceptable. Only manuscripts that included post intervention vaccination rates were included. Two authors independently reviewed each article for data extraction and quality assessment. Three reviewers independently classified interventions according to predefined criteria.

Results: Manuscripts were classified according to the Community Guide and results were reported according to the RE-AIM framework. 51 manuscripts met eligibility criteria: 2 informational interventions, 18 behavioral interventions and 31 environmental interventions. Factors associated with HPV vaccine uptake were increased vaccine availability, decreased financial barriers and interventions targeting providers and patients.

Conclusion: Population based vaccination strategies that increased vaccine availability reached the greatest number of adolescents and were most successful in achieving high rates of vaccination. Interventions that targeted providers and patients were also successful.

A SURVEY OF PEDIATRIC RESIDENT PHYSICIANS' AND NURSES' KNOWLEDGE OF SEVERITY ASSESSMENT OF ACUTE CHEST SYNDROME AND ROLE OF INCENTIVE SPIROMETRY IN MANAGEMENT

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Background: Acute chest syndrome (ACS) is the most common cause of death in children with sickle cell disease (SCD). Hematologists need to be aware of assessment of ACS severity to guide therapy and measures to prevent ACS. An ACS severity assessment tool has been utilized in research but not validated in the real-world setting. Existing guidelines including from NHLBI do not provide a uniform grading for ACS severity. In contrast, evidence for role of incentive spirometry in preventing and decreasing severity of ACS is strong and incentive spirometry recommendations are included in guidelines.

Objectives: To assess the current knowledge of resident physicians and nurses regarding two aspects of ACS: Severity assessment and Incentive spirometry.

Design/Method: Our tertiary care hospital admits over 20 patients with SCD per month on the pediatric floor. Pediatric residents and nurses learn about ACS management and prevention through 2 didactic sessions on SCD/year and bedside teaching. An anonymous survey was administered to 40 pediatric residents/20 pediatric nurses who routinely engage in care of ACS patients. This was followed by a house-staff education session on ACS.

Results: SEVERITY SCORING: 15% residents/5% nurses had been educated on the use of ACS severity assessment in past. An overwhelming 92% felt that a scoring system would be useful for assessing their patient's condition and guiding management, however only 5% residents /3% nurses had used a severity scoring for ACS in the past. A clinical vignette on ACS was answered incorrectly by 60% of the residents and nurses. INCENTIVE SPIROMETRY: 91% responded they were aware that incentive spirometry can decrease the severity of and improve outcomes of ACS. 90% of residents/95% nurses thought that the patients are compliant less than 50% of the time with incentive spirometry which is almost always ordered.

Conclusion: The knowledge of residents and nurses regarding severity assessment of ACS is limited and greater efforts are needed to educate them to include this assessment in their management decisions. The importance of incentive spirometry is recognized by house-staff, however, patient compliance is below desirable. Reinforcement is needed to improve ACS outcomes. Our pilot study identifies room for quality improvement at several steps in the care process for SCD.

FEBRILE NEUTROPENIA IN CHILDREN WITH CANCER: THE ROLE OF HOSPITALIZATION UNTIL FEVER RESOLUTION

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Background: Febrile neutropenia (FN) is a frequent complication of cancer treatment and contributes to the burden of hospitalization in children with cancer. Although most children with FN do not have serious infections, the best strategy to reduce hospital time in this population is not established.

Objectives: To develop a rational strategy to reduce hospital time for pediatric oncology patients with FN, we described our institutional experience and explored clinical features associated with a higher risk of infectious complications in this population.

Design/Method: We conducted a retrospective cohort study of patients admitted to UCSF Benioff Children's Hospital Oakland (Oakland, California, United States). Records of all FN admissions from 1/2009 to 7/2015 were reviewed. Patients with nonmalignant marrow dysfunction, histiocytosis, FN as a symptom of cancer relapse, previous hematopoietic stem cell transplantation, and patients receiving induction chemotherapy for acute lymphoblastic leukemia were excluded. Serious infection was defined as bacteremia, viremia, septic shock, bacterial/fungal deep-tissue infection (proven or probable), or infection requiring intensive care.

Results: We analyzed 194 FN episodes among 139 subjects (42% female) with median age 5.7 years (interquartile range [IQR] 3 – 12.7). Median length of stay was 6 days (IQR 4 – 11), fevers resolved a median 2 days (IQR 1 – 4) after admission, and patients spent a median 3 days (IQR 2 – 6) hospitalized after fever resolution. Serious infections, most commonly bacteremia, complicated 45 admissions (24%) and were diagnosed prior to fever resolution in 76% of cases. Prior history of serious infection, fever recurrence after 1 day afebrile, and temperature 39.5 C or above during the first day of the episode significantly increased the risk of serious infection.

Conclusion: Only a quarter of subjects with FN developed serious infections, and most of these infections were diagnosed prior to fever resolution. For patients lacking high-risk features, hospital discharge 24 hours after fever resolution may safely reduce the burden of hospitalization. Prospective data are needed to further assess the safety and feasibility of this approach.

A SYSTEMATIC REVIEW OF THE LITERATURE FOR SEVERITY PREDICTORS IN PEDIATRIC SICKLE CELL ANEMIA PATIENTS

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Background: All patients with HbSS (SCA) share the same genetic mutation but the clinical phenotype is variable and difficult to predict early in life. The only available cure for SCA is hematopoietic stem cell transplant (HSCT). Early trials of HSCT in SCA patients revealed that SCA patients have higher complication rates which increase with age than other patients undergoing HSCT. If a reliable severity predictor existed, HSCT could be performed in those patients with SCA who are at highest risk of SCA complications prior to the onset of vasculopathy and organ damage.

Objectives: The goal of this project was to systematically review the literature to determine which disease severity predictors have been validated in pediatric patients with SCA.

Design/Method: A search of PubMed, Cochrane Clinical Trials Register, and Scopus was performed using the following terms: sickle cell anemia or disease, complications, mortality, classification, prognosis, severity of illness, predictive value of test, risk, proportional hazards model, stroke risk, hematopoietic stem transplantation methods. Data were extracted using a standardized data collection form.

Results: The full text of 53 of the 590 (9.0%) references identified was reviewed based on the title/abstract. Thirty-three articles (62.3%) are included in this analysis; 20 articles were excluded based on pre-determined exclusion criteria. Fetal hemoglobin (HbF) and alpha globin gene number were the most commonly studied severity predictors (7 studies each) with hemoglobin (6), white blood cell count (5) and absolute reticulocyte count (4) rounding out the top 5 studied predictors in this systematic review. Nearly three quarters (5/7) of the HbF studies reported beneficial effects with increasing HbF levels; however, increased HbF levels were not associated with lower rates of hospitalization or stroke risk in two articles. Increasing ARC was positively associated with increasing risk of cerebro-vascular complications in all 3 of the reports in which it was studied, while alpha thalassemia trait was protective against stroke and abnormal TCD, but not rate of painful crisis.

Conclusion: The ability to predict SCA complications was mixed for all studied variables, including HbF. More reliable predictors of disease complications are urgently needed to guide therapeutic decisions in pediatric patients with SCA.

MEASLES IMMUNE STATUS IN AN INNER CITY PEDIATRIC ONCOLOGY PATIENT COHORT DURING THE MEASLES OUTBREAK OF 2015

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Background: Survivors of pediatric cancer are at risk of long-term consequences of therapy one of which is loss of pre-existing protective antibody predisposing them to illnesses such as Measles. Measles in recipients of immunosuppressive chemotherapy can have mortality rates up to 50%. Up to 35% of children < 7 Years lose humoral immunity to measles as a result of chemotherapy induced alterations in immune system. Despite proven strategies of the WHO for improving measles vaccine coverage, the disease still continues to circulate leading to outbreaks in developed countries. In 2015, the US experienced a major measles outbreak related to an amusement park in California. 189 cases (40% < 18 years) were reported across 24 states including our state. Measles is highly contagious from 48 hours prior to the first symptoms. Our pediatric oncology practice shares office and floor space with other pediatric practices, placing our patients at risk for measles infection.

Objectives: Measles protective humoral immune status was checked in our patients because of the new risk of Measles in the period of the outbreak from January-June 2015. At the time, it was not our standard practice to check measles titer prior to initiation of chemotherapy.

Design/Method: Patients <21 years receiving chemotherapy between January 2015-June 2015 in our department were included in the prospective review. We defined immunity according to our lab standards.

Results: A total of 21 (13 female) patients were included. Three patients (15%) had non protective measles antibody levels. 2 of the patients were < 3 years at diagnosis and had leukemia, one was an adolescent with sarcoma. All three came weekly to the clinic and were admitted to floor for chemotherapy during this period and thus shared the common clinic and floor space. None of the patients developed measles. All are in remission.

Conclusion: Measles outbreaks in the US pose a grave threat to recipients of chemotherapy. This danger is increased in the nosocomial setting with shared clinical space. Universal vaccination, stringent isolation in pediatric clinical areas and standard practice of checking measles immunity in all patients prior to chemotherapy initiation may prevent this devastating disease in this sensitive population.

ADENOTONSILLECTOMY IN SICKLE CELL DISEASE: IS TRANSFUSION NEEDED?

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Background: Adenotonsillar hypertrophy in patients with sickle cell disease (SCD) can predispose to several complications including obstructive sleep apnea, vasoocclusive crisis (VOC), pulmonary hypertension, and acute chest syndrome (ACS). Traditionally, all children with sickle cell disease (SCD) indicated for adenoidectomy and/or tonsillectomy have been exposed to exchange transfusion preoperatively aiming at reduction of both surgical and SCD-related complications in the postoperative period.

Objectives: To address the need for transfusion in patients with SCD undergoing adenotonsillectomy and to report its risks and benefits.

Design/Method: All patients with SCD admitted in Sultan Qaboos University Hospital for adenoidectomy, tonsillectomy or both from July 2006 till January 2015 were included in the study. Between 2006 and 2012, patients' files were reviewed for retrospective data recoding. After 2012, the study has been prospective.

Results: Our cohort included 70 patients with SCD (39 males and 31 females), with an age ranging between 4 and 18 years. According to their transfusion need prior to surgery, the patients were categorized into 3 groups; namely: no transfusion (group I), simple transfusion (group II) and exchange transfusion (group III). The 3 groups included 23, 33 and 14 patients respectively. There was no significant difference between the 3 studied groups as regards main post-operative complications of SCD. Vasoocclusive crisis occurred in a comparable number of cases in all three groups (2, 1 and 1 respectively). Acute chest syndrome developed in 1 patient in both non-transfusion group and exchange transfusion group, and 2 patients in simple transfusion group. The pre-transfusion average hemoglobin value was significantly lower in simple transfusion group in comparison to the other 2 groups. Of note, patients with simple transfusion required almost half blood volume compared to those with exchange transfusion (9.1 ± 3.3 ml/kg vs. 17.7 ± 6.7 ml/kg), with statistically highly significant difference between both groups ($p=0.000$).

Conclusion: We conclude that it is safe to do adenotonsillectomy without simple or exchange transfusion pre-operatively in patients with SCD, maintaining a hemoglobin level above 8 g/dl. Transfusion does not improve surgical or SCD-related outcome.

A POPULATION BASED STUDY OF UPTAKE OF HUMAN PAPILLOMA VIRUS (HPV) VACCINE IN CANCER SURVIVORS

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Background: The quadrivalent HPV vaccine was FDA approved in 2006 and 2009 for females and males respectively. The national immunization survey indicates vaccine initiation rates plateaued at 53% in US females (MMWR 62(29); 591-595, 2013). Cancer survivors represent a unique population who will benefit from a cancer preventive vaccine.

Objectives: To estimate the proportion of institutional cancer survivors who initiated and completed a HPV vaccine course and to evaluate the North Carolina Immunization Registry (NCIR) in ascertainment of HPV uptake.

Design/Method: Following IRB approval, we identified cancer patients born between 1984 and 2002 in the institutional cancer center registry. Patients who did not attain first remission, had less than 6 months of follow-up, or who had no NCIR record were excluded from analysis. Identified patients were linked to their NCIR record via a manual search. Valid linkage was confirmed by name, birth date, and address matching of the registry to the institution medical record. NCIR record was abstracted for receipt and number of HPV vaccine doses and other childhood vaccines. Institutional medical records were abstracted for demographic characteristics, cancer diagnosis and treatment, report of receipt of HPV vaccine, and dates of recurrence, last cancer treatment, and last visit to an institutional oncology clinic. We used descriptive statistics to summarize the study population and proportion with vaccine uptake.

Results: Eligible patients (n=985) were a mean of 10.1 years of age at cancer diagnosis; half were female. Nine percent of females and 0.2% of males had received HPV vaccine prior to their cancer diagnosis. Among those not vaccinated prior to diagnosis, NCIR linkage indicated that 21% of cancer patients initiated HPV vaccination, 54% of whom completed the series of three doses. The proportion of cancer survivors who initiated HPV vaccination was 29% among females and 14% among males. Predictors of vaccine uptake are pending analysis.

Conclusion: A substantial number of cancer survivors have not received the HPV vaccine, and represents a missed opportunity. Access to robust state immunization registries allows oncology and survivorship clinics to assess gaps in vaccination, target vaccine delivery, and fulfill Healthy People 2020 objectives.

MANAGEMENT OF INTRAHEPATIC CHOLESTASIS IN PATIENTS WITH HbSS DISEASE: TWO CASE REPORTS

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Background: Intrahepatic cholestasis, or sickle hepatopathy, is a rare complication seen in patients with hemoglobin SS. In this condition, sickling within hepatic sinusoids can lead to stasis, hypoxia and swelling of the liver parenchyma, thereby resulting in pressure on the intrahepatic bile ducts, leading to intracanalicular cholestasis. Patients ultimately present with severe conjugated hyperbilirubinemia; however, they can have varied degrees of clinical compromise.

Objectives: There is little data on the evolution of sickle hepatopathy in pediatric patients. Furthermore, there is no consensus on the optimal management of intrahepatic cholestasis. We present two cases of pediatric patients with intrahepatic cholestasis secondary to sickle cell disease hoping to better elucidate the course of disease progression and management in the future.

Design/Method: A retrospective chart review was performed on two teenaged male patients with hemoglobin SS at Texas Children's Hospital in Houston, Texas.

Results: The first patient was a 15 year-old male with hemoglobin SS and Gilbert syndrome presenting with fever and cough. He was admitted for management of acute chest syndrome. During hospitalization, he had persistently elevated conjugated bilirubin levels, peaking at 52.4 mg/dL. Liver enzymes were elevated and PT/INR remained normal. Liver biopsy was done following discharge showing intrahepatic cholestasis with sinusoidal sickle cell aggregates. The second patient was an 18 year-old male with hemoglobin SS and Gilbert syndrome. He was on chronic transfusions and was transfused five days prior to presenting with scleral icterus and dark urine. His CBC and hemoglobin profile were concerning for hyperhemolysis. Total bilirubin peaked at 40.8 mg/dL, with a conjugated bilirubin of 38.3 mg/dl, suggesting that hyperhemolysis was not causing his hyperbilirubinemia. AST, ALT and PT/INR were mildly elevated. MRCP was negative for obstruction. Both patients were managed conservatively and discharged on ursodiol with improvement.

Conclusion: Adult sickle cell patients with intrahepatic cholestasis can often have a more severe course than pediatric patients often requiring liver transplant. In contrast, intrahepatic cholestasis in pediatric patients is more benign in its course. Without signs of hepatic dysfunction or encephalopathy patients could be managed conservatively with close observation.

CLINICAL OUTCOMES OF PEDIATRIC PATIENTS WITH FEVER AND SUSPECTED NEUTROPENIA IN THE EMERGENCY DEPARTMENT--DOES TIME TO ANTIBIOTIC ADMINISTRATION MATTER?

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Background: In adults with febrile neutropenia (FN), decreasing time to antibiotic administration (TTA) appears to be associated with improved outcomes including decreased mortality, length of stay, and bacteremia. However, in pediatric FN patients, multiple reports have failed to convincingly show that decreasing TTA improves length of stay (LOS), bacteremia, or mortality. In a pediatric emergency care setting, prompt identification of FN and rapid administration of antibiotics has become a recommended practice (“gold standard” <60min), and many quality improvement (QI) projects invest ample time and money into meeting this recommendation.

Objectives: This study sought to identify whether a TTA <60min was significantly associated with improved outcomes in pediatric FN.

Design/Method: A retrospective electronic chart review of pediatric FN episodes presenting from November 2013 through May 2015 at Children's Hospital and Research Center Oakland Emergency Department was completed to extract patient demographics, TTA, and outcomes data. This was performed in tandem with a QI project that implemented a standardized process and order set during this time, which resulted in a significant decrease in TTA. Clinical outcomes including admission, LOS, fluid resuscitation, pediatric intensive care unit (PICU) admission, mortality, and administration of additional antibiotics were examined.

Results: A total of 229 occurrences of fever and suspected neutropenia were recorded. Between three subgroups of the 90 admitted neutropenic patients who had TTA <60min, TTA 60-90min, and TTA >90min, there was no significant difference in any measured outcome including, notably, need for PICU admission, mean fluid resuscitation, mean LOS and mortality.

Conclusion: While TTA is currently used as a surrogate quality of care (QOC) measure for emergency care of patients with fever and suspected neutropenia, evidence that TTA <60min improves outcomes in a pediatric population as compared to TTA >60min is lacking. Further larger multicenter prospective studies are required to determine the value of this presumed quality control measure.

CORRELATION OF BMI WITH EARLY BIOMARKERS IN PEDIATRIC PATIENTS WITH SICKLE CELL DISEASE

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Background: Children with sickle cell disease (SCD) have significantly lower height, weight, and body mass index (BMI) compared with standard growth curves. Previous publications have revealed a consistent pattern of diminished growth among individuals with SCD with evidence linking growth failure to poor nutrient intake, hemolysis, chronic anemia, and a high metabolic rate. Several studies have evaluated the association between BMI and clinical manifestations of sickle cell disease. It has been demonstrated that in children with sickle cell disease higher BMI is associated with higher visual-motor abilities and academic achievement scores¹. Specific sickle cell therapies such as hydroxyurea and blood transfusions could improve growth and cognitive function². The ability to predict growth and development during the first years of life would allow physicians to provide early dietary nutritional interventions and institute early hydroxyurea therapy.

Objectives: The goal of our study is to evaluate correlations of early biomarkers of disease severity with BMI in children with SCD.

Design/Method: We performed a retrospective chart review of patients with SCD followed at Marian Anderson Center at St. Christopher's Hospital for Children, Philadelphia. We identified 129 consecutive patients who met the inclusion criteria. Spearman correlations were calculated to explore associations of BMI percentile in different age groups with steady state biomarkers of anemia, hemolysis and inflammation between 1 and 4 years of life. In addition, steady state hemoglobin, reticulocyte counts, white blood cell count, absolute neutrophil count and platelet counts were each recoded into three categories ("high," "medium" and "low") and differences in BMI percentile associated with these categories were assessed with Kruskal-Wallis tests.

Results: No significant correlations were found between any of the steady state markers and BMI in either set of analyses.

Conclusion: We saw no significant correlation between markers of anemia, hemolysis and inflammation during first years of life and BMI in different age groups. It is important to note that the BMI in most of our patients was either normal or close to normal compared with the WHO standards, possibly impeding any demonstration of statistically significant correlations. Further prospective studies and larger sample size are required to clearly elucidate this association.

INCREASING OBSERVATION VERSUS PHARMACOLOGIC THERAPY AT PRESENTATION WITH A STANDARDIZED CLINICAL ASSESSMENT AND MANAGEMENT PLAN (SCAMP®) IN LOW RISK PATIENTS WITH IMMUNE THROMBOCYTOPENIA (ITP)

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Background: Despite published recommendations, there is wide practice variation in the treatment of pediatric ITP. SCAMPs are tools used to evaluate variation in clinical practice and prospectively evaluate strategies for improving care.

Objectives: To compare initial rates of an observation-only management strategy (compared to pharmacologic therapy) in newly diagnosed pediatric ITP cases before and after the development of a SCAMP.

Design/Method: Retrospective data were collected on children with ITP from 2003-2009. We developed a SCAMP for ITP implemented in 2012 and revised in 2014. Eligibility criteria included platelets <30 kcells/ μ L at diagnosis, no prior treatment, duration from onset <4 weeks, and age 1-16 years. Bleeding was graded using the Buchanan and Adix score (J Pediatr, 2002). The first SCAMP guideline recommended observation unless bleeding score was ≥ 3 , for which IVIG or steroids were recommended. The second iteration subdivided grade 3 bleeding scores into lower and higher risk groups, with observation recommended for low-risk grade 3 patients.

Results: Prior to the SCAMP, 39% (204/524) of patients were initially observed. After implementation of the first SCAMP, there was a significant increase in patients initially observed (55%, $p=0.05$). Of 40 patients enrolled, 23(57%) had grade 3-4 bleeding, and 17 (43%) had grade ≤ 2 bleeding. In the second iteration, initial observation rates significantly increased to 74% ($p=0.0001$); however, this cohort exhibited less bleeding. Only 35% (11/31) of patients presented with an initial bleeding score ≥ 3 . Of the 7 patients with low-risk grade 3 bleeding, only 3 received pharmacologic treatment, whereas all 4 high-risk patients were treated.

Conclusion: Our institution historically treated the majority of newly diagnosed ITP patients with pharmacologic therapy (39% observed). The initial SCAMP corresponded to a difference in practice, with increased fraction observed. Buchanan and Adix Grade 3 bleeding covers a wide range of severity. The modified SCAMP took this into account, with a concomitant ability to discriminate high and low risk, and treat accordingly. While rates of initial observation increased to 74%, patients in this group also had lower bleeding scores. Implementation of the ITP SCAMP encourages consistency in treatment; future analysis will determine the extent to which this changes clinical practice.

HIGH SCHOOL GRADUATION RATE OF CHILDREN IN A COMPREHENSIVE SICKLE CELL DISEASE PROGRAM COMPARES FAVORABLY TO PEERS WITHOUT DISEASE

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Background: Children with sickle cell disease may experience complications with cognitive development and academic performance. As many as 50% of children living with sickle cell disease will fail at least one grade. Many patients will experience strokes, silent cerebral infarction, and/or neuro-cognitive impairment. These complications can result in poor academic performance. School attendance can be adversely affected by frequent pain crises.

Hospitalizations for pain last approximately 5.9 days, while pain may persist up to 10 days. According to the National Center for Education Statistics, African American students had a 68% graduation rate in the 2011-2012 academic year, nationwide. The graduation rates for African American students in Cleveland Municipal and Akron city school districts were 64% and 76%, respectively. Patients with sickle cell disease are expected to have lower graduation rates.

Objectives: Measure the graduation rate of children receiving care at a Sickle Cell Program, and compare this rate to disease free peers.

Design/Method: Our clinic is located in Akron, OH. In addition to disease management, our clinic offers educational assessment, nurse school visits, and IEP/504 plan assistance. We reviewed our population for individuals who would have been expected to graduate between 2011 and 2016 based on age. This review was conducted from December 2015-January 2016.

Results: Twenty-seven patients were identified. Seven patients were excluded (3 transitioned to adult care with no record of graduation, 3 lost to follow up, and 1 moved geographically). We reviewed 20 patient records (mean age = 20.6; 17-23 yrs.). Eighteen (90%) patients graduated, or were on track to graduate on time by spring 2016.

Conclusion: Sickle cell patients receiving comprehensive care can achieve graduation rates comparable to disease free peers. Disease management, educational assessment, nurse school visits, and IEP/504 plans may contribute. Future studies should examine which services are likely to improve achievement in children with sickle cell disease.

ROUTINE TRANSFUSION EXPERIENCE IN PEDIATRIC PATIENTS USING PLATELET COMPONENTS PREPARED WITH AMOTOSALEN AND UVA PATHOGEN INACTIVATION

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Background: A photochemical treatment process (PCT) utilizing amotosalen and UVA light (INTERCEPT Blood System™) has been developed for inactivation of viruses, bacteria, parasites, and leukocytes that can contaminate blood components intended for transfusion. Treated components have demonstrated retention of therapeutic efficacy in randomized controlled clinical trials and European post-marketing surveillance studies, and this process is in use in >100 centers in 20 countries. As of December 2014, INTERCEPT has been FDA approved for use in the US.

Objectives: The objective of this study was to further characterize the safety profile of INTERCEPT-treated platelets components (PCT-PLT) administered in the pediatric patient population.

Design/Method: This open label, observational hemovigilance program of PCT-PLT transfusions was conducted in 21 clinical centers in 11 countries. All transfusions were monitored for adverse events (AEs) occurring within 24 hours post-transfusion and for serious adverse events (SAEs) up to seven days post transfusion. All AEs were assessed for severity (Grade 0-4), and causal relationship to PCT-PLT transfusion. There were no inclusion criteria other than the need for transfusion.

Results: Pediatric patients (n = 242) received 642 PCT-PLT transfusions. The mean age was 8.1 years (range <1-18). Approximately half of the patients had hematology-oncology diseases (48.8%), of which some required conventional chemotherapy (40.9%) or hematopoietic stem cell transplantation (12.8%). The primary diagnosis for the remaining patients was general medical (45.0%), cardiovascular surgery (4.5%), or solid organ transplantation (0.8%). The mean number of PCT-PLT transfusions received was 4.6 (range 1 - 66). By sign/symptom the relative frequency of AEs attributed to platelet transfusion were pruritus/urticaria/rash (5.8%), fever/chills (4.5%), tachycardia (0.8%), or dyspnea (0.8%). No patient experienced an SAE judged to be related to PCT-PLT. No AEs occurred in neonate patients under 28 days old (n=46). No case of transfusion-related acute lung injury or transfusion-transmitted infection, and no deaths were attributed to the transfusion of PCT-PLT.

Conclusion: This longitudinal hemovigilance safety program for routine transfusions of PCT-PLT demonstrated a low rate of AEs, and a safety profile consistent with that previously reported for conventional platelet components.

PREDICTORS OF COMPLICATIONS IN CHILDREN WITH SICKLE CELL DISEASE AND SICKLE CELL TRAIT HOSPITALIZED AT ST DAMIEN HOSPITAL FROM JANUARY 2014 TO DECEMBER 2014

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Background: More than 300,000 children are born each year with severe forms of hemoglobinopathies, for which genes are carried by nearly 5 % of the world population (WHO, 2011). Sickle cell disease (SCD) is a genetic hemoglobinopathy that has serious psychosocial and intellectual development consequences.

Objectives: The principal objective of this study is to determine predictors of complications such as infection and sequestration crisis in children with SCD and sickle cell trait (SCT) who were hospitalized at St Damien Hospital (SDH) in Port-au-Prince, Haiti, from January to December 2014.

Design/Method: A cross-sectional study was conducted on children younger than fifteen years of age with SCD and SCT hospitalized in SDH during the study period. Chart reviews were performed to collect key variables such as gender, age, genotype and level of anemia. The prevalence among hospitalized children and the proportion of complications were determined. Odds ratios for the associations between clinical and demographic characteristics and complications are reported. Statistical significance of these associations was evaluated using Mantel-Haenszel chi square.

Results: The prevalence of SCD and SCT among the children hospitalized in SDH was 4.30%. Among the 141 children included in this study, the SS genotype was the most frequent (74.47%), and the mean hemoglobin (Hb) level was 6.3 g/dL. The symptomatology was dominated by fever (52.48%), mucocutaneous pallor (48.23%), jaundice (45.39%) and cough (20.57%). 60.99% of the children had severe anemia (Hb level of less than 7g/dL), 74.4% of them with the genotype SS. 53.19% of the children developed complications. The mortality rate was 0.02%, all the deceased having the genotype SS. The odds of developing a complication was significantly higher among children aged 5 years old or more (OR=3.76; P=0.0002), and an Hb level of less than 7 g/dL was found to be a significant protective factor (OR=0.22; P=0.000051).

Conclusion: The main cause of hospitalization of children with SCD and SCT appears to be severe decompensated anemia. The complications occur mainly in children of 5 years old and more, and an Hb level of less than 7g/dl was found to be a protective factor against the complications mainly due to vaso-occlusion.

IMPLEMENTATION OF PARAMETER TRANSFUSION ORDERS FOR STEM CELL TRANSPLANT RECIPIENTS RESULTS IN INCREASED NURSING AUTONOMY, DECREASED TRANSFUSION DELAYS, AND IMPROVED PATIENT CARE

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Background: Oncology and Stem cell transplant (SCT) inpatients require frequent complete blood count (CBC) monitoring and blood product transfusions. This can be a cumbersome task for the clinical team, at times resulting in care delays.

Objectives: Create, pilot and establish a transfusion parameter order set on a high acuity inpatient oncology unit for the SCT patient cohort enabling nurses to independently initiate transfusions, and expedite patient care while allowing the clinical team to focus on more complex patient care issues.

Design/Method: An order set entailing nursing transfusion parameter process was created and implemented for SCT recipients. This order set includes parameters for packed red blood cell (PRBC) and platelet transfusions based on patient specific clinical needs including pre-medications and post-transfusion diuretics options. Parameter orders were initiated on September 15th 2013. General oncology patients continued preexisting process with clinicians following up daily results, and then generating individual orders for clinically indicated transfusions. Data points were collected for both groups of patients (SCT and General oncology): lab draw time, transfusion order submit time, blood product component distribution time, and time of administration of blood product. Data was collected at 3 different time points: prior to implementation, during pilot, and 2 years post order set establishment.

Results: Median time between lab draw at baseline in the SCT group was 315 minutes (range 30-996), this decreased to 135 minutes (range 40-842) during the pilot and further decreased to 118 min (range 45-882) with established order set; significant for a 63% decrease. In the comparison oncology group no significant decrease was observed over identical time-periods. Time from lab draw time to product administration for SCT group from pre-implementation to following establishment decreased by a median of 47 minutes.

Conclusion: Implementation of parameter order sets for blood product transfusion facilitates nursing autonomy to initiate indicated transfusions, decreases transfusion delays, and improves patient care delivery. Based on the positive results of this successful quality improvement initiative, there is great potential for systems that increase nursing autonomy. Future directions include a wider implementation of such order sets and surveys to understand nursing, clinician, and patient perceptions of parameter order sets on patient care delivery.

BLOOD EXCHANGE TRANSFUSION SAFETY FOR PRIAPISM IN SICKLE CELL DISEASE: A SINGLE INSTITUTION REVIEW

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Background: Males with sickle cell disease (SCD) have a 29-42% lifetime probability of developing priapism (1). Management of priapism is controversial and not evidence-based. Red cell exchange transfusion has been used to manage sickle related complications but several case reports have described acute neurological events following exchange transfusion for priapism (2,3), which limits enthusiasm for routine adoption of this therapy. Presently there are little data characterizing exchange transfusions utility and safety in treating priapism.

Objectives: To determine and compare the incidence of adverse events seen in patients with SCD receiving red cell exchange transfusion for refractory priapism and secondary stroke prophylaxis.

Design/Method: The University of North Carolina's blood bank database was used to identify patients with SCD who were enrolled on chronic exchange transfusion program for refractory priapism from years 2004- 2015. An age-matched cohort of seven patients enrolled in exchange protocol for secondary stroke prophylaxis was identified. The first exchange procedure for both groups will be used for comparison. Adverse events such as vital sign instability and acute neurologic events were collected. Data collected will be analyzed to determine if there is a difference in adverse events in the priapism group compared to those receiving exchange transfusions for secondary stroke prophylaxis.

Results: We identified seven patients with SCD who were enrolled on a red cell exchange protocol for refractory priapism. We evaluated 6 episodes of exchange transfusions per patient. The mean age was 24; six patients have HbSS and one patient has HbSC. Two episodes of hypotension were recorded in one patient on two separate procedures. This resolved after decreasing the inlet pump flow rate to the patient. No adverse neurologic events were recorded. One patient experienced lip tingling that resolved with calcium carbonate tablets. The comparison data for the patients being transfused for secondary stroke prevention is being collected.

Conclusion: Although exchange transfusion is infrequently used for treating refractory priapism in patients with SCD, the incidence of adverse events appears to be minimal. Analysis is ongoing to compare the safety of red cell exchange transfusion for priapism to stroke. Future controlled trials using blood exchange transfusion for refractory priapism are needed. References: 1. Olujohungbe, Br. J. Haematol, 2013. 2. Rackoff, J Pediatr, 1992. 3. Siegel, J Urol, 1993

BESTIRON: A SINGLE-CENTER, DOUBLE-BLIND, RANDOMIZED, 12 WEEK SUPERIORITY STUDY COMPARING NOVAFERRUM® TO FERROUS SULFATE IN YOUNG CHILDREN WITH NUTRITIONAL IRON DEFICIENCY ANEMIA (IDA)

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Background: Iron deficiency anemia (IDA) is prevalent in young children whose diet includes prolonged breastfeeding without iron supplementation and/or excessive cow milk consumption, yet few data guide clinical decision-making regarding optimal management. The BESTIRON study (Clinicaltrials.gov NCT01904864) was initiated to compare ferrous sulfate with NovaFerrum®, an oral iron polysaccharide hypothesized to be better absorbed and tolerated than iron salts.

Objectives: The primary aim was to compare the efficacy of NovaFerrum® to ferrous sulfate in improving hemoglobin concentration during a 12 week treatment period. Secondary aims included comparison of adverse effects, reconstitution of iron stores and adherence between groups as well as the efficacy of a once daily low-dose regimen of 3 mg/kg elemental iron.

Design/Method: This study was a randomized, controlled, double-blinded single center superiority trial. Eligible patients 9 to 48 months of age with confirmed nutritional IDA by history and laboratory studies were randomized 1:1 to receive either ferrous sulfate or NovaFerrum (each 15 mg/mL of elemental iron) for 12 weeks.

Results: Eighty patients (the targeted accrual) enrolled in the study. They were predominantly male (55%) and Latino (Caucasian/White) (57%), with a median age of 19 months (range 11 – 41). The primary outcome was change in hemoglobin concentration upon serial measurements over 12 weeks. Given a mean baseline hemoglobin value of 7.8 g/dL, we predicted the mean hemoglobin values to be 12 g/dL and 11 g/dL at week 12 respectively in the NovaFerrum® and ferrous sulfate groups. The pooled results to date demonstrate median baseline hemoglobin of 7.8 g/dL with improvement to a week 12 median hemoglobin value of 11.6 g/dL. Complete results will be available in late January 2016 and presented at the ASPHO Annual meeting.

Conclusion: IDA is a major health problem in young children globally. Limited scientific data support current treatment approaches for IDA. Ferrous sulfate at 3-6 mg/kg/day in divided doses is considered “standard of care”. Thus, lower once daily iron dosing and/or NovaFerrum® proving superior in the BESTIRON clinical trial could have a substantial impact on the treatment of young children with nutritional IDA. We acknowledge Gensavis Pharmaceuticals, LLC for their support of this investigator-initiated study.

COEXISTING JUVENILE DERMATOMYOSITIS AND SICKLE CELL DISEASE: MAINTAINING A HIGH INDEX OF SUSPICION

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Background: Sickle cell disease (SCD) is a chronic disease frequently marked by multisystem morbidity. Vaso-occlusive crisis (VOC) is a common cause of musculoskeletal pain in SCD.

However, it is important to keep a broad differential, considering other etiologies of pain.

Objectives: To describe a novel presentation of Juvenile Dermatomyositis (JDM) in a patient with SCD. This case illustrates the challenge of identifying JDM in the context of multiple SCD-related comorbidities.

Design/Method: Case report.

Results: An 11 year old female with SCD, eczema, and avascular necrosis (AVN) of the knees, hips and shoulders presented with musculoskeletal (MSK) pain, limp and diffuse erythematous macular skin lesions. She had been lost to follow up for over a year due to deteriorating social circumstances. She was diagnosed with and treated for VOC and acute chest syndrome. While her VOC and eczema resolved, she continued to have severe diffuse MSK pain. She had persistent violaceous discoloration of her eyelids and erythematous maculopapular lesions overlying the dorsum of her MCP and PIP joints and extensor surfaces of her elbows and knees. Nailfold capillaries appeared dilated and tortuous. She developed edema of her proximal and distal extremities, dysphagia, dysarthria, and muscle weakness. Brain MRI did not reveal infarct. Laboratory evaluation revealed elevated CPK of 1300. MRI revealed diffuse edema of the hip girdle and pelvic muscles. The diagnosis of JDM was confirmed with detection of anti-MJ antibodies. Her course was further complicated by GI vasculitis. Treatment to date has included methylprednisolone, prednisone, methotrexate, and cyclophosphamide.

Conclusion: This is the first known case report of concomitant JDM and SCD in a pediatric patient, which has proven to be a diagnostic and therapeutic challenge. JDM symptoms may have been present prior to or early in the described hospitalization. Lack of routine follow up prevented earlier identification of the symptoms. When initially hospitalized, these symptoms were readily masked by the severity of her SCD-related co-morbidities and eczema. Her SCD-related AVNs have complicated treatment which will likely yield further insult to her bone integrity. Her case reminds us to maintain a high degree of suspicion in patients with SCD for alternate diagnoses with overlapping symptomatology.

LONG-TERM CLINICAL AND HEMATOLOGIC OUTCOMES OF SPLENECTOMY IN CHILDREN WITH CONGENITAL HEMOLYTIC ANEMIA

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Background: Children with congenital hemolytic anemia (CHA) often require splenectomy to control complications such as severe anemia, hypersplenism, and splenic sequestration. Favorable short term outcomes following either total splenectomy (TS) or partial splenectomy (PS) have been reported. However, the long-term outcomes following splenectomy remain poorly described.

Objectives: The purpose of this pilot study was to define the long-term outcomes of children with CHA following TS or PS at a single institution.

Design/Method: We collected data on children with CHA who underwent TS or PS from 1996 to 2010 at Duke University using the Research Electronic Data Capture (REDCap) database. Children were included if they had follow-up data at 2, 3, 4, or 5 years following surgery. Hematologic outcomes (hemoglobin, reticulocyte, bilirubin), clinical outcomes, as well as adverse events (AE) (infections, stroke, acute chest syndrome (ACS)) were summarized.

Results: Thirty-three children were included, 9 with hereditary spherocytosis (HS), 17 with sickle cell disease (SCD), and 7 with other types of CHA. Mean age at splenectomy was 5.5 years (range 2-15). Mean follow-up was 3.8 years (range 2-5) with 67% having at least 4 years. TS was performed in 9 children and PS in 24 children. Children with HS had an increase in hemoglobin from baseline, decrease in reticulocyte percentage, and bilirubin, which remained stable over the 5 years. Hematologic outcomes remained stable for SCD over the 5 year follow-up. The most common AE was ACS in SCD (6 episodes). There was one patient with SCD who had recurrent salmonella osteomyelitis but no other serious bacterial infections or episodes of sepsis were identified. No patients with a PS required a second surgery for TS. Post-operatively, 32 children received prophylactic antibiotics, with 23 continuing antibiotics at 5 year follow-up.

Conclusion: In conclusion, long-term clinical and hematologic outcomes for children with HS improve after TS or PS. In children with SCD, clinical outcomes are improved, but hematologic laboratory values are unchanged. Adverse events after surgery are not infrequent in children with SCD. These pilot findings suggest that a multicenter study may better define important outcomes following different types of splenectomy in children with CHA.

TWO CASES OF EPSILON GAMMA DELTA BETA THALASSEMIA, A RARE CAUSE OF FETAL AND NEONATAL ANEMIA

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Background: The beta-globin cluster on chromosome 11p15.4 includes five genes essential for the production of normal hemoglobin: HBE (Epsilon-globin), HBG1 (Gamma-1-globin), HBG2 (Gamma-2-globin), HBD (Delta-globin), and HBB (Beta-globin). Epsilon Gamma Delta Beta thalassemia ($\epsilon\gamma\delta\beta$ -T) results from deletion of this gene cluster and is usually associated with prenatal and neonatal anemia that improves over time. It is rare, with fewer than 100 cases reported and fewer than 30 deletions described.

Objectives: To describe the clinical course and medical management of two unrelated infants with unique $\epsilon\gamma\delta\beta$ -T deletions.

Design/Method: Case series of 2 affected newborns, one diagnosed prenatally and the second diagnosed postnatally, with $\epsilon\gamma\delta\beta$ -T.

Results: Baby E was diagnosed prenatally after a chromosome microarray was performed for fetal ascites. She had an approximately 1.3 Mb deletion that included 21 genes in the interval. She was supported with three in-utero red blood cell transfusions and born at 37 weeks gestation. At birth, her hemoglobin was 12.7g/dL, MCV 90.5 fL., and reticulocyte count over 18%. She reached her physiologic nadir at 5 ½ weeks gestational age at a hemoglobin of 7.3 g/dL and required no further transfusions. Testing of her parents revealed she had a de novo mutation. Baby J was born at 28 weeks gestation, with a hemoglobin of 5.6g/dL, MCV of 87.2fL, and reticulocyte count of 14.2%. He required four transfusions of red blood cells. Alpha and beta thalassemia were ruled out, and bone marrow examination was unremarkable. Polymerase chain reaction and multiplex ligation-dependent probe amplification identified a contiguous heterozygous deletion involving the beta globin gene cluster. Further analysis with SNP microarray confirmed a 175 kb interstitial deletion. A CBC at age 22 months showed hemoglobin of 10.4 g/dL, RBC count of $5.6 \times 10^6/\mu\text{L}$ and an MCV of 59.3. Chromosomal analysis on his parents was not available but his father's CBC revealed microcytosis with an elevated red blood cell count making it likely that this was inherited.

Conclusion: $\epsilon\gamma\delta\beta$ -T is a rare cause of severe fetal and neonatal anemia and can lead to premature birth or fetal demise. Both pre and postnatal detection can have good outcomes when managed appropriately.

THE ASSOCIATION OF AGE, DISEASE MODIFYING THERAPY, AND VENTRICULAR GLOBAL LONGITUDINAL STRAIN IN CHILDREN WITH HEMOLYTIC ANEMIAS

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Background: Patients with sickle cell disease (SCD) have increased risk of cardiopulmonary disease with subsequent higher morbidity and premature mortality. Decreased myocardial deformability is an early sign of myocardial systolic dysfunction and may result from preceding restrictive cardiomyopathy. Few studies have investigated right and left ventricular global longitudinal strain (RVGLS and LVGLS) among children with SCD or non-sickling hemolytic anemias; none has investigated the role of disease-modifying therapies (hydroxyurea, chronic transfusions) and elevated tricuspid regurgitant velocity (TRV) on strain in SCD.

Objectives: 1) compare RVGLS and LVGLS in pediatric SCD with other pediatric non-sickling hemolytic anemias, 2) investigate the association of age, disease-modifying therapies, TRV, and global longitudinal strain in SCD.

Design/Method: Prospective measurement of RVGLS and LVGLS by speckle-tracking and TRV by 2D M-mode echocardiography in children with Hb-SS and HbS β 0thalassemia (n=151) and non-sickling hemolytic anemias (hereditary spherocytosis, Hb-E, pyruvate kinase deficiency; n=16) ages 5-19 performed with central reading by one single cardiologist. TRV was categorized as normal (<2.5 m/s) or elevated (\geq 2.5 m/s).

Results: In univariate analysis, increased (worsening) RVGLS and LVGLS were associated with age and any disease-modifying therapy in children with SCD (p=0.00011 and 0.029). When controlling for age in a multivariate model, however, treatment was no longer associated with strain. For each 1 year increase in age, there is an increase in RVGLS of 0.26 (p=0.0016). Elevated TRV was associated with increased LVGLS in SCD (rho=-0.17, p=0.048). In non-sickling hemolytic anemias, age was associated with increased LVGLS (rho=0.63, p=0.096). LVGLS but not RVGLS was significantly decreased in SCD compared with non-sickling hemolytic anemias (-22.6 vs. -21.4, p=0.049). More patients with SCD had elevated TRV compared with non-sickling hemolytic anemias (26.4 % vs. 0%, p=0.029).

Conclusion: Global longitudinal cardiac strain declines with age in children with hemolytic anemias and may represent an early marker of pathologic cardiac change. Elevated TRV was more common in SCD than in non-sickling hemolytic anemias and may modulate LVGLS. Global longitudinal strain should be further studied in longitudinal prospective cohorts of patients with hemolytic anemias for its value as a marker of early cardiac damage.

MXI1 AND MXI0 HAVE DIFFERENTIAL EFFECTS ON NEUROBLASTOMA PATHOGENESIS AND CHEMOSENSITIVITY

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Background: Neuroblastoma is the most common extracranial malignancy of childhood. The Myc family of proteins regulates cell growth and proliferation and has been implicated in the etiology of many cancers, and MYCN amplified neuroblastoma is associated with a poor prognosis. Investigating specific tumor pathways will further our understanding of neuroblastoma pathogenesis and lead to future therapeutic options. Mxi1 is a member of the MAD family that inhibits N-Myc activity. Mxi0 is an alternatively spliced variant of Mxi1 with a different first exon (Exon 0) whose function has not been determined.

Objectives: Test the hypothesis that Mxi1 and Mxi0 differentially impact N-Myc-dependent neuroblastoma cell proliferation.

Design/Method: We expressed Mxi1 and Mxi0 in SHEP neuroblastoma cells, and SHEP cells stably transfected to express high levels of MYCN (SHEP/MYCN). We also utilized native neuroblastoma cell lines with inducible expression of Mxi1 and Mxi0. Cell proliferation and survival were quantified using BrdU and MTT assays, respectively. The impact of Mxi1 and Mxi0 on N-Myc expression was measured by RT-PCR and immunoblot analysis.

Results: Overexpression of Mxi1 inhibits neuroblastoma cell viability. Conversely, overexpression of Mxi0 in neuroblastoma cell lines leads to increased viability, suggesting that Mxi0 has a counter-regulatory role to that of Mxi1. Further examination reveals that these changes in viability are partially due to changes in cell proliferation, with Mxi1 decreasing proliferation and Mxi0 augmenting it. Additionally, we observed that N-Myc levels decrease in response to Mxi1 expression, and increase when Mxi0 is expressed. Compared with Mxi1, expression of Mxi0 results in enhanced chemoresistance of neuroblastoma cells to doxorubicin or etoposide.

Conclusion: Overexpression of Mxi1 in neuroblastoma cell lines leads to inhibition of N-Myc-mediated cell proliferation, while Mxi0 appears to promote cell growth. Mxi1 expression enhances chemosensitivity of neuroblastoma cells, while Mxi0 has the opposite effect. These effects may partially be due to alterations in N-Myc expression. A better understanding of the interactions among Mxi1, Mxi0 and N-Myc and how the relative expression levels of these proteins affect neuroblastoma physiology may aid in developing more effective targeted therapies to improve outcomes in pediatric neuroblastoma patients.

SCREENING FOR IRON DEFICIENCY ANEMIA: A COST-EFFECTIVENESS ANALYSIS

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Background: There are currently no standard national guidelines regarding the optimal time of screening for iron deficiency anemia (IDA) in infants and children. The United States Preventive Services Task Force, CDC and American Academy of Pediatrics all recommend screening different age groups and populations based on IDA risk and the potential for subsequent poor outcomes.

Objectives: The aim of this study was to compare the cost-effectiveness of screening for IDA at varying ages within both a high risk group and the general population.

Design/Method: We used a Markov decision analysis model to estimate the cost-effectiveness of screening for IDA in 9, 12 or 18 month-olds within high-risk groups or the entire population. Identical hypothetical cohorts were evaluated over 27 months, tracking anemia severity over time and the possibility of neurodevelopmental outcomes with undiagnosed severe anemia. Clinical outcomes, utilities and costs were all obtained via literature review. We varied parameter estimates in one-way sensitivity analyses.

Results: In the base case, screening high-risk 9 month olds gained 0.0054 quality-adjusted life years (QALYs) and cost \$4.49 more than no screening, or \$838/QALY gained. Screening all 9 month olds cost \$5593/QALY gained, and screening all 12 month olds cost \$15,403/QALY gained. Other strategies were eliminated due to dominance. Using an accepted standard of \$50,000 dollars/QALY gained as being cost effective, screening all 12 month olds is the most cost effective strategy. Varying the most uncertain variables in our model over plausible ranges, specifically probability of neurodevelopmental outcomes, probability of anemia in high-risk populations, and the probability of being high-risk, the preferred strategy remained screening all 12 month olds. In a probabilistic sensitivity analysis, varying all parameters simultaneously over plausible distributions resulted in screening all 12 month olds being favored in 99.98% at a \$100,000/QALY threshold.

Conclusion: Screening all children at 12 months of age for IDA is an economically reasonable strategy. In light of this, reexamination of the various currently suggested guidelines may be warranted.

THE USE OF PONATINIB, AN FGFR INHIBITOR, IN THE TREATMENT OF NEUROBLASTOMA

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Background: Neuroblastoma remains the most common solid extracranial solid tumor in children. Approximately 600 new diagnoses are made each year. Despite advances in therapy, including a multimodal approach, high risk neuroblastoma remains very difficult to treat. Current long term survival rates for high risk neuroblastoma are approximately forty percent. Biologically targeted novel therapeutics are potential treatments for neuroblastoma that could improve cure rates. Aberrant growth factor receptor (GFR) expression and receptor kinase signaling are associated with the pathogenesis of many malignancies. These kinases therefore serve as targets for a number of novel therapies. Fibroblast growth factors (FGFs) activate their cognate receptors (FGFR1-4) to stimulate cell proliferation and migration, and FGFR inhibition is effective in a variety of preclinical cancer models.

Objectives: To test the novel pan-FGFR inhibitor ponatinib for efficacy in preclinical models of neuroblastoma.

Design/Method: We treated a panel of established neuroblastoma tumor cell lines with increasing concentrations of Ponatinib and viability was determined using MTT assays. Additionally, neuroblastoma cell migration into a wound before and after treatment with ponatinib was monitored at 24 hour time intervals. Cells were treated with Ponatinib and western blots using antibodies for downstream targets of FGFR4 were performed.

Results: All neuroblastoma cell lines tested were sensitive to Ponatinib with IC50 values in the nanomolar to micromolar range. Migration of neuroblastoma cells was inhibited by treatment with Ponatinib. Phospho-MEK and phospho-ERK were significantly decreased after treatment with Ponatinib.

Conclusion: Treatment of neuroblastoma tumor cells with Ponatinib causes cell death and reduces cell migration. Inhibition of FGFR family members represents a novel therapeutic strategy for neuroblastoma, and further preclinical studies of Ponatinib and additional FGFR inhibitors are warranted.

HEREDITARY HEMOLYTIC ANEMIA DUE TO RED CELL MONOVALENT CATION LEAK IN A PATIENT WITH A NOVEL BAND 3 MUTATION

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Background: The inherited stomatocytoses are a group of hemolytic anemia disorders characterized by altered red blood cell (RBC) membrane permeability to monovalent cations. Cryohydrocytosis is one subtype where the cation leak is mild at 37 °C but significantly increases when temperatures approaches 0°C. Single amino acid substitutions in the transport domain of band 3 caused by mutations in SLC4A1 have been demonstrated as causative of this phenotype.

Objectives: We describe a novel SLC4A1 mutation associated with monovalent cation leak, particularly marked at 4°C, in a patient with congenital hemolytic anemia.

Design/Method: Next-generation sequence analysis of 32 genes associated with hemolytic anemias was performed in a 2-year old female who had presented with neonatal hemolytic anemia and jaundice with a family history positive for hemolysis. Further RBC phenotypic analysis included ektacytometry, red cell cytogram, and measurement of intracellular K⁺ and Na⁺ content at 4°C compared to control samples.

Results: The patient's hemoglobin was normal at 13.1 g/dL with an elevated reticulocyte count (10.36%) indicating persistent hemolysis. The elevated mean corpuscular hemoglobin concentration (39.1 g/dL) and the red cell cytogram showing the majority of cells in the hyperchromic zone is consistent with increased cell density. Ektacytometry of the patient's RBCs produced a curve indicating impressive cellular dehydration with low Omin (the hypotonic osmolality where 50% of the cells hemolyze in an osmotic fragility assay) of 73 mOsm/kg (normal: 149.6 ± 8.1); a low El (Elongation Index) max of 0.52 (normal: 0.59 ± 0.01) indicating decreased deformability; and low Ohyp of 298 mOsm/kg (normal: 460.9 ± 13.6) indicating increased intracellular viscosity. The RBC intracellular K⁺ cation content was reduced to 155 ± 3.7 mmol/kg Hb (controls: 270 ± 3.1 and 268 ± 3). Next-generation sequence analysis of the patient's sample revealed a novel heterozygous variant in SLC4A1 gene (c.2173A>G) causing a single amino acid substitution in the transport domain of band 3 (p.S725G).

Conclusion: We report a novel genetic defect in SLC4A1 associated with significant RBC cation leak at cold temperatures in a patient with congenital hemolytic anemia. The substitution p.Ser725Gly is possibly a novel cryohydrocytosis mutation converting band 3 from an anion exchanger into an unregulated cation channel.

THE NATURAL HISTORY, TREATMENT AND SURVEILLANCE OF GANGLIONEUROMAS IN CHILDREN AND ADOLESCENTS

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Background: In comparison to the most malignant form of Peripheral Neuroblastic Tumors (pNTs), neuroblastoma (NB), Ganglioneuromas (GN) demonstrate more favourable histological and clinical features. Surgery is often performed due to symptoms and/or theoretical concerns that GN may transform into NB; however, many publications have identified significant GN-surgical morbidities.

Objectives: Our study compares the natural history, biological and clinical features of GN & Ganglioneuroblastoma-Intermixed (GNB-I) managed by surgery or observation to inform recommendations for potential surveillance approaches for GN.

Design/Method: This retrospective study includes all patients (N=74) with histological diagnosis of GN (73%) and GNB-I (27%) at Sick Kids between 1990-2014. Clinical, pathological features, tumor dimensions and management were recorded.

Results: Median age at diagnosis was 6 yrs [0.2 – 17.8 yrs]. The median maximal tumor diameter was 6.8 cm [1.4-16.9 cm] and volume was 76.6 mls [1.6-1089 mls]. Forty-seven (64%) patients had 1st line surgery (with or without biopsy); 27 were observed and 8/27 later underwent resection. Observed patients were more likely to be older [median 8.2 yrs vs 5.86 yrs] and diagnosed more recently. Median volume increase between diagnosis and surgery was 30%; 18/55 (33%) had postoperative complications. Image defined risk factors (IDRF) were associated with increased complications (p=0.004) and residual disease (p=0.006). Median growth was 0.42 cm/year. There was a trend for increased growth rates with GNB-I pathology. No post-operative growth or recurrence occurred in surgical patients. For 85% of patients, surveillance (median 6-monthly imaging), did not alter clinical management. At median follow-up 2.5 years [0-15 years], all patients were alive: 33 had complete response, 22 partial response, 16 stable disease and 3 progressive disease. Fifty-one (69%) were asymptomatic. There was an increased incidence of symptoms in surgical patients (tumor-related (N=8), post-operative (N=5)) compared to observation patients (N=3). Pathology classification changed at resection for five cases, but no GN was reclassified to NB.

Conclusion: GN and GNB-I have a slow growth rate and resection may be associated with significant morbidity. Watch and wait approaches may be considered for patients with GN and GNB-I.

LONG-TERM FOLLOW-UP OF POLYCYTHEMIA DUE TO DE NOVO EPOR MUTATION: THERAPEUTIC IMPLICATION

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Background: Polycythemia are extremely rare disorders in childhood. Over the past decade, several gene mutations have been discovered as cause of congenital polycythemia (CP), including erythropoietin-receptor gene mutation (EpoR).

Objectives: Describe the clinical characteristic and long-term follow-up of patient with EpoR mutation.

Design/Method: Single case report, with 14 yrs. follow-up. EpoR sequencing were performed through Sanger sequencing, as previously published, on genomic DNA from peripheral blood mononuclear cells, and from nail in the proband to confirm germline mutation.

Results: This French Canadian male was incidentally found to be polycythemic at the age of 2 yrs. old (Hb 17.5g/L, Hct 0.52 with no other abnormalities). He had no evidence of oxygen desaturation, and a normal calculated p50. Bone marrow revealed no morphologic and cytogenetic abnormalities. Epo level was undetectable, and In vitro testing revealed increased erythroid sensitivity with very rare Epo-independent erythroid growth. Search for JAK2 V617G and exon 12 somatic mutations were negative. A germline, heterozygous G6002A EPOR mutation was detected. Although this mutation had been previously reported among 16 other EpoR-mutations causing the dominantly inherited primary familial congenital polycythemia (PFCP), this mutation was found in no other family members. Given the development of moderate to severe headaches, phlebotomies were eventually initiated at the age of four to maintain a hematocrit <0.45. Over 14 yrs. of follow-up, he developed mild arterial hypertension, and hyperuricemia, but never had thrombotic complications under aspirin prophylaxis. Anti-hypertensive therapy was switched to enalapril at the age of 16 yrs. old. At the age of 17, in spite of well-controlled hematocrit level, anti-migraine agent zolmitriptan, a serotonin 5-HT receptor agonist was initiated due to worsening headaches. Phlebotomies were ceased for up to 24 weeks given stable hematocrit since the introduction of this medication. Bone marrow remained normal without evidence of marrow fibrosis.

Conclusion: Although usually benign, inherited EpoR mutation may cause vascular complications such as hypertension. Given that serotonin has a known role in erythropoiesis, we propose that zolmitriptan alone, or in combination with angiotensin antagonist may be beneficial. Its effect should be evaluated in further studies.

ASSOCIATION OF CLINICAL MORBIDITIES AND PLEXIFORM NEUROFIBROMA VOLUME CHANGES IN NEUROFIBROMATOSIS TYPE 1

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Background: Neurofibromatosis Type 1 (NF1) is an autosomal dominant disorder characterized by mutation in the NF1 gene. Approximately 25-40% of patients with NF1 will develop plexiform neurofibromas (PN). Though histologically benign, PN can be associated with significant morbidities. Ongoing clinical trials are evaluating the effect of targeted therapies on PN volume. However, no previous study has assessed for an association between an increase in PN volume and development of morbidities.

Objectives: To utilize data obtained through the National Institutes of Health (NIH) NF1 Natural History study to assess the hypothesis that increasing PN volume in NF1 is associated with increased morbidity.

Design/Method: Retrospective chart review of patients enrolled on the NF1 Natural History study with ≥ 10 years of historical data available. Patient morbidities were assessed at two time-points: time of baseline PN MRI with volumetric analysis and time of MRI with maximum PN volume. Morbidities evaluated included the presence of pain, motor dysfunction, airway compromise, bowel or bladder dysfunction, vision loss and PN related surgery.

Results: Twenty-four patients with 35 distinct PN were included, with median PN volume 163 mL at baseline and 469 mL at maximum assessment. At baseline, 15 of 35 PN had at least one associated morbidity. There was an increase in the number of PN requiring scheduled pain medications comparing baseline (2/35) to maximum volumes (11/35). Based on their locations, 24 of the 35 PN had the potential for motor related morbidity. Of these, the PN that had motor impairment at baseline (8/24) or maximum volumes (14/24), had larger volumes compared to those that did not have motor morbidity (514 mL larger at baseline (95% CI 27, 1092), 719 mL larger at maximum (95% CI 31, 3271)).

Conclusion: Many patients with NF1 had significant PN related morbidities even at baseline assessment, and this study reinforces the need for long-term evaluation to see changes in PN associated morbidities. There was an increase in motor morbidity with increased PN volume as well as a trend towards increased need for pain medications with increased PN volume. Future analyses of larger patient populations are ongoing and may help elucidate these associations.

PREGNANCY OUTCOMES AMONG MOTHERS OF PATIENTS WITH INHERITED BONE MARROW FAILURE SYNDROMES

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Background: Pregnancies in females with Fanconi anemia (FA), dyskeratosis congenita (DC), Diamond-Blackfan anemia (DBA), and Shwachman-Diamond syndrome (SDS) are associated with increased complications. There are no studies of pregnancy outcomes in unaffected mothers of patients with inherited bone marrow failure syndromes (IBMFS).

Objectives: To determine outcomes of pregnancies with IBMFS-affected offspring in unaffected mothers of patients with IBMFS.

Design/Method: We evaluated pregnancy data from questionnaires completed by unaffected IBMFS mothers (56 FA, 42 DC, 47 DBA, and 20 SDS). Healthy female relatives with unaffected children (n=38) served as controls. Pregnancy outcomes were compared across groups. Complications occurring at >20 weeks gestation were evaluated and compared within each group for those mothers who had both affected and unaffected offspring.

Results: The median number of pregnancies was similar [3 (range 1-8), 3 (1-10), 3 (1-8), 3 (2-6), and 2.5 (1-6)] for mothers of FA, DC, DBA, SDS, and controls, respectively. Age at first and last pregnancy, and % of mothers having miscarriage, abortion or stillbirth was similar across groups. In FA pregnancies, affected fetuses were more likely to have IUGR (28/71 vs 3/80; $p < 0.0001$) and low birthweight (2.28 vs 3.2 kg; $p < 0.00001$) than unaffected. In DC, affected pregnancies more commonly had fetal distress (14/54 vs 10/64; $p < 0.0001$), IUGR (21 vs 5; $p < 0.0001$), low birthweight (2.7 v 3.18; $p < 0.0001$) and tended to be born preterm (<37 weeks; 15 vs 8; $p = 0.06$). In DBA, affected fetuses were more likely to have fetal distress (10/53 vs 1/69; $p = 0.001$) due to severe anemia, low birthweight (2.75 vs 3.2; $p = 0.0005$), preterm birth (14 vs 4; $p = 0.002$), and IUGR (8 vs 2; $p = 0.02$). In SDS, affected pregnancies more commonly had prolonged labor with fetal distress (4/22 vs 0/23; $p = 0.05$) and low birthweight (2.75 vs 3.2; $p = 0.04$) than unaffected. C-section for complications occurred more often in affected than unaffected pregnancies within each IBMFS ($p < 0.02$).

Conclusion: Pregnancy with an IBMFS-affected offspring was associated with increased complications; IUGR and low birthweight were common in affected children. Other adverse outcomes varied by syndrome, likely contributed to higher C-section rates and may reflect the phenotype for each IBMFS.

SPECTRUM OF CENTRAL NERVOUS SYSTEM TUMORS SEEN IN PATIENTS WITH NEUROFIBROMATOSIS TYPE 1 AND TUBEROUS SCLEROSIS COMPLEX: A SINGLE CENTER EXPERIENCE

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Background: Neurocutaneous syndromes (NS) represent a group of inherited cancer predisposition syndromes characterized by tumors of the nervous system, eyes, skin, viscera and other parts of the body. They include Neurofibromatosis (NF1/ NF2), Tuberous Sclerosis Complex (TS), Ataxia Telangiectasia, Sturge-Weber Syndrome and von-Hippel-Lindau disease.

Objectives: We retrospectively reviewed all patients with NF1 and TS who are being followed for CNS tumors at our institution and characterized the CNS tumors seen in this group. Data was collected regarding age at which NS diagnosed, how diagnosis of NS made, age NS related tumor diagnosed, clinical presentation of tumor, radiological features of tumor, pathology of tumor, treatment and outcome.

Design/Method: Case Series

Results: NF1 patients (N=14): Eight patients were diagnosed with an NF1 related tumor by the age of 10 years. 7 patients had optic tract gliomas. Two patients had hemispheric tumors (Corpus Callosum Pilocytic Astrocytoma and Parieto-occipital Pleomorphic Xanthoastrocytoma (PXA)), 5 patients had brainstem tumors (midbrain, pons, and medulla), 2 patients had tumors of the cerebellum and 2 patients had cervical spinal cord lesions. 6 patients who had their tumors resected were found to have Pilocytic Astrocytomas (4), PXA (1) or Plexiform Neurofibroma (1). 2 patients had a recurrence after tumor resection (PXA and Pilocytic Astrocytoma of the Corpus Callosum). 5 patients have received treatment with chemotherapy (Vincristine, Carboplatin, Vinblastine, and Gleevec). No patient has succumbed to their tumor. TS Patients (N=5): All 5 patients had Subependymal Giant Cell Astrocytomas (SEGAs) -3 unilateral (lateral ventricle, foramen of Munro) and 2 bilateral (foramina of Munro, thalamus). 1 patient was diagnosed prenatally and 1 was diagnosed at 3 months. The other three patients were diagnosed by 11 years of age. In 2 patients new onset headaches indicated SEGA progression. Both had their SEGAs resected without recurrence and both tumors were found to be WHO grade 1 Astrocytomas. In 2 patients the SEGAs are being managed by mTOR inhibition.

Conclusion: No patient in our cohort has been diagnosed with a malignant CNS tumor. The PXA seen in one patient has atypical radiological features and progressed after resection. Both patients with TS who are being managed by mTOR inhibition have not shown progression of their SEGAs.

PULMONARY ARTERIOVENOUS MALFORMATIONS: AN UNCHARACTERIZED PHENOTYPE OF DYSKERATOSIS CONGENITA

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Background: Dyskeratosis congenita (DC) is a cancer-prone inherited bone marrow failure (BMF) syndrome caused by germline mutations in telomere biology genes. The triad of reticular skin pigmentation, dysplastic nails and oral leukoplakia is diagnostic. Many patients may present with other manifestations; all are at risk of other medical problems including pulmonary fibrosis (PF) and liver disease. Pulmonary arterio-venous malformations (PAVMs) have been reported in a limited number of DC patients, often in relation to hepatopulmonary syndrome (HPS). PAVMs can lead to clinically significant right-to-left shunting resulting in decreased oxygenation and respiratory insufficiency.

Objectives: To characterize PAVMs as a phenotype of DC.

Design/Method: In this IRB-approved multi-institutional case series we evaluated patients of any age, race and gender diagnosed with DC and PAVMs concurrently or at separate times. Data were obtained by retrospective review of medical records by the primary institution and maintained at NCI.

Results: We report thirteen unrelated patients with DC and PAVMs; nine (70%) had no evidence of liver disease or portal hypertension at PAVM diagnosis. The median age at DC diagnosis was 13 years (range 1-27) and 15 years (range 3-32) for PAVM. The genetic cause of DC varied (one patient with DKC1, five TINF2, two TERT, one RTEL1, one PARN, three with unknown gene). Ten patients (77%) underwent hematopoietic cell transplant (HCT) for BMF or myelodysplasia. Two patients' PAVMs were diagnosed prior to DC diagnosis, and five (38%) were prior to HCT. Diffusion capacity for carbon monoxide (DLCO) was decreased out of proportion to other pulmonary function tests (PFTs), including in patients with PF, with reported range of 12-55% of predicted. Bubble echocardiography with agitated saline was indicative of PAVMs in all but one patient. The majority of PAVMs in DC were multiple and microscopic.

Conclusion: This case series establishes PAVMs as an important pulmonary phenotype of DC that can occur independently of HPS. Clinicians should be vigilant of respiratory symptoms and abnormal PFTs, particularly decreased DLCO, which are not explained by other pulmonary pathology. Early detection of PAVMs is key to timely symptomatic management, however further research and clinical trials are needed to determine a curative treatment for these patients.

MIBG THERAPY AS A REASONABLE OPTION FOR RELAPSED/REFRACTORY NEUROBLASTOMA (NB) IN A LOW/MIDDLE INCOME COUNTRY (LMIC) SETTING? A 10-YEAR EXPERIENCE

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Background: 131-MIBG has been used in the treatment of relapsed/refractory NB for the past 30years,with response rates of around 20-40%.It is now used in regimens, often in conjunction with chemotherapy or myeloablative therapy.Data from LMICs is lacking.We describe here our experiences with 131-MIBG therapy in the treatment of NB.

Objectives: To evaluate the role of MIBG therapy in relapsed/refractory Neuroblastoma

Design/Method: Retrospective audit of patients with NB at Tata Memorial Hospital, who received MIBG therapy in frontline or relapsed/refractory settings from 2005 to 2014. MIBG therapy was administered at the Radiation Medicine Centre, a neighboring institution. Apart from the routine evaluation, all patients underwent 131-MIBG scans and Urinary Vanillyl mandelic Acid (VMA) levels prior to treatment. A few patients underwent Computerised Tomograms (CTScans) and/or Fluorodeoxyglucose Positron EmissionTomography (FDG-PET scans).The dose of 131-I MIBG was 10-12mci/kg body weight, and capped at 150mci.Children were isolated after treatment, and caregivers screened for exposure to the agent. Reassessment was done by clinical evaluation, MIBG scans and Urinary VMA levels.

Results: There was data on 31children who received a total of 46courses of MIBG therapy (median 1; range1-6courses). Median age was 6years, and male: female ratio 20:11. Intent was palliative in 21patients (total 28courses); most were high risk NB and had received multiple courses of treatment, including Autologous Stem Cell Transplant in 3/21. Response rate was 45 % (12/28), with 4 patients alive at last follow up. Median time to progression was 7months. Ten patients received a total of 19courses of MIBG therapy as part of frontline therapy (inoperable mass- 4patients, refractory disease- 2patients, residual post-operative mass-4patients). Response rate was 40%, with 5/10 alive at last followup. The most common toxicity was grade3/4cytopenia, documented in 30%patients, and often delaying further courses.

Conclusion: With the limitations of a retrospective study, it is feasible both in relapsed/refractoryas well as frontline NB in LMICs, with acceptable toxicities. MIBG therapy offers a reasonable salvage strategy in LMIC settings, where other aggressive salvage therapies are often not possible. We hope that incorporation of MIBG therapy in the frontline treatment regimen at our centre in the near future will help improve outcomes in High Risk NB.

CANCER PREDISPOSITION IN DIAMOND BLACKFAN ANEMIA: AN UPDATE FROM THE DIAMOND BLACKFAN ANEMIA REGISTRY

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Background: Diamond Blackfan anemia (DBA) is an inherited bone marrow failure syndrome characterized by red cell aplasia and congenital anomalies. DBA is known in the majority of cases to be caused by haploinsufficiency of one of the small or large ribosomal protein (RP) subunits. In addition, there is a cancer predisposition in DBA. Indeed, somatic and germline RP mutations have been associated with a number of malignancies.

Objectives: To quantitate the incidence of neoplasia in patients with DBA.

Design/Method: The DBA Registry of North America (DBAR), the largest established patient cohort with prospective follow-up since 1991, was interrogated to ascertain the incidence of neoplasia in DBA. The relative risk of all cancers in DBA (excluding myelodysplastic syndrome [MDS]) will be compared with the general population. A competing-risks approach will be used to estimate cause-specific hazard functions and cumulative incidence curves for DBA, as done previously.

Results: The DBAR reported the first quantitative assessment of incidence of neoplasia in 608 DBA patients (median age, 18 years) with analysis through August 2010. Seventeen patients who had not received a BMT had 1 or more cancers and 4 patients had MDS. The significantly elevated O/E (observed to expected) ratios were 36, 33, 28, and 287 respectively, for colon carcinoma (N=3), osteosarcoma (N=2), acute myeloid leukemia (AML; N=2) and MDS (N=4). As of December 2015 (N=708), with a median patient age of 22 years, 16 additional patients who had not received a BMT had 1 or more cancers and 4 additional patients developed MDS. There is a total of 32 cancers reported in 28 patients, including 10 patients with gastrointestinal carcinoma, 4 with sarcoma, and 3 with AML; there are 8 patients with MDS. A statistical analysis will be available at the time of presentation. Not included in our analysis are 3 patients who developed colorectal cancer in two and OS in one, respectively, following hematopoietic stem cell transplantation.

Conclusion: Our extended analyses including additional follow-up and more patients will inform our assessment of cancer types and risks that are unique to DBA.

INCIDENCE OF HYPONATREMIA IN PEDIATRIC ONCOLOGY PATIENTS

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Background: Hyponatremia (serum Na <135mEq/L) is the most frequent electrolyte abnormality in children. Previous research has reported that hyponatremia affects between 3.4-49% of hospitalized pediatric patients, but no studies have been done to evaluate the incidence of hyponatremia in pediatric oncology patients. In oncology the etiology of hyponatremia depends of many factors, illness, type of cancer, type of chemotherapy, type of hydration during chemotherapy.

Objectives: To determine the incidence of hyponatremia in pediatric oncology patients by comparing those admitted for chemotherapy to those admitted for acute illness

Design/Method: Retrospective cohort study involving chart review of all pediatric oncology admissions to the Children's Hospital of Illinois over an 18 month period.

Results: During the study period, 74 eligible patients were admitted to receive chemotherapy and 63 due to acute illness. There was no significant difference between the two groups with regards to sex ($p=0.1385$), and age ($p=0.9896$). Most patients received fluids with 0.45% or 0.9% normal saline. A serum Na of < 135 was found in 15/74 (20%) patients admitted for chemotherapy and 27/63 (42%) of those admitted for acute illness ($p=0.0043$). Even when accounting for differences in fluid type, hyponatremia was 3.1 times more likely to occur in patients admitted for acute illness in contrast to those admitted for scheduled chemotherapy (OR=3.1 [1.4, 6.7], $p=0.0044$). In 45% patients had hyponatremia was present at the time of admission and 31% in the first 24 hours. None of the patients had symptomatic hyponatremia. There was no difference in the hospital length of stay ($p=.00579$) between the two groups

Conclusion: Among the oncology patients those who present with acute illness are more likely to have or develop hyponatremia during their admission. Hyponatremia was subclinical and did not prolong the length of stay. We plan to compare the incidence of hyponatremia in patients receiving different regimens of chemotherapy and in patients with leukemia versus solid tumors.

CONGENITAL DYSERYTHROPOIETIC ANEMIA TYPE I DUE TO NOVEL CDAN1 MUTATIONS

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Background: Congenital dyserythropoietic anemias (CDA) are a heterogeneous group of rare genetic disorders characterized by ineffective erythropoiesis with characteristic abnormalities of bone marrow erythroid precursors, leading to anemia with suboptimal reticulocytosis, splenomegaly and iron overload frequently disproportionate to the history of transfusions.

Objectives: To describe two novel variants in CDAN1 associated with severe CDA I phenotype.

Design/Method: Case report and gene sequencing after family's informed consent.

Results: A 5-year-old Caucasian male was referred to our clinic for evaluation of a transfusion-dependent, non-immune hemolytic anemia with suboptimal reticulocytosis and skeletal deformities involving his fingers and toes. The child had presented soon after birth with severe neonatal jaundice and hepatosplenomegaly. In the blood smear red cells showed marked anisopoikilocytosis with dacryocytes, red cell fragments and macrocytes. In the bone marrow aspirate, erythroid cells showed prominent dyserythropoiesis, including megaloblastoid maturation, binucleation, nuclear contour irregularities and chromatin bridges; occasional multinucleated erythroids were present. Next-Generation sequence analysis of 29 genes associated with hemolytic and dyserythropoietic anemias was performed on DNA isolated from peripheral blood. The patient was found to be compound heterozygous for two mutations in CDAN1 confirming the suspected diagnosis of CDA I. The first mutation, c.3051_3052delTG, is a previously unreported deletion that results in a frameshift. The second mutation, c.3071C>T (p.P1024L), is a missense variant that affects a highly conserved amino acid residue. Through the use of mutation prediction software, the amino acid substitution P1024L is predicted to be "deleterious" and "probably damaging". This variant is known as rs145041909 and was found in ExAC database, with very low MAF of 0.0001. Patient is currently managed with regular blood transfusions and iron chelation which has been effective, as monitored by MRI for liver iron, while the family is considering the option to try interferon-alpha therapy.

Conclusion: CDA should be considered in the differential diagnosis of non-immune hemolytic anemia with suboptimal reticulocytosis. Next-Generation sequencing can provide a definitive diagnosis, may unveil new disease-causing mutations and may allow the consideration of other therapies like interferon-alfa that has been found to increase hemoglobin levels and decrease iron overload in patients with CDA I.

MXI1 AND MXI0, PUTATIVE N-MYC ANTAGONISTS IN NEUROBLASTOMA, DISPLAY DISTINCT SUBCELLULAR LOCALIZATION PATTERNS

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Background: The Myc family regulates cell growth and has been implicated in the etiology of many cancers, including neuroblastoma. Mxi1, a member of the MAD family, inhibits N-Myc activity. Mxi0 is an alternatively spliced variant of Mxi1 with a different first exon (Exon 0) whose function has not been determined. These proteins appear to have differential functions in neuroblastoma pathogenesis: Mxi1 inhibits neuroblastoma cell proliferation, while Mxi0 promotes it. While Mxi1 and Mxi0 are mostly homologous, including their Sin3 repressive domains, they possess distinct N-terminal exons, suggesting a critical role of Exon 0 in the differential function of Mxi0.

Objectives: Determine the role of subcellular localization as a potential mechanism for the differential function of Mxi0.

Design/Method: We created GFP-tagged constructs of Mxi1, Mxi0, and Exon 0 to assess cellular localization of these proteins. Proteins were expressed in 293T cells, and subcellular localization of Mxi1, Mxi0, and Exon 0 was detected by immunofluorescence. To assess whether these proteins undergo nuclear/cytoplasmic translocation, cells were treated with Leptomycin B (LMB) to block nuclear export.

Results: Examination of Mxi1 and Mxi0 subcellular location reveals that Mxi1 resides in the nucleus, while Mxi0 is found primarily in the cytoplasm. Exon 0 also displays cytoplasmic localization, indicating that the presence of Exon 0 contributes to differential localization. Treatment with LMB resulted in accumulation of Mxi0 in the nucleus, suggesting that Mxi0 cycles in and out of the nucleus in response to appropriate signals. This effect appears to be mediated by Exon 0, as it also accumulates in the nucleus after nuclear export inhibition.

Conclusion: Mxi0 and Mxi1 exhibit distinct subcellular localization patterns, with Mxi1 residing in the nucleus and Mxi0 found predominantly in the cytoplasm. Exon 0 directs the cytoplasmic localization of Mxi0. Finally, nuclear export inhibition leads to nuclear accumulation of Mxi0, suggesting that the Mxi0 protein translocates in response to appropriate signals. A better understanding of how Mxi0 impacts neuroblastoma physiology and how Exon 0 imparts the differential function of Mxi0 may aid in developing more effective targeted therapies to improve outcomes in children with neuroblastoma.

CHARACTERIZATION OF PEDIATRIC MALIGNANCIES WITH INI1 NEGATIVE IMMUNOHISTOCHEMISTRY AND INACTIVATING MUTATIONS IN THE SWI/SNF COMPLEX

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Background: SWI/SNF subunit mutations have been identified in many cancer types and these mutations lead to specific vulnerabilities, which may be targeted with novel therapies. In a recent phase I clinical trial of an EZH2 inhibitor in adults with advanced cancers, tumor responses were seen in patients with loss of the SMARCB1 subunit as detected by negative INI1 immunohistochemistry (IHC) and in a patient with negative SMARCA4 IHC. Data suggest loss of ARID1A function also results in susceptibility to EZH2 inhibition. A phase 1 study of an EZH2 inhibitor is currently underway in children with relapsed or refractory INI1 negative tumors.

Objectives: To identify and characterize pediatric malignancies with INI1 loss by IHC and inactivating mutations in the SWI/SNF complex.

Design/Method: We conducted a search of the pathology database for tumors with loss of INI1 over a 15 year period (2000-2015). Tumors from 396 pediatric participants in a clinical sequencing study were subjected to targeted next-generation sequencing. Tumors with mutations in the SWI/SNF subunits SMARCB1, SMARCA4, and ARID1A were identified.

Results: From the pathology database, 78 patients were identified with tumors with INI1 loss by IHC. Tumor types included atypical teratoid rhabdoid tumor (n=41), rhabdoid tumor (n=23), epithelioid sarcoma (n=7), chordoma (n=2), and one each of choroid plexus carcinoma, neuroblastoma, papillary carcinoma, glomus tumor, and synovial sarcoma. Tumor sequencing revealed three patients with inactivating mutations in one or more of the SWI/SNF complex subunits: ARID1A, SMARCA4, and SMARCB1. Diagnoses included two patients with glioblastoma multiforme and one patient with malignant rhabdoid tumor of the kidney. Missense mutations with unknown functional significance in at least one of the three genes were present in 18 cases. Relevant IHC tests to evaluate functional consequence of these variants of unknown significance (VUS) are underway.

Conclusion: INI1 loss or inactivating SWI/SNF complex mutations were identified in a variety of pediatric malignancies, some not previously recognized to harbor SWI/SNF inactivation. These results may have implications for the design of future clinical trials of EZH2 inhibitors in pediatric cancer patients.

SUCCESSFUL FECAL MICROBIOTA TRANSPLANTATION FOR REFRACTORY C DIFFICILE IN A HIGH RISK NEUROBLASTOMA CHILD

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Background: Clostridium difficile infection has gained relevance in last decades, particularly among pediatric cancer patients. Metronidazole has been patterned as primary choice for treatment whereas Vancomycin, even in long courses, has been elected as 2nd line for relapsing infections. In case of multiple recurrences or refractory infection the drug choices are scarce and with no proven efficacy in pediatric patients. Fecal microbiota transplantation has evolved as a safe and successful tool for patients failing antimicrobial therapy but minimal pediatric data are available to warrant its use in childhood, namely to those under immunosuppressive treatment.

Objectives: 1st end point was eradication of recurrent C difficile infection. 2nd end point was demonstration of procedure safety.

Design/Method: A 4 years old boy with high risk neuroblastoma developed abdominal pain and diarrhea caused by C difficile while in chemotherapy. Metronidazole used in first place induced symptoms relief but other bouts occurred with the same features, despite administration of oral vancomycin and vancomycin taper. Fecal microbiota transplantation was then considered. The father was selected for donation after health overview including screening for STD, viral infections and parasitic infestation. After taking 4 days of Vancomycin 10mg/kg QID, the boy was admitted and a duodenal probe was placed. Stools from the donor were collected and 30g of the stuff were homogenized in 50ml of saline, then filtered twice before the infusion of 25ml of the final solution. After flushed with 15ml of saline the probe was removed.

Results: In the 14th day after the procedure a stool test was negative for both toxins and DNA of the agent. No side effects were reported neither during the transplantation nor through the days after.

Conclusion: Fecal microbiota transplantation has been expected to overcome unresponsive C difficile infections. Fidaxomicin could be an option but has no approval in our settings. Although promising also for children, fecal transplantation needs to be more extensively studied.

IDENTIFICATION OF RECURRENT TARGETABLE MAPK PATHWAY MUTATIONS IN MALIGNANT EPITHELIOID GLIONEURONAL TUMORS

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Background: Malignant epithelioid glioneuronal tumor (MEGNT) is a rare high-grade brain tumor that exhibits features of both glial and neuronal differentiation and is not included in the current WHO classification. Limited case series describe a highly aggressive tumor with poor survival and have shed little light on MEGNT biology. An improved understanding of the genetic alterations underlying MEGNT is necessary.

Objectives: The aim of our study was to molecularly characterize MEGNT, provide insight into the biology of this tumor and identify potential targets for treatment.

Design/Method: Whole exome sequencing (WES) and transcriptome sequencing (RNA-seq) were performed on pre-treatment tumor samples from three patients with MEGNT, as well as two additional post-radiation samples from one of these patients. Blood was available for germline WES in one case. Clinical information was obtained retrospectively by chart review.

Results: All three patients underwent subtotal (Patients 1 and 2) or gross total (Patient 3) resection followed by involved field radiation therapy. Patients 1 and 3 had disease recurrence less than a year after treatment. Patient 2 has stable disease six months off therapy. Targeted clinical testing revealed Patient 1 to have both a KIAA1549-BRAF fusion and a BRAF V600E mutation; WES identified an additional TSC1 frameshift mutation. RNA-seq analysis of patient 2 revealed an in-frame NTRK2-BEND5 fusion that is rarely found in pediatric high grade glioma. Patient 3 was found to have a BRAF V600E mutation by WES and RNA-seq revealed an in-frame SOS1-MAP4K3 fusion that has been previously reported in a case of thyroid cancer, but not CNS tumors. A post-XRT sample from this patient revealed TSC1 and TP53 mutations that were not seen in the primary tumor.

Conclusion: Potentially targetable somatic alterations targeting the MAPK pathway were identified in all three cases of MEGNT, with TSC1 mutations indicating activation of mTOR signalling also found in two tumors. Molecular studies of larger series of MEGNTs are needed to confirm the primary role of these pathways in this rare tumor. Clinical trials evaluating the efficacy of agents (BRAF, MEK, NTRK, and mTOR inhibitors) targeting the genetic lesions identified in these patients are indicated.

AUTOPHAGY INHIBITION AUGMENTS THE EFFECT OF VORINOSTAT IN PEDIATRIC CANCER CELLS

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Background: Vorinostat, a histone deacetylase (HDAC) inhibitor, has been of interest in adult and pediatric cancers. However, there is some concern that the effects of the HDAC inhibitors are compensated by autophagy. Hydroxychloroquine, an autophagy inhibitor, treatment leads to the accumulation of autophagosomes, and accelerates tumor cell death. We hypothesize that by combining a HDAC inhibitor with hydroxychloroquine, there will be an improved anti-tumor response compared to HDAC inhibitor alone in pediatric cancer cell lines.

Objectives: To determine if there is an improved efficacy of vorinostat when combined with hydroxychloroquine in pediatric solid tumor cell lines.

Design/Method: Different pediatric cancer cell lines were treated with varying concentrations of vorinostat or hydroxychloroquine, and cell viability was measured. Dose-response curves were plotted to determine IC₅₀ (inhibitory concentration 50%). Western blot analysis was performed to measure expression of proliferation and autophagy markers.

Results: The IC₅₀ of vorinostat and hydroxychloroquine was in the range of 0.5-1.25 μ M and 25-50 μ M, respectively. The combination treatment resulted in a dramatic decrease in cell viability, with these two drugs cooperating in a dose-dependent manner. Hydroxychloroquine treatment resulted in profound conversion of LC3-I to LC3-II, indicative of autophagy blockade, and this effect was greater in cells treated with both vorinostat and hydroxychloroquine alone. Finally, exposure to the combination of vorinostat and hydroxychloroquine resulted in decreased levels of phospho-ERK compared to single-agent treatment, signifying reduced cell proliferation. Taken together, our data demonstrate that when autophagy was inhibited by hydroxychloroquine in the presence of vorinostat, autophagosomes accumulated and cell viability/proliferation reduced.

Conclusion: Our results show a clear and improved response when vorinostat is combined with hydroxychloroquine compared to vorinostat alone. We also observed an increase in autophagy inhibition as well as a decrease in cell proliferation in combination studies. Furthermore the IC₅₀ concentration of vorinostat, about 200ng/ml, necessary for effect is well within the achievable clinical range of 150-500ng/ml. This combination of drugs has yet to be explored in pediatrics but has the potential to enhance the effect of an established chemotherapy agent with a well-known and easily accessible non-cancer drug.

CLR1404, A TUMOR-SELECTIVE ALKYL PHOSPHOCOLINE ANALOG INCREASES RADIATION SENSITIVITY IN SOLID TUMORS

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Background: Drugs that radiosensitize tumor cells while sparing normal tissues could have a significant impact on the efficacy of cancer radiotherapy. CLR1404 is a novel alkyl phosphocholine analog and belongs to the family of synthetic anti-tumor alkyl phospholipid compounds, some of which have demonstrated radiosensitizing capabilities. CLR1404 shows tumor-selective uptake in a wide variety of malignant tissues, and therefore we hypothesized that CLR1404 could be used as a tumor-targeted radiosensitizer to augment radiation response in a variety of solid tumors.

Objectives: To examine the capabilities of CLR1404 as tumor-targeted radiosensitizer to augment radiation response in a variety of solid tumors.

Design/Method: We examined the radiosensitizing effect of CLR1404 on several pediatric and adult solid tumor-derived human cell lines in vitro and in vivo. The selective uptake of CLR1404 in cancer cells versus normal cells was evaluated by flow cytometry, using a CLR1404-Bodipy fluorescent derivative. The in vitro radiosensitization of cancer cells was evaluated by clonogenic survival assay using CLR1404 at different concentrations with or without external beam radiation (XRT). Tumor growth rate after radiosensitization with CLR1404 followed by XRT was examined in vivo in xenograft-bearing athymic nude mice.

Results: CLR1404 demonstrated significantly higher uptake and retention in all cancer lines tested (neuroblastoma: CHLA20, NB-1691, SK-N-AS; rhabdomyosarcoma: RD, Rh-30, Rh-41; Ewing sarcoma: TC-71, TC-106; and prostate carcinoma: PC3) when compared to uptake in normal human fibroblasts ($p < 0.05$). CLR1404 significantly reduced clonogenic survival in a dose dependent manner when combined with XRT (CHLA20, Rh-30 and PC3; $p < 0.01$). Treatment of human tumor xenografts with fractionated external beam radiation combined with CLR1404 revealed a significant increase in tumor growth delay compared with CLR1404 or radiation treatment alone (Rh-30, TC-71, PC3; $p < 0.01$). There was no observable toxicity during or after the treatment.

Conclusion: We conclude that tumor targeted CLR1404 has the capacity to augment the therapeutic response to external beam radiation in a variety of solid tumors. Given the importance of radiotherapy in pediatric cancer treatment strategies, our data warrant further pre-clinical testing with the goal to translate our findings into future clinical trials.

SUCCESSFUL TREATMENT WITH PLAQUE BRACHYTHERAPY IN RECURRENT RELAPSED RETINOBLASTOMA

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Background: Retinoblastoma is the most common ocular tumor in pediatrics. Standard of care currently includes local control (laser therapy), surgical approach (enucleation), radiation and chemotherapy as potential treatment options. Despite advances in chemotherapy administration, allowing pediatric oncologist to use intra-arterial and intravitreal chemotherapy in an attempt to avoid systemic chemotherapy side effects, recurrent cases continue to be challenging to treat while trying to preserve sight through avoiding enucleation. The use of plaque brachytherapy is not yet a well-established option in recurrent retinoblastoma.

Objectives: Discuss the role of brachytherapy in relapsed retinoblastoma patients.

Design/Method: Case report

Results: A 15 month old male diagnosed with bilateral retinoblastoma group C disease in his right eye and group D in his left eye after presenting to his pediatrician with mild strabismus. He had an extensive treatment history due to continued disease recurrence. He has been followed closely with exams under anesthesia (EUAs) and local control with different laser therapies. He received five cycles of systemic chemotherapy (vincristine, carboplatin, and etoposide), followed by intra-arterial chemotherapy (including: melphalan, carboplatin, topotecan and etoposide combinations) and then intravitreal chemotherapy (melphalan), and including left eye enucleation due continued disease recurrence. Despite all these measures a central macular tumor remained measuring 9cm x 12cm with a 4cm depth and choroidal invasion without seeding on the right eye. It was then decided to attempt plaque brachytherapy as salvage treatment. The plaque used was an EP2340N (Eye Physics 2340 Notched). It was a gold ophthalmic plaque with Iodine-125 seeds, 22mm in diameter containing 32 sources with varying activity from 0.53 millicuries to 3.17 millicuries delivering 45 Gy to depth of 7mm for treatment time of 48 hours. He tolerated brachytherapy well, with no significant immediate side effects and a continued excellent response with no evidence of active tumor 27 weeks after initial plaque placement.

Conclusion: An excellent disease response can be seen with plaque brachytherapy, as seen in our case. The use of plaque brachytherapy should be considered a viable treatment option for retinoblastoma relapse cases. Further research is needed to determine how to maximize incorporation of brachytherapy within standard of care practices for retinoblastoma.

ONCOLOGIC FOLLOW-UP NOT NECESSARY FOR PEDIATRIC APPENDICEAL CARCINOID TUMORS

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Background: Patients with small, well-differentiated appendiceal carcinoid tumors are at a very low risk for recurrence. Current NCCN guidelines recommend monitoring “as clinically indicated.” There is practice variation between providers and institutions regarding extent and duration of follow-up.

Objectives: Characterize follow-up of patients with appendiceal carcinoid tumors.

Design/Method: A retrospective chart review was performed at our institution of patients with a pathology diagnosis of appendiceal carcinoid from 2000-2015. Variables analyzed included demographics, tumor location, size, extent of invasion, surgical intervention, postoperative staging, surveillance, and tumor recurrence. Costs of follow-up, including financial, time, and family anxiety were noted.

Results: Thirty patients were incidentally diagnosed with carcinoid tumor of the appendix after undergoing appendectomy as clinically indicated. Average age was 13.5 ± 2.8 years (range 8-18). Mean tumor size was 5.4 ± 4 mm (range microscopic – 15mm) with most occurring at appendiceal tip (n=18, 60%). No node infiltration was found, though three patients had perineural and one patient had lymphovascular invasion. Six tumors (20%) had appendiceal perforation and five tumors had transmural invasion into mesoappendix. Nineteen (63%) patients were referred to oncology postoperatively for staging and surveillance examinations including ultrasonography (n=11, 65%), MRI (n=7, 41%) and CT (n=6, 35%) scans. The majority (79%, n=15) underwent serial 5-HIAA testing. Mean oncologic follow-up was 36 ± 34 months with 58% (n=11) continuing surveillance. Two patients have ongoing follow-up 10 years after diagnosis, including referral to cancer survivor clinic. All surveillance testing was normal and no patients required further interventions. At least two patients traveled >4 hours for clinic visits and one patient commented on stressors related to the cancer diagnosis. Medical cost of follow-up including clinic visits, laboratory monitoring, and imaging ranged from \$8,500 to \$44,400 per patient. No patient without oncologic follow-up re-presented to surgery or oncology clinics.

Conclusion: Appendectomy is an adequate treatment for pediatric appendiceal carcinoid <16mm despite presence of histologic risk factors. Length and intensity of post-operative follow-up varied within our institution from no follow-up to prolonged surveillance. Based on our findings, we recommend minimal or no oncologic follow-up as prolonged surveillance did not lead to identification of recurrences, but rather heightened family inconvenience, anxiety, and cost of medical care.

INVESTIGATING THE ROLE OF THE TRANSCRIPTIONAL CO-ACTIVATOR TAZ IN ALVEOLAR RHABDOMYOSARCOMA

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Background: Alveolar rhabdomyosarcomas (ARMSs) are aggressive pediatric malignancies originating from primitive mesenchymal tissue and associated with skeletal muscle lineage. Sarcomagenesis is driven by the signature PAX3-FOXO1 fusion gene. Using a genetically defined model of ARMS based on early expression of PAX3-FOXO1 in human skeletal muscle precursors, our laboratory identified PAX3-FOXO1-mediated transcriptional changes that silence the Hippo pathway, a recently described tumor suppressor network widely dysregulated in human cancer. TAZ (transcriptional co-activator with PDZ-binding motif), a transcriptional co-activator ordinarily kept in check by upstream Hippo kinases, has been implicated in adult epithelial cancers. TAZ is a known regulator of wild-type PAX3, and although it conveys a mesenchymal phenotype, its role in sarcomas has not been reported.

Objectives: Investigate the oncogenic role of TAZ in ARMS tumorigenesis.

Design/Method: After confirming TAZ upregulation in our ARMS model, we determined using the NIH Oncogenomics database that TAZ is upregulated in human RMS tissue samples. We then examined basal TAZ expression in human ARMS cell lines cultured as monolayers and spheres, and used loss-of-function with two independent, lentivirally-delivered, TAZ shRNAs to interrogate the role of TAZ in supporting transformation in vitro. Last, we used a dox-inducible TAZ shRNA system in murine xenografts to interrogate the role of TAZ in supporting tumorigenesis in vivo.

Results: TAZ is expressed in human ARMS cell lines, and enriched in ARMS rhabdospheres, suggesting an increase in stemness. TAZ-directed shRNAs suppressed TAZ at both the mRNA and protein level, and caused a profound growth arrest. In vivo mouse xenograft studies rendered a strong phenotype, with tumors from the mice treated with doxycycline exhibiting decreased tumor growth and prolonged survival (median survival 17 days in the sucrose group vs 31 days in the dox group, $p < 0.0001$).

Conclusion: The transcriptional co-activator TAZ supports ARMS cell growth in vitro and in vivo, suggesting silencing of the Hippo tumor suppressor pathway. Future studies will investigate the mechanism through which this occurs, and will determine how TAZ alters the transcriptional output or physically interacts with PAX3-FOXO1. While PAX3-FOXO1 is currently not therapeutically tractable, we hypothesize that targeting TAZ may be an attractive approach for treating patients with ARMS.

MESENTERIC LYMPHATIC MALFORMATIONS IN CHILDREN

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Background: Lymphatic malformations are vascular anomalies that typically occur in the head and neck, and less frequently in the mesentery.

Objectives: To describe the clinical characteristics, treatment and outcome of children with mesenteric lymphatic malformations from a single institution.

Design/Method: A retrospective analysis of children diagnosed with mesenteric lymphatic malformations between 2006 and 2015 was performed.

Results: The median age at diagnosis of 16 patients was 4 years. Approximately two-thirds of the patients were male. The most common presenting symptom was abdominal pain. Less commonly patients presented with a volvulus (N=2) or a small bowel obstruction (N=2). Four patients were febrile at presentation, two of which had documented bacterial infections. Diagnosis was confirmed by histopathology and when assessed, immunostaining was positive for D2-40, a marker for lymphatic endothelium. 15 patients underwent a gross total resection, 12 of which had partial bowel resection. Two patients had post-operative complications involving fever, feeding intolerance, and/or perforation. One patient underwent a biopsy alone followed by observation, has remained asymptomatic and has had stable growth of the malformation proportionate to size on imaging at 12 year follow-up. Length of follow-up for all patients ranged from 0-149 months with no recorded recurrences.

Conclusion: Mesenteric lymphatic malformations in pediatrics are rare and patients commonly present with abdominal pain. Differential diagnosis includes abdominal solid tumors. Surgical resection has often been standard of care at our institution, however alternative management strategies, including medical therapy or sclerotherapy, warrant further investigation.

NOVEL SYNTHETIC LETHALITY CONCOMITANT INHIBITION OF THE HEDGEHOG AND MAMMALIAN TARGET OF RAPAMYCIN PATHWAYS IN ALVEOLAR RHABDOMYOSARCOMA

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Background: Rhabdomyosarcoma is the most common pediatric soft-tissue sarcoma. Hedgehog pathway effectors GLI1 and/or GLI2 are over-expressed in the majority of embryonal RMS cells and aberrant HH pathway activation confers a poor prognosis in rhabdomyosarcoma. Canonical HH signaling pathway activation modulates the expression of GLI transcription factors. Besides the canonical HH pathway, GLI proteins can also be activated in a non-canonical manner via phosphorylation by PI3K/AKT, mTOR/S6, RAS or MAPK/ERK. Crosstalk between HH and PI3K/AKT/mTOR signaling has been observed in different tumor entities and there is mounting evidence showing that canonical as well as non-canonical mechanisms can lead to HH activation.

Objectives: Using already existed cancer therapy ATO and Temozolomide to Co-inhibit Hedgehog and PI3K/mTOR pathways as a novel approach for synergistic apoptosis induction and tumor growth reduction in alveolar RMS.

Design/Method: We inhibited HH signaling in combination with inhibition of HH-interacting pathway-PI3K/AKT/mTOR signaling. The respective signaling inhibitors Arsenic Trioxide (ATO) and Temozolomide are established cancer therapies.

Results: ATO and Temozolomide synergistically reduce the alveolar RMS viability and proliferation; it also dampens the proliferation of alveolar RMS cells-derived xenograft tumors thereby blocking their growth. Synergistic drug interaction is confirmed by calculation of combination index (CI<0.6). In a RH30 xenograft model, combination treatment resulted in 80% inhibition of tumor growth. Western blotting results showed the p70S6K, 4-EBP1, total AKT and p-AKT protein expression were inhibited by the combination treatment in RH30 cells.

Conclusion: Combined Hedgehog and PI3K/mTOR inhibition represents a promising novel approach for synergistic apoptosis induction and tumor growth reduction with implications for new treatment strategies in alveolar RMS.

CLINICAL AND GENETIC FINDINGS IN SERTOLI-LEYDIG CELL TUMORS, JUVENILE GRANULOSA CELL TUMORS AND GYNANDROBLASTOMA: AN UPDATE FROM THE INTERNATIONAL OVARIAN AND TESTICULAR STROMAL TUMOR (OTST) REGISTRY

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Background: Ovarian sex cord-stromal tumors occur in children, adolescents and young adults. They include juvenile granulosa cell tumors (JGCT), Sertoli-Leydig cell tumors (SLCT), and gynandroblastomas and may be associated with germline mutations in DICER1.

Objectives: To investigate the clinical and biologic aspects of these rare tumors.

Design/Method: For each participant, available pathology was centrally reviewed and germline DICER1 testing was performed. Comparisons were made among DICER1 test result groups using Pearson's Chi-square or Fisher's exact tests and Wilcoxon rank-sum tests.

Results: Seventy-three individuals with SLCT, JGCT, or gynandroblastoma have enrolled in the OTST Registry since December 2011. Overall median age at diagnosis was 15 years (InterQuartile Range 8-21). Forty-five percent (n=33) were stage 1a. Sixty-three percent of SLCT and gynandroblastoma (n=46) were intermediately or poorly differentiated. Twenty-two percent (n=16) of SLCT had heterologous elements, including 14% sarcomatous (n=10) and 11% (n=8) with a retiform pattern. Nineteen percent (n=14) of patients had thyroid nodules and 8% (n=6) had thyroid cancer. Four percent (n=3) of patients developed metachronous ovarian stromal tumors, and 4% (n=3) of patients had pleuropulmonary blastoma. In addition 14% (n=10) reported other non DICER1-related tumors, 12% (n=9) recurred and 4% (n=3) died of progressive disease. Forty percent (n=23) of the 57 patients tested had germline DICER1 mutations. Of patients with SLCT, 53% (20/38) of tested patients had germline DICER1 mutations as did 3 of 4 patients with gynandroblastoma. Preliminary analyses show 5 additional SLCTs with biallelic somatic DICER1 mutations. Compared to DICER1 germline negative patients, the prevalence of thyroid nodules (39% vs. 9%, p=0.009) and thyroid cancer (26% vs. 0%, p=0.003) was significantly higher among germline positive patients. Germline DICER1 mutations do not appear to impact outcome of the primary tumor, but are a risk factor for other tumors. The impact of biallelic somatic mutations in DICER1 is under investigation.

Conclusion: Enrollment is ongoing. More than half of individuals with SLCT and 3 of 4 patients with gynandroblastoma had germline mutations in DICER1. Biallelic somatic DICER1 mutations were also found in SLCT. These findings warrant further investigation of germline and somatic DICER1 mutations and review of screening guidelines.

VINCRIStINE, IRINOTECAN, AND TEMOZOLOMIDE FOR RELAPSED RHABDOMYOSARCOMA

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Background: Rhabdomyosarcoma (RMS) is the most common soft tissue sarcoma in children with overall survival ranging from 15-75% based on risk group. Anecdotal reports describe the use of vincristine, irinotecan and temozolomide (VIT) for patients with relapsed RMS.

Objectives: We determined response rate (RR) and progression-free survival (PFS) for patients with relapsed RMS treated with VIT.

Design/Method: A retrospective review of patients with relapsed RMS treated with VIT from 5 tertiary care hospitals from 2000-2013. Characteristics including age at diagnosis, histologic subtype, primary tumor location, chemotherapy and local control at time of relapse, number of relapses, time to recurrence, survival time and number of prior salvage regimens were collected. Response was assessed by the treating institutions.

Results: The median age of 20 patients was 8 years (range 0.5-17 years) at diagnosis; 65% were male. 65% had alveolar RMS; 25% had metastatic disease at diagnosis. Doxorubicin-based chemotherapy was used upfront in 4 (20%). 75% received upfront chemotherapy with vincristine, actinomycin and cyclophosphamide. Median time to relapse was 15 months (range 2.7-45 months). VIT was used as 1st, 2nd, 3rd or 4th line of therapy in 5, 7, 6 and 2 patients, respectively. 6% of patients had ≥ 2 sites of relapse, 24% had solitary distant relapses, and the remainder had local relapse. Dose of vincristine was 1.5 mg/m². Irinotecan (50 mg/m² intravenously or 70-100 mg/m² orally) was administered daily for 5 days. Temozolomide 100-150 mg/m² was administered orally daily x 5 days. Local control included radiation for 45%, and surgery for 35% patients. Best response to VIT was as follows: 3 (CR), 0 (PR), 5 (SD) and 12 (PD) for an overall RR of 15%. The PFS at 3 months was 37%. At a median follow up of 8 months, 2 patients were alive without disease, 3 were alive with disease and 15 patients had died of progressive disease.

Conclusion: Our retrospective study demonstrates that VIT has moderate activity in patients with relapsed rhabdomyosarcoma. Further study of this backbone in combination with newer agents is warranted.

SYSTEMIC CISPLATIN EXPOSURE DURING INFANCY AND ADOLESCENCE IMPAIRS RETRIEVAL OF OBJECT MEMORY, CONTEXTUAL-OBJECT DISCRIMINATION AND CONTEXT AND CUED FEAR CONDITIONING IN ADULTHOOD: EVIDENCE FOR AGE-DEPENDENT AND CISPLATIN-DRIVEN DISRUPTION OF MEMORY FUNCTIONS

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Background: Impairments in memory, attention and executive function affect 15-50% of childhood leukemia survivors and has been associated with methotrexate exposure. Systemic cisplatin is used to treat a variety of childhood and adult cancers, yet the risk and extent of cognitive impairment due to platinum-based chemotherapy is unknown. Systemic cisplatin is CNS penetrating and is cytotoxic to neurons, neuronal stem cells and hippocampal dendrites. Survivors of non-leukemic cancers may be at risk for significant memory impairment related to cisplatin driven neurotoxicity.

Objectives: Explore the effects of systemic cisplatin on hippocampal and amygdala-dependent memory functions in a juvenile rat model.

Design/Method: Twenty-four male Sprague Dawley rats were obtained weaned at post-natal day 21 or 31. Cisplatin (2mg/kg/day for 5 consecutive days, intraperitoneal) was administered in infancy (post-natal day 25) and adolescence (post-natal day 35). Matched controls received normal saline intraperitoneally. Validated hippocampus-dependent memory testing was completed during adulthood (post-natal day >65), including novel object exploration and contextual object discrimination. Object exploration was recorded in seconds and a discrimination ratio was calculated by dividing the difference in exploratory time between objects by total exploratory time. Context and cued fear conditioning was performed to examine hippocampus and amygdala function, respectively. Percent of time spent freezing in response to context stimulus and cued stimulus was observed. Comparisons were made using unpaired t-test.

Results: During novel object testing cisplatin treated adolescents showed significantly poor retrieval of a familiar object as compared to controls ($p=0.033$). Both cisplatin treated infants and adolescents, however, showed poor discrimination for an out-of-context familiar object as compared to controls (infants: $p = 0.08$; adolescents: $p = 0.017$). Finally, cisplatin treated infants showed near significant diminished freezing response to conditioned context stimulus ($p=0.059$). Cisplatin treated infants also showed significant diminished response to conditioned cued stimulus ($p=0.015$).

Conclusion: Hippocampal-dependent memory functions are impaired in rats exposed to systemic cisplatin during infancy and adolescence. The type and degree of hippocampal dysfunction differs depending on age at time of cisplatin exposure. Further, exposure during infancy affected both hippocampus and amygdala function, signifying a more global effect on memory functions at this age.

ACTIVATING TRANSCRIPTION FACTOR-6 α DEPENDENT REGULATION OF RHEB-mTOR AND NOTCH SIGNALING CONTRIBUTES TO CHEMORESISTANCE IN OSTEOSARCOMA

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Background: The optimal treatment strategy for patients with refractory and/or metastatic osteosarcoma (OS) is yet to be defined and continues to be a persistent challenge. The high degree of genetic aberrations and tumor heterogeneity has impeded the identification and testing of effective therapeutic targets. Therefore, finding and characterizing cellular mechanisms, which contribute to OS chemoresistance is a promising strategy for designing therapies that can change the outlook for patients with this disease.

Objectives: Endoplasmic reticulum (ER) stress pathways are known to promote survival and progression of cancer cells. The objective of the current study is to examine the role of this pathway in promoting chemoresistance in OS.

Design/Method: We utilized immunohistochemistry, Western blotting, qPCR and immunofluorescence and bioinformatics tools and techniques to examine the role of activating transcription factor-6 (ATF6) and its downstream effectors on OS cells and patient samples.

Results: Using pathway analysis of gene expression datasets of human OS primary tumors, protein processing in the ER was found to be significantly enriched in OS tumors as compared to normal tissue. We confirmed the activation of ER stress pathways IRE-1, PERK and ATF6 α in human OS cell lines and found that while all three pathways were differentially activated in the OS cell lines, only ATF6 α activation significantly enhanced chemoresistance to cisplatin, irinotecan and combinatorial treatment with cisplatin and the mTOR inhibitor rapamycin. This occurred via inhibition of Bax activation, suppression of RHEB-mTOR and inhibition of NOTCH signaling. Our findings highlight a novel mechanism of chemo-resistance in OS. Retrospective analysis of primary tumors from patients with OS showed that about 60% of these tumors expressed high levels of the ER stress induced transcription factor ATF6 α and its downstream pro-survival effectors such as BiP and PDI. This expression was associated with poor histological response and/ or poor survival in patients

Conclusion: Our findings emphasize a previously uncharacterized role for ATF6 α as the nexus of a unique and versatile signaling network that regulates pathways that is crucial for the pathogenesis and therapy resistance of OS. Hence therapeutic targeting of the ATF6 α pathway holds promise as an innovative and effective treatment strategy for OS.

GLUT-1 POSITIVE HEPATIC HEMANGIOMA AS A CANCER PREDISPOSITION CONDITION

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Background: Hepatic infantile hemangioma (HIH) is a benign vascular tumor with a natural course of proliferation, stabilization and involution. Angiosarcoma is a rare but highly fatal soft tissue sarcoma of endothelial cell origin. Reviewing the literature, from 34 cases of pediatric hepatic angiosarcoma, 20 had co- or pre-existing hepatic hemangioma. There are no accepted guidelines for long-term monitoring of hepatic hemangiomas, nor are accepted standards of care in pediatrics for treatment of angiosarcoma.

Objectives: To describe our experience with hepatic hemangiomas associated with hepatic angiosarcoma and integrate our results with published literature.

Design/Method: Both patients were three-years-old, unrelated, presenting with abdominal distension, constipation and the history of small, untreated, cutaneous infantile hemangioma.

Results: Case one is a girl admitted with multiple, diffuse hepatic hemangiomas that required liver transplantation. Histologic analysis of the resected liver revealed GLUT-1 positive HIH and islands of highly proliferative cellular atypia with malignant transformation. One year after the transplant, surveillance imaging detected pulmonary nodules. Two of the nodules were resected and histology revealed the same pathology. She completed six cycles of ifosfamide/doxorubicin and now remains in complete remission sixteen months after diagnosis. Case two is a boy admitted with a large hepatic mass, hypothyroidism and multiple pulmonary nodules. He underwent gross total resection and tumor pathology showed GLUT-1 positive HIH and islands of angiosarcoma. His disease progressed rapidly on sorafenib therapy. Therapy was changed to ifosfamide/doxorubicin, and after an initial partial response, his disease again progressed. He was subsequently switched to bevacizumab/gemcitabine/docetaxel, and despite good quality of life, he again experienced progressive disease. The newly formed metastatic hepatic nodules proved to be Glut-1 positive infantile hemangioma. He died fourteen months after diagnosis due to massive intratumoral hemorrhage.

Conclusion: HIH may be a risk factor for developing angiosarcoma at a very young age. We recommend that hepatic Glut-1 positive hemangioma to be added to the potential cancer predisposition conditions. These patients should be monitored prospectively in vascular anomalies or cancer predisposition clinics, so that the incidence/true risk of developing angiosarcoma can be ascertained. Hopefully, early detection of atypical progression may lead to life-saving medical intervention.

THE ROLE OF INTEGRIN BETA-3 AND INTEGRIN SIGNALING IN DRIVING METASTATIC EWING SARCOMA

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Background: Despite advances in diagnostic and therapeutic approaches, metastatic Ewing sarcoma (ES) continues to have extremely poor overall survival. The mechanisms driving metastasis remain largely unknown, necessitating examinations into molecular mechanisms of pathogenesis, novel targets and investigational therapies. Integrins, such as ITGB3, are a family of cell-surface proteins participating in important cell-surface-mediated intracellular signaling pathways involved in regulating critical tumor cell properties such as differentiation, proliferation, dissemination and apoptosis. Our hypothesis is that upregulation of ITGB3 and its downstream signaling events perform important roles in metastasis of ES and may be a potential therapeutic target.

Objectives: To investigate the role of ITGB3 and its downstream signaling pathways in driving establishment of metastasis in ES.

Design/Method: We performed in vivo studies designed to gain insights into metastatic transcriptome and proteomic signatures for ES. Established human ES cells (TC71 and A673) were orthotopically transplanted into the tibia of mice and, after 4-6 weeks, the primary bone tumors as well as distal metastatic lesions were isolated and processed. We completed proteomic studies using reverse-phase protein array comparing protein expression profiles of primary ES tumors to the corresponding metastatic lesions in the lung and secondary bone sites. We used Western blot analysis to validate the results.

Results: The array showed significant alterations in a few key signaling molecules, including upregulation of ITGB3 in both metastatic lung and secondary bone lesions compared to primary bone lesions, with a 2.67 fold change ($p < 0.0012$). We validated ITGB3 upregulation by performing protein isolation from the previously resected primary and metastatic tumors and individually assessing expression of ITGB3 using Western blot analysis, confirming consistently elevated ITGB3 expression in the metastatic sites compared to the primary tumors for both ES cell line models.

Conclusion: These results suggest that ITGB3 and its downstream signaling events may play a key role in the ability of ES to establish metastatic foci and may serve as a potential therapeutic target. We continue to investigate this pathway both in vitro and in vivo, using ITGB3 knockdown and overexpression approaches to assess proliferation, apoptosis and invasion/migration, as well as small molecule inhibitors to investigate this pathway as a potential therapeutic target.

EXERCISE PRECONDITIONING MITIGATES DOXORUBICIN UPTAKE IN CARDIAC TISSUE

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Background: Anthracyclines are commonly used anti-neoplastic agents in pediatric oncology. However, their use is limited due to their potentially severe cardiac toxicity. Attempts to mitigate cardiotoxicity have included dose limitation and the use of iron chelators such as dexrazoxane. Recent preclinical data has shown that low to moderate intensity exercise attenuates long-term cardiotoxicity in animals receiving chronic doxorubicin treatment. Little is known about the effect of exercise on doxorubicin diffusion into cardiac tissues.

Objectives: To determine whether exercise preconditioning prior to treatment reduces doxorubicin uptake in the hearts of tumor-bearing mice.

Design/Method: 2.5×10^6 TC 71 Ewing's Sarcoma cells were injected subcutaneously into 14 nude mice. Tumors were allowed to grow for 10 days. Animals were then allocated to exercise (6) and no exercise groups (6). Animals in the exercise group were exercised on a treadmill for 45 min/day at a rate of 12m/min for 5 consecutive days followed by a 2 day rest period; exercise was then repeated for a second week. 24 hours after the final exercise session 12 of the 14 animals received a 10mg/kg bolus dose of doxorubicin via tail vein injection. The remaining 2 animals served as tissue controls. Organs were excised 30 minutes post injection. Organ tissue was weighed prior to homogenization. All tissue samples were then evaluated for doxorubicin uptake using acid isopropanol extraction and spectrophotometry.

Results: The average heart size of exercise trained animals was larger (20.8g) than non-exercise trained animals (15.9g). After adjustment for cardiac tissue size, exercise preconditioned animals had significantly less doxorubicin present in cardiac tissue compared to unexercised controls, 224.6 vs 595.5 fluorescent units ($p = 0.04$, Fig 1). Interestingly, this may be a cardiac specific effect; there was no change in doxorubicin levels in liver or soleus muscle between exercised and non-exercised mice (Fig 1).

Conclusion: We found that exercise preconditioning decreases doxorubicin uptake by cardiac tissue. Currently, we are evaluating both cardiac vasculature and expression of MDR transporters, which may impact doxorubicin uptake, to identify the mechanism by which exercise preconditioning reduces doxorubicin in cardiac tissue.

IDENTIFICATION OF MOLECULAR ABERRATIONS CONTRIBUTING TO BONE SARCOMA RADIOTHERAPEUTIC RESISTANCE

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Background: Osteosarcoma (OS) and Ewing sarcoma (EWS) are the most common pediatric bone cancers, and patients with OS and EWS have dismal five year overall survival rates of 20-30% for metastatic disease. Adequate local control is imperative for patient survival, but little has been done to elucidate mechanisms of bone sarcoma radioresistance. EWS is considered radiosensitive, and OS is relatively radioresistant. We hypothesize there are specific mechanisms that contribute to forms of radiotherapeutic resistance in bone sarcomas.

Objectives: Elucidate mechanisms of radiotherapeutic resistance in OS and EWS.

Design/Method: We administered radiation in vitro to three OS cell lines and three EWS cell lines to establish radiation-treated populations. The controls for each population were respective wild type cells which did not receive radiation. We characterized radiation-treated population phenotypes with proliferation, invasion/migration, and clonogenic assays, as well as cell survival after repeat radiation exposure. We also performed microarray gene expression (GEX) and reverse phase protein array (RPPA) in the radiation-treated populations.

Results: There were some significant changes in cell proliferation and clonogenicity, but these changes were not consistent in all OS and EWS populations. We noted no difference in the cell survival of any of the radiation-treated cell lines when re-exposed to radiation. However, we did see an upwards trend in the invasiveness of various radiation-treated cell lines. Our GEX and RPPA data also revealed two pathways of interest with statistically significant differences in both RNA and protein expression: KLF4 pathway and mTOR pathway. Derangements in both have been linked to multiple cancers, and the mTOR pathway has been implicated in the pathogenesis of bone sarcomas.

Conclusion: Our data suggest increased invasiveness as well as demonstrate statistically significant differences in both RNA and protein expression in pathophysiologically relevant pathways in radiation-treated bone sarcoma cells. We conclude that these findings warrant further investigation in both in vitro and in vivo models to elucidate mechanisms of radiotherapeutic resistance, and we are currently developing a Ewing sarcoma mouse model using our radiation-treated cell populations. We also plan to apply relevant radiosensitizers to this model with the goal to translate significant results to improvement in outcomes for patients with bone sarcomas.

EXPANSION AND TRANSDUCTION OF CLINICALLY RELEVANT GAMMA DELTA T CELLS

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Background: Immunotherapy relies on several patient-specific parameters, including i) cell number before and after expansion, ii) targeting immune cells to tumors, iii) cell survival and function after infusion, and iv) on- and off-target adverse events. Novel approaches, such as expansion of gamma delta T cells, as opposed to alpha beta T cells, are being pursued. Gamma delta T cells are reasonable candidates for anti-neoplastic immunotherapy because they i) possess inherent anti-tumorigenicity, ii) require no priming, iii) direct tumor killing via recognition of stress-responsive ligands, and, as we show, iv) can be expanded in cGMP serum free media (SFM). Bioengineering of gamma delta T cells to express chimeric antigen receptors (CARs) can augment their anti-cancer effects. High-risk neuroblastoma is an appropriate choice for gamma delta T cell-based immunotherapy as naïve gamma delta T cells are cytotoxic to neuroblastoma cells and neuroblastoma cells express known target antigens.

Objectives: Optimize expansion and transduction of anti-neuroblastoma gamma delta T cells.

Design/Method: The effectiveness of gamma delta T cell expansion stimulated by IL-2 and bisphosphonates was evaluated in several SFMs. The expanded gamma delta T cells were evaluated for transduction efficiency using lentiviral vectors. Expanded naïve and modified gamma delta T cells were assessed for cytotoxicity toward neuroblastoma cells.

Results: Of the SFM cultures, only one showed reliable expansion to clinically relevant numbers. OpTmizer media supplemented with high-dose IL-2 led to robust expansion as well as efficient transduction across multiple donors, comparable to that observed for alpha beta T cells with similar multiplicity of infection. Naïve gamma delta T cells were cytotoxic toward a neuroblastoma cell line, which was enhanced by addition of an anti-GD2 CAR.

Conclusion: An optimized method of gamma delta T cell expansion and transduction was developed that can be tested in early phase clinical trials. The absence of MHC-restriction affords the opportunity, with appropriate elimination of alpha beta T cells, for use in the allogeneic setting with limited risk of graft versus host disease, and the use of SFM provides a clinically safer and potentially more efficacious cellular immunotherapy. Gamma delta T cells display cytotoxicity toward neuroblastoma that increases with the addition of an anti-GD2 CAR.

PAR1 ACTIVATES NF- κ B AND PROMOTES METASTASIS IN OSTEOSARCOMA

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Background: Osteosarcoma is the most common primary bone cancer in children and adolescents. Despite real improvements in patient outcomes over the past decades, a diagnosis of metastatic osteosarcoma portends an exceptionally poor prognosis: the five-year survival rate of patients with metastases is less than 25% even with neoadjuvant chemotherapy treatment. PAR1, a G-protein coupled cell surface receptor, activates an intracellular signaling cascade when acted upon by thrombin, a secreted serine protease important in the coagulation cascade. PAR1 expression has been associated with increased osteosarcoma invasion and metastasis; we sought to determine the molecular mechanism by which this increase occurs. In endothelial cells, our laboratory observed that PAR1 stimulation caused activation of the inflammatory transcription factor family NF- κ B. NF- κ B activation is closely associated with the tissue invasion and extravasation steps of metastasis in osteosarcoma and other cancers. We hypothesized that an intracellular signaling complex, the CARMA3 / Bcl10 / MALT1 signalosome, may play a role in this signal transduction.

Objectives: To identify the mechanism by which PAR1 activates NF- κ B in osteosarcoma and to determine whether this pathway is suitable for pharmacological inhibition.

Design/Method: Activation of NF- κ B was examined using immunoblotting of phosphorylated Inhibitor of kappa-B (I κ B) and through the use of a luciferase reporter assay. NF- κ B-dependent gene transcription was evaluated by real-time PCR. To study osteosarcoma invasiveness in vitro, we used a transwell chamber (Boyden chamber) assay in which cells invaded through a matrigel layer.

Results: We found that treatment of U2OS human osteosarcoma cells with either thrombin or with the PAR1-specific peptide agonist TRAP6 induced robust activation of the canonical NF- κ B signaling pathway. Specifically, we observed PAR1-dependent phosphorylation of I κ B, transcriptional activation of an NF- κ B luciferase reporter plasmid, and nuclear translocation of the RelA subunit of NF- κ B. Further, we discovered that siRNA-mediated knockdown of MALT1 completely abrogated PAR1-dependent NF- κ B activation in osteosarcoma cells. Additional gene expression profile array data detailing the metastatic reprogramming in PAR1-stimulated osteosarcoma cells will be presented.

Conclusion: PAR1 stimulation caused NF- κ B activation in a MALT1-dependent fashion in osteosarcoma cells. MALT1 proteolytic activity inhibition may be a potential therapeutic strategy to combat osteosarcoma in the future.

PHASE 1 STUDY EVALUATING THE SAFETY AND PHARMACOKINETICS OF PANITUMUMAB IN CHILDREN WITH SOLID TUMORS

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Background: Panitumumab is a human anti-epidermal growth factor receptor (EGFR) antibody approved for treatment of metastatic colorectal cancer in adults. Some pediatric solid tumors express EGFR and limited studies have indicated that anti-EGFR therapies may have anti-tumor activity in this population. No clinical trial has reported on the use of panitumumab in pediatric patients.

Objectives: To evaluate safety, pharmacokinetics, and efficacy of panitumumab monotherapy in pediatric patients with relapsed/refractory solid tumors.

Design/Method: Patients of 1 to <18 years old were eligible. EGFR expression status was evaluated by IHC. Six dose cohorts (4-6 patients) were planned using a rolling 6 dose escalation design: A: 2.5 mg/kg weekly, B: 6 mg/kg every 2 weeks, and C: 9 mg/kg every 3 weeks, each with 2 age groups (group 1: 12 to <18 yrs; group 2: 1 to <12 yrs). Dose limiting toxicities (DLTs) were assessed using CTCAEv.3.0. Pharmacokinetics was assessed during the first 8 weeks to determine first dose kinetics and steady state. Response was evaluated every 8 weeks using modified RECIST v1.0 criteria.

Results: Enrolled patients (total=31; group 1=17; group 2=14) had CNS tumors [13 (41.9%)], bone sarcomas [10 (32.3%)], soft tissue sarcomas [6 (19.4%)] and Wilms tumors [2 (6.5%)]. DLTs during DLT evaluation period were reported in 5 (22.7%) patients, including 1 patient each in cohorts A1 (apnoea, peripheral motor neuropathy, respiratory acidosis and seizure) and A2 (elevated alanine aminotransferase), and 3 patients in B2 (cerebral haemorrhage, hypoxia, reduced neutrophils and platelets). Skin and gastrointestinal adverse events were reported in 74.2% (6.5% grade 3) and 67.7% (12.9% grade 3) total patients, respectively. Among 16 patients with baseline measurable disease, the best response was stable disease in 4 patients, all with CNS tumors. The pharmacokinetic parameter estimates (6 mg/kg cohort) were similar to those in adult patients, with a mean half-life of 4-5 days after first dose. Mean pharmacokinetic profiles for group 2 were similar or a trend of lower exposure (C_{max} and AUC) compared to group 1.

Conclusion: The safety and pharmacokinetic profile of panitumumab in pediatric patients was similar to that in adults. Trial was sponsored by Amgen, Inc.

CONDITIONAL SURVIVAL AND PREDICTORS OF LATE DEATH IN PATIENTS WITH EWING SARCOMA

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Background: Long term survivors of Ewing sarcoma (EWS) are at considerable risk for future complications, including late relapse and death. Data on prognostic factors for late death in those who have survived beyond five years are lacking.

Objectives: We utilized data from the Surveillance, Epidemiology, and End Results (SEER) database to conduct a retrospective cohort study with the following aims. First, we sought to utilize this population-based registry to describe clinical features and clinical outcomes of patients with EWS who have survived 5 years from initial diagnosis. Second, we aimed to identify univariate and multivariable prognostic factors for death in 5-year survivors of Ewing sarcoma and thereby enable more risk-stratified care during follow-up.

Design/Method: We conducted a retrospective cohort study using the Surveillance, Epidemiology, and End Results (SEER) database. We obtained clinical features and outcome data on 1,351 patients with EWS who had survived 60 months or greater. From these data, we performed univariate and multivariable analyses of overall survival using log-rank tests and Cox proportional hazards models.

Results: Of 1,351 patients in the cohort, there were 209 deaths, 144 (69%) of which were reported to be due to EWS. The OS for five-year survivors at 10 years was 87.5% (95% confidence interval 85.4-89.3%). Univariate adverse prognostic factors for late death in 5-year survivors included age >18 years at initial diagnosis, male sex, and axial/pelvic primary site. Initial stage was not prognostic. Independent adverse prognostic factors for late death included black race [hazard ratio (HR) 2.16, P=0.01], age \geq 18 years at diagnosis (HR 2.02, P<0.001), male sex (HR 1.43, P=0.01), and axial/pelvic primary site (HR 1.43, P=0.02).

Conclusion: The majority of late deaths in five-year survivors are due to EWS. Black race, age > 18 at diagnosis, male sex, and axial/pelvic primary site (but not stage at diagnosis) are independently associated with increased risk of late death.

USE OF DENOSUMAB IN THE TREATMENT OF CENTRAL GIANT CELL GRANULOMA

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Background: Central giant cell granuloma (CGCG) is a benign osteolytic neoplasm of the jaw characterized by a mass that is infiltrated with osteoclast like giant cells. It is typically slow growing and painless but can cause loosening and displacement of teeth as well as anatomical distortion of teeth. The management of CGCG is conservative though a minority of patients may require more aggressive surgical management of the affected area. Denosumab, a RANK-L inhibitor, has been demonstrated to induce regression of giant cell tumor of bone (GCTB) though a distinct condition shares many similarities with CGCG.

Objectives: To evaluate the off label use of denosumab in the management of CGCG.

Design/Method: A 14-year-old male presented with an 8-year history of a large recurrent and progressive, non-tender mandibular biopsy proven CGCG. Although initially treated with numerous attempts at curettage, on subsequent progression, he also received intralesional steroids and calcitonin. With recurrence and ongoing progression, there was consideration of a more definitive surgical management consisting of partial mandibulectomy and reconstruction. To avoid a potentially morbid procedure, off label use of denosumab was initiated based on its current use in patients with GCTB. The patient received Denosumab 120mg SC every week for three weeks followed by Denosumab 120mg SC every month. Response to therapy was based on panoramic dental radiographs as well as physical exam.

Results: Initial exam prior to start of denosumab showed an opaque, greyish, 2.5cm lesion of the anterior mandible that was nontender, nonmobile. Adjacent teeth were also loosened and mobile. Radiographs showed a radiolucent multiloculated anterior mandibular lesion. After four weeks of treatment with denosumab, the lesion showed regression on the lateral and medial aspects of the lesion with increased cortical stability. Radiograph showed calcification of the lesion. After 6 months of denosumab there is almost complete resolution of the lesion. There were no toxicities or adverse events from denosumab treatment.

Conclusion: Although the underlying pathogenesis of CGCG is unclear, various studies implicate dysregulation of odontoclasts, osteoclasts associated with resorption of deciduous teeth. As such, we hypothesize that inhibition of the RANK/RANK-L signaling pathway in this disease may be an effective therapeutic modality.

GENOME-WIDE DNA METHYLATION ANALYSIS DEFINE EPIGENETIC SIGNATURES IN PEDIATRIC SARCOMA TUMORS

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Background: Pediatric sarcomas are a diverse group of malignancies of the bone and soft tissue that accounts for approximately 15 - 20% of pediatric cancer. Only a subset of sarcomas harbor known recurrent genomic alterations or oncogenic gene fusions that are pathognomonic. Tumors that lack such recurrent alterations frequently represent a diagnostic challenge. Epigenetic modifications, such as global or specific changes in DNA methylation, are increasingly being recognized as a primary mechanism of oncogenesis in pediatric cancer. Genome-wide methylation profiling is emerging as a powerful tool to identify biologically and clinically relevant subgroups. To date, few studies with limited sample sizes have examined genome-wide DNA methylation in pediatric sarcomas.

Objectives: Using the Illumina Infinium Human Methylation450 BeadChip Array (450K array) platform, we performed genome-wide DNA methylation analysis on a pilot/discovery cohort of pediatric sarcomas to identify their associated gene, promoter, and CpG island methylation signatures and explore key clinical and biological associations.

Design/Method: We analyzed DNA from 61 pediatric sarcoma samples, including osteogenic sarcoma (n = 21), Ewing sarcoma (n = 15), rhabdomyosarcoma (n = 10) and synovial sarcoma (n = 15). Unsupervised hierarchical clustering analysis was performed to compare epigenetic signatures between and among disease subtypes.

Results: Unsupervised hierarchical clustering analysis revealed that osteogenic sarcoma, Ewing sarcoma, and synovial sarcoma tumours have distinct DNA methylation profiles whose distribution is associated with known histological subtypes. Although the DNA methylation profiles of rhabdomyosarcomas do not cluster distinctly, they tend to be grouped with either osteogenic or synovial sarcomas.

Conclusion: We were able to identify epigenetic signatures that are distinctly associated with known histologic subtypes of pediatric sarcoma. These results suggest that DNA methylation profiling has diagnostic utility in these tumours. An exploratory analysis investigating the clinical and prognostic significance of the genetic/epigenetic changes is currently ongoing.

RECURRENT PEDIATRIC EPENDYMOMAS EXHIBIT INCREASED TUMORIGENICITY IN MOUSE BRAINS OF PATIENT-DERIVED XENOGRAFT MODELS

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Background: Ependymoma (EPN) is the third most common malignant pediatric brain tumor. Current standard treatment is maximally safe surgical resection followed by radiation therapy. Chemotherapies have not been proven to increase survival outcomes (5-year Event Free Survival 40-85%). Prognosis is even more dismal in those with recurrent EPN which occurs in nearly half of the patients, and there are no known curative options. Therefore, it is imperative to learn more about the biology of recurrent diseases and identify the cellular driver of EPN recurrence, as well as understanding the mechanisms of therapy resistance. We hypothesize that ependymoma recurrence is driven by a subpopulation of therapy-resistant tumors cells with enhanced tumorigenicity in SCID mice.

Objectives: To study the tumorigenicity of recurrent pediatric ependymomas at the different clinical stages, whether at diagnosis, first recurrence, second recurrence, or beyond.

Design/Method: Over the last 10 years, we have collected a total of 77 pediatric ependymoma patient tumor samples from across the country. Of those, we identified 9 patients with recurrent ependymomas in which we have collected tumor samples from each recurrence (n=9 sets). The median age of these patients is 6 years old (ranges from 2 – 10 years). The median time to first recurrence is 35 months (ranges from 9 – 61 months). Each set has from 1 to 5 recurrences. To study the tumorigenicity of these brain tumors at the different clinical stages, we directly implanted tumor cells (1×10^5 cells/mouse) from all 9 patients into the matched locations in the brains of SCID mice (e.g., human cerebral tumors to mouse cerebrum, human cerebellar tumors to mouse cerebellum) and monitored for tumor formation.

Results: In 3 of the 9 sets, tumor formation was confirmed in mouse brains from the latest recurrent patient tumor, while samples from the same patient from earlier stages either did not form tumors in mouse brains or are currently pending. Tumor formation in the remaining models are still pending.

Conclusion: Our preliminary findings demonstrate progressive enhancement of tumorigenicity during ependymoma recurrence. This has become a very unique and extremely valuable platform to study brain tumor recurrence.

IN VIVO TUMOR DESTRUCTION THROUGH CRYOABLATION WITH LIQUID NITROGEN FOR SUBSEQUENT USE AS AUTOLOGOUS GRAFT IN PEDIATRIC PATIENTS WITH MALIGNANT BONE TUMORS IN A BRAZILIAN HOSPITAL

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Background: Bone reconstruction after resection of malignant tumors block is a subject of constant debate. For nearly 20 years it has been developed the biological reconstruction method of in vivo tumor destruction through cryoablation with liquid nitrogen, which is now an option in the treatment of pediatric patients with bone tumors.

Objectives: Present the preliminary results of the bone reconstruction through the redeployment of bone tumor after treatment with liquid nitrogen in pediatric patients with bone tumors in Hospital Pequeno Principe.

Design/Method: This retrospective study included patients diagnosed with Ewing's sarcoma and osteosarcoma treated by the departments of Pediatric Oncology and Pediatric Orthopaedics of Pequeno Príncipe Hospital, from September 2005 to December 2012, who performed bone reconstruction through the redeployment of bone tumor after treatment with liquid nitrogen.

Results: Seven patients were analyzed, with a mean age of 10 years, ranging between 5 and 15 years. The local recurrence rate was 0%. The consolidation time varied between 3 and 6 months, occurring on average 4.5 months after surgery. The limb function after consolidation was classified between good and excellent. They recorded three deaths, unrelated to the applied technique.

Conclusion: This technique offers an alternative biological reconstruction, with the added benefits of allowing perfect bone fitting, easy adjustment to ligaments and tendons, not depend on bone bank or foreign material, provide more rapid consolidation, and have lower cost and greater graft longevity.

PHASE I STUDY OF BRAF INHIBITOR (VEMURAFENIB) IN COMBINATION WITH THE MTOR INHIBITOR (EVEROLIMUS) IN BRAFV600E POSITIVE PEDIATRIC AND AYA BRAIN TUMORS

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Background: Vemurafenib has been US FDA approved for the treatment of relapsed or refractory BRAF V600 mutation positive malignant melanoma. It has demonstrated activity in multiple non-melanoma BRAF V600 mutation cancers as well. [1] Resistance always develops with monotherapy. Pre-clinical studies demonstrate that concurrent mTOR inhibition can overcome the innate or acquired resistance to BRAF inhibition.

Objectives: We hypothesized that combination of vemurafenib plus everolimus, an MTOR inhibitor will be well tolerated. Secondary objectives included the efficacy of the combination therapy for BRAFV600E positive pediatric and AYA brain tumors

Design/Method: We conducted phase I study of vemurafenib and everolimus for BRAF mutated tumor that includes pediatric and AYA brain tumor. We applied standard 3+3 design with step wise dose modification. Dose for Vemurafenib was started at 480 mg/day and Everolimus was started at 2.5 mg/day.

Results: Five patients with BRAFV600E brain tumor with age range from 10 to 38 were treated, two glioblastoma, one optic pathway glioma, one pleomorphic xanthoastrocytoma, one anaplastic astrocytoma. All of the patients were previously treated including BRAF inhibitor as monotherapy for three patients. 480-720 mg/day of Vemurafenib and 2.5-5 mg/day of Everolimus were given for 3-17 months. Toxicities included Grade 3 rash. Two heavily pre-treated patients showed progression of disease after 3 and 4 cycles of treatment. One discontinued the treatment due to non-compliance although radiographic partial response was seen. Two patients are active on the study with partial response and stable disease for over 6 months.

Conclusion: The combination therapy was well tolerated with one exception of Grade 3 rash and the patient was able to continue the treatment with dose modification. Treatment effect was observed with the combination therapy even for the patients previously treated with BRAF inhibitor monotherapy. This study emphasizes the importance of genomic profiling of pediatric and AYA brain tumors. [1] Hyman, Puzanov, Subbiah, et al., N Engl J Med, 2015

RESULTS OF TREATMENT OF PEDIATRIC PATIENTS WITH OSTEOSARCOMA AND EWING'S TUMOR IN A BRAZILIAN HOSPITAL

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Background: The primary malignant bone tumors are the sixth most common malignancies in children and third in adolescents after leukemia and lymphoma. The recommended treatment is chemotherapy following a clear margin resection and/or radiotherapy.

Objectives: To evaluate aspects of the diagnosis, treatment outcomes, and possible prognostic factors in patients with Ewing's sarcoma and osteosarcoma.

Design/Method: This retrospective study included 57 patients diagnosed with Ewing's sarcoma (30 patients) and osteosarcoma (27 patients) treated by the departments of Pediatric Oncology and Pediatric Orthopaedics of Pequeno Príncipe Hospital, from January 1998 to December / 2008, according to the Brazilian Protocol.

Results: The mean age was 11 years, 24 males and 33 females were analyzed, the mean tumor size was 11 cm. The period between early symptoms onset and diagnosis was 19 weeks, the metastases rate by the time of the diagnosis was 35%. The most frequent surgery was resection with reconstruction (68%), followed by amputation (21%) and resection without reconstruction (19%). Twenty patients had recurrences, mainly pulmonary and at primary site, and the survival rate in five years was 40%. There was statistical significance between the presence of metastases at diagnosis or relapse and shorter survival. There was no statistical significance between time to diagnosis and survival.

Conclusion: Despite the optimistic expectation as advances in diagnostic tools and therapy of tumors of osteosarcoma and Ewing, children with locally advanced disease and / or metastasis at diagnosis still have a poor prognosis.

**CHILDREN WITH MEDULLOBLASTOMA AND HIGH-GRADE GLIOMA:
RACIAL/ETHNIC AND SOCIOECONOMIC DISPARITIES IN SURVIVAL OUTCOME**

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Background: Disparities within pediatric oncology outcomes are not well studied. The few studies that have evaluated racial/ethnic differences in children with central nervous system (CNS) tumors have yielded inconsistent results. Furthermore, no pediatric CNS tumor study has examined racial/ethnic differences in the context of socioeconomic factors.

Objectives: We examined racial/ethnic differences in survival outcomes for pediatric medulloblastoma and high-grade glioma, and whether neighborhood socioeconomic characteristics mitigated racial/ethnic differences.

Design/Method: We collected data on all California children (age ≤ 19 years) with a first diagnosis of high-grade glioma or medulloblastoma between 1997 and 2012. The primary outcome measure was overall survival (OS). Cox regression covariates included gender, age, race/ethnicity, neighborhood socioeconomic status (SES), and insurance status.

Results: A total of 174 medulloblastoma patients and 203 high-grade glioma patients were identified. Using Cox regression analysis, medulloblastoma patients with public health insurance had worse outcome (public/medicaid vs private: hazard ratio [HR] = 1.78; 95% confidence interval [CI] = 1.24 to 2.56). No survival differences in race/ethnicity were found for medulloblastoma patients after adjustment for SES and insurance status. However, racial differences were found for high-grade glioma patients, even after adjustment for SES. Non-Hispanic black high-grade glioma patients had worse outcome than their white counterparts (non-Hispanic black vs white: HR = 1.84; 95% CI = 1.01 to 3.37).

Conclusion: Our population-based study examined racial/ethnic differences in survival for pediatric medulloblastoma and high-grade glioma, while adjusting for socioeconomic and neighborhood characteristics. Alarmingly, medulloblastoma patients with public health insurance fared worse than those with private insurance regardless of other status. In comparison, racial disparities were found for pediatric high-grade glioma even after adjusting for SES. Future research needs to uncover remediable reasons for these disparities.

TAXOTERE, AVASTIN, GEMCITABINE "TAG" CHEMOTHERAPY FOR HIGH RISK AND RELAPSED ADOLESCENT AND YOUNG ADULT (AYA) SARCOMA PATIENTS

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Background: Adolescent and young adult (AYA) patients with high-risk recurrent/metastatic sarcomas have very poor prognosis, with few living 2 years. There are currently no standard treatments for these patients. Docetaxol (Taxotere, T), Bevacizumab (Avastin, A), and Gemcitabine (Gemzar, G) have activity in sarcomas. One study of 3 children using "TAG" yielded a partial response in 2 patients, and stable disease in one (JPHO 2012 34:524-7).

Objectives: We report our preliminary experience with this novel combination for 22 high-risk sarcoma AYA patients.

Design/Method: From 2000-2011, three week cycles of TAG (T=100m/m² Day 8, A=15mg/m² Day 1, G=1000 mg/m² days 1 and 8) was given to 22 AYAs with relapsed sarcomas (5 had Ewings Sarcoma, 8 Osteosarcoma, and 9 other) for up to 11 cycles. The median age was 26 (2-51), 14 were male, 11 had multiple relapses. Nineteen (86%) had failed multiple chemotherapy regimens, 17 with multiple surgeries, and 9 with radiation.

Results: Median overall and progression free survival were 18.5 and 6 months respectively. Seven of 22 patients (32%) achieved clinical remission (CR), with 3 having sustained remission. 6 had partial responses (PR) (30% reduction by RECIST), 4 had stable disease, while 5 had progressive disease. Side effects include: mucositis, nasolacrimal duct obliteration, septal perforation, infection and thrombosis. 111 cycles of TAG were given with no toxic deaths, organ failure or need to stop prescribed therapy.

Conclusion: In our uncontrolled study, the combination of Taxotere, Avastin and Gemcitabine, "TAG" showed response (CR + PR) in 59% of relapsed, pretreated, or very high-risk young sarcoma patients. TAG's toxicities were manageable. TAG may offer a choice to prolong life in highly treated, relapsed, high-risk AYA sarcoma patients.

FUNCTIONAL SCREENING REVEALS TARGETABLE VULNERABILITIES IN HIGH RISK MEDULLOBLASTOMA

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Background: Medulloblastoma (MB) is the most common malignant pediatric brain tumor. Molecular profiling recently enabled the classification of MB into four distinct subgroups, of which group 3 patients have the worst prognosis.

Objectives: We aimed to discover and validate targetable lesions in MB using a high-throughput functional screen.

Design/Method: We performed kinase inhibitor screening on group 3-like MB cell lines D341, D425 and CHLA-01-Med. Comparing the sensitivities of the individual cell lines to each other, >400 primary leukemia samples and >100 established human cancer cell lines we identified recurring "hits" within pathways that were specific to particular lines. We then used targeted western blotting to evaluate the biochemical correlates of these pathways. In vivo efficacy was assessed using a murine model and clinically available inhibitors. Lastly, primary patient cells were expanded in an intracranial murine model then plated on our functional screen, the results interpreted as with the cell line data.

Results: Kinase screening revealed clustering of sensitivity to mTOR inhibitors, IGFR inhibitors and aurora kinase inhibitors in D341, D425 and CHLA-01-Med cells, respectively. Western blotting corroborated that these pathways were hyperactivated in the cell line of interest. Uniquely, exome sequencing of D341 revealed a novel somatic variant (A415V) with unknown functional significance in the tumor suppressor gene, TSC2. Molecular analysis of the TSC2 A415V mutation demonstrated diminished TSC1-interaction and protein destabilization in a heterologous expression system. In vivo studies showed targeted tumor suppression when using an FDA-approved mTOR inhibitor against D341 cells with minimal suppression of CHLA-01-Med cells, confirming that the screening reveals specific targetable pathways. Perhaps most importantly, we successfully obtained inhibitor data on a primary patient tumor, which is an important proof-of-concept that this tool can provide reliable information on primary samples in less than 72 hours.

Conclusion: Taken together, these findings indicate that a subset of high-risk MB patients may have functionally relevant hyperactivation of targetable pathways, some of which may not have been found on traditional exome sequencing. This functional screen may offer an additional tool to inform adjunct treatment decisions in this complex and heterogeneous disease.

A COMBINATION APPROACH TARGETING OSTEOSARCOMA CELLS IN-VITRO USING IL-11R α CAR T-CELLS WITH ANTI-PD-1 BLOCKADE

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Background: Osteosarcoma (OS) is the most common primary malignant bone tumor in children and adolescents. Survival has remained stagnant for the past 20 years and new therapeutic combinations are desperately needed. Previous studies using IL-11R α CAR T-cells have shown benefit for the treatment of OS. However, IL-11R α CAR T-cell therapy alone did not completely eradicate the tumor. Up-regulation of the immune checkpoint pathway programmed death-1 (PD-1) and its ligand (PD-L1) in tumor cells have shown to limit immunotherapeutic efficacy. Anti-PD-1 blockade has shown survival and prognostic benefit in various tumors.

Objectives: To investigate a combination approach using IL-11R α CAR T-cells and an anti-PD-1 antibody to treat OS cells.

Design/Method: IL-11R α CAR T-cells were generated from peripheral blood mononuclear cells (PBMCs). Baseline PD-1 expression was determined by flow cytometry during cell expansion. CAR T-cells were co-cultured in-vitro with human LM7 OS cells with and without an anti-PD-1 antibody. Cytotoxicity was measured and compared for both groups using a calcein release assay. Change in PD-1 expression was also analyzed by flow cytometry in both untreated and anti-PD-1 treated CAR T-cells after co-culture at different time points. Purified T-cells served as control.

Results: PD-1 expression increased during CAR T-cell and purified T-cell expansion when compared to baseline PD-1 expression. After exposure to tumor cells, surface PD-1 expression decreased on both CAR T-cells and purified T-cells. Successful blockade of surface PD-1 expression was achieved via an anti-PD-1 antibody. Blockade of the PD-1/PD-L1 pathway using the anti-PD-1 antibody in combination with the IL-11R α CAR T-cell therapy did not provide additional benefit against LM7 cells (compared to IL-11R α CAR T-cells alone.) The same response was noted with control T-cells in combination with an anti-PD-1 antibody (compared to control T-cells alone).

Conclusion: Combination therapy with IL-11R α CAR T-cells and an anti-PD-1 antibody against LM7 OS cells did not provide additional benefit to the IL-11R α CAR T-cell therapy alone. Further studies are needed to test how to better combine these therapies, understand the downstream effects of blocking the PD1/PDL-1 pathway in OS, and how blocking this pathway may have an impact on other immunosuppressive pathways.

TARGETING AUTOPHAGY IN MYC AMPLIFIED MEDULLOBLASTOMA

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Background: Medulloblastoma harboring multiple copy numbers the MYC oncogene is associated with therapeutic resistance and relapse. Current literature implicates a role for autophagy in oncogene driven malignant transformation, tumor growth and survival. Notably in a recent publication by (Guo et al 2013) it was noted that KRAS driven tumors rely on autophagy to sustain cellular metabolism and evade cell death. Similarly, it was noted in a MYC induced lymphoma model that shRNAs directed against ATG5, an essential autophagy gene, augmented cell death following p53 activation (Amravadi et al 2007). Based on the current literature and our preliminary data, we hypothesized that MYC driven medulloblastoma have high autophagy, which is the key mechanism of therapeutic resistance and cell survival.

Objectives: Primary objective is to establish that increased MYC expression induces higher levels of autophagy in medulloblastoma cells, and that chemical inhibitors of autophagy can augment the effect of cytotoxic drugs used in treatment of medulloblastoma.

Design/Method: The experimental model used to test this hypothesis were DAOY cells which are medulloblastoma cells derived from pediatric patient tumor with no known MYC amplification. Oncogenic MYC was introduced using a lentiviral construct (DAOY-MYC) and empty expression vector (DAOY-CTR) as the control in order to generate these isogenic cell lines. The primary assays utilized to assess autophagy and autophagic flux used the detection of LC3B and p62 protein levels by immunoblotting with and without lysomotrophic agents.

Results: DAOY-MYC cells have consistently demonstrated higher basal autophagy compared to DAOY-CTR – as demonstrated by detection of higher LC3B proteins when not treated with lysomotrophic agent. One-hour treatment with HCQ demonstrates similar flux in both the cell lines, indicating the presence of functional autophagy. Furthermore, this phenotype was lost in when MYC was inhibited using RNAi in DAOY-MYC cells. Moreover, p62 protein expression was diminished in DAOY-MYC cells.

Conclusion: Introducing MYC into medulloblastoma cells increases autophagy under basal growth conditions. This phenotype where autophagy is increased has been noted in our lab in other cell lines driven by KRAS oncogene, highlighting a shared resistance mechanism by these two distinct oncogenes.

USING IMAGING AND COMPUTATIONAL TOOLS TO IMPROVE RISK STRATIFICATION IN CHILDREN WITH BONE CANCER

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Background: Tumor necrosis (TN) remains the most significant predictor of survival for patients with non-metastatic osteosarcoma. Interpretation of TN, which provides data only after the first 10 weeks of chemotherapy, provides information too late to make clinically meaningful adjustments to therapy. We propose that modern technology such as digital whole slide image (WSI) and image pattern recognition will provide the basis for further enhancements in the interpretation of this important biomarker.

Objectives: To accurately identify features of tumor necrosis by image pattern recognition (IPR) on histology whole slide images (WSI) of resected osteosarcoma.

Design/Method: We have developed an investigative team of clinical scientists at University of Texas Southwestern Dallas and computer scientists at University of Texas Dallas. Archival samples for 50 patients treated at Children's Medical Center Dallas, between 1995-2015, have been identified. Each case is represented by a single tumor slide at the time of biopsy when available (used in image segmentation) and 8-50 slides / case at time of resection when necrosis is determined. Slides are scanned using an Aperio Scanscope© and stored on a portable 3.0 terabyte hard-drive in SVS format (a compressed TIFF file format). Using a tumor map, created at the time of original histological evaluation, slides are digitally knit into a single whole slide image. Image segmentation, which requires feature identification based on regional color, cellular shape and regional cellular density, is ongoing.

Results: We have retrieved tumor maps, tumor biopsies and tumor resection specimens from archival stores on 50, 33 and 50 cases of high-grade osteosarcoma respectively. We have completed the digitization of 25 cases and have developed the computational tool to digitally knit all single slides (8-50 / case) into a single whole slide image (WSI). We have initiated the process of image segmentation and prospective re-evaluation of tumor necrosis on all test cases by two pathologists, blinded to each other's interpretation in the development of necrosis-digital analysis software.

Conclusion: We have begun to develop the necessary technology that will automate the interpretation of TN in osteosarcoma and will prospectively study this in comparison to routinely evaluated TN in newly diagnosed patients.

ESTABLISHING A BASELINE TIME-FRAME FOR SYMPTOM ONSET TO DEFINITIVE DIAGNOSIS OF CHILDREN WITH NEWLY-DIAGNOSED CNS TUMORS

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Background: Central nervous system (CNS) tumors are the most common solid tumors of childhood and adolescence, and the leading disease-related cause of death between one and nineteen years of age in the United States. In the United Kingdom (UK), recognition of delay in diagnosis led to the development of a program called 'HeadSmart', designed to enhance the awareness of signs and symptoms of brain cancer in children among both healthcare providers and the general public, with the goal of reducing the delay in diagnosis. Apart from a single report of diagnostic delays in children with low-grade gliomas, no additional reports have evaluated this delay in the United States since the late 1980s.

Objectives: To establish an accurate Ohio baseline from symptom onset to definitive diagnosis in children with newly-diagnosed CNS tumors.

Design/Method: The medical records were retrospectively reviewed for over 300 children with newly-diagnosed CNS tumors from January 2004 to August 2015 at Nationwide Children's Hospital. Since our electronic medical record system began in late 2006, we had usable data on only 171 patients (57%). Records were reviewed for age, gender, tumor type, presenting symptoms, number of healthcare visits prior to diagnosis, time interval (in months) from onset of symptoms to definitive diagnosis and any associated genetic syndromes.

Results: Of the 171 patients with newly-diagnosed CNS tumors, 26 children had a known pre-disposition syndrome (Neurofibromatosis Types 1 and 2, and tuberous sclerosis). Among the remaining 144 children, the median time interval from symptom onset to definitive diagnosis was 42 days while the mean symptom interval was 138 days (range < 1 to 2,190 days). Additionally, the most common presenting symptoms among our institutional cohort were headache (53%), nausea and vomiting (43%), unsteady gait (29%), visual disturbances (25%) and seizures (12%).

Conclusion: We have documented and quantified the contemporary delay in diagnosis of childhood brain tumors in central Ohio, to serve as a "benchmark" for our future planned interventions to reduce the time interval from symptom onset to diagnosis through adaptation of the UK 'HeadSmart' program throughout the State of Ohio and ultimately throughout the USA.

PROTEIN PHOSPHATASE 1 REGULATORY SUBUNIT 1A (PPP1R1A) PROMOTES TUMOR GROWTH AND METASTASIS IN EWING SARCOMA

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Background: Ewing sarcoma (ES) is a highly invasive and metastatic pediatric solid tumor. Patients with metastatic disease have dismal outcome (30%). EWS/FLI is the master regulator of ES and acts as an aberrant transcription factor to dysregulate downstream targets involved in cancer phenotypes. Previously we reviewed EWS/FLI RNA-sequencing analyses using public datasets from multiple model systems and identified core targets of EWS/FLI. In this study, we focus on PPP1R1A, a protein phosphatase 1 inhibitor and potential regulator of cell migration.

Objectives: To define the role of PPP1R1A in ES pathogenesis, and evaluate its potential as specific therapeutic target for ES especially metastatic tumors.

Design/Method: We examined the expression of PPP1R1A in ES cells and tumors by western blotting and public data mining. We characterized EWS/FLI regulation of PPP1R1A using ChIP-sequencing data analyses, quantitative RT-PCR and luciferase assay. By combining shRNA knockdown and soft agar as well as Boyden chamber assays, we assessed the effect of PPP1R1A on oncogenic transformation and cell migration. We further tested if PPP1R1A is associated with tumor growth and metastasis in an orthotopic xenograft mouse model. Next we characterized the molecular mechanism underlying the role of PPP1R1A by knockdown/rescue functional assays.

Results: We found that PPP1R1A is highly expressed in ES but not the putative cell of origin, mesenchymal stem cells. PPP1R1A is directly up-regulated by EWS/FLI via a GGAA microsatellite enhancer element. Depletion of PPP1R1A decreased oncogenic transformation and limited xenograft tumor growth ($p=0.0001$). Furthermore, reduction of PPP1R1A decreased cell migration and metastasis in animals ($p=0.004$). We demonstrate that phosphorylation at Thr35 and activation of PPP1R1A by protein kinase A (PKA), and subsequent PP1 binding and inhibition, is required for PPP1R1A function, as evidenced by rescuing of PPP1R1A induced phenotypes by constitutively active (T35D) but not PP1 binding deficient (T35D/R8A/K9A) PPP1R1A. Consistently, we found that ES cell lines were sensitive to the treatment of PKA inhibitors (H89 and PKI 5-24).

Conclusion: Collectively, our data suggest that PPP1R1A and related pathway plays a positive role in tumorigenesis and metastasis in ES. Targeting PKA/PPP1R1A/PP1 pathway has potential therapeutic value for the treatment of primary and metastatic ES.

NEURONAL AND MIXED NEURONAL-GLIAL CELL TUMORS: A REVIEW OF PEDIATRIC CASES AT A SINGLE CENTER

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Background: Brain tumors are the second most common cause of cancer in children, and the most common solid tumor. Neuronal and mixed neuronal-glioma tumors of the central nervous system (CNS) are relatively rare. In 2007, the World Health Organization (WHO) classification was revised to include four additional tumor types for a total of 13 subtypes. Although there are two published meta-analyses, both studies included mixed populations with many adult patients. To our knowledge there is no available neuronal-glioma tumor case series including a large number of pediatric patients from one center.

Objectives: To describe the demographic and clinical characteristics, treatment and outcomes of neuroglial tumors in pediatric patients at a tertiary care center.

Design/Method: This study is a retrospective review of patients age less than 21 years diagnosed by surgical pathology with neuronal or mixed neuronal-glioma tumor subtypes based on the 2007 WHO Classification at our tertiary care children's hospital between 1999-2014. Cases that met eligibility were reviewed and data including demographic, clinical, imaging, pathology, treatment, morbidity and mortality were extracted from the hospital CNS database. A neuropathologist and neuroradiologist participated in patient selection to adjust pathologic patient classifications diagnosed prior to the 2007 WHO guidelines.

Results: 51 patients met eligibility criteria with an average follow up time of three years. The predominant tumor subtypes were ganglioglioma (33.3%) and dysembryoplastic neuroepithelial tumors (23.5%). 46 patients were treated with surgery alone (90.1%), three patients received chemotherapy (5.9%) and two patients received radiation (3.9%). Nine patients had progression of their tumor after the first resection with an average time to progression of 35 months. Patients who had progression were more likely to present with seizures (77% v. 47%) and more likely to undergo subtotal resection. Overall survival was 96%.

Conclusion: Neuronal and mixed neuronal-glioma tumors of the CNS are extremely rare, and understanding the differences between the neuroglial tumor subtypes remains difficult. This study contributes to the pediatric literature by describing for the first time the diagnosis, treatment and prognoses of these rare tumor types in children.

EWING FAMILY OF TUMORS OF THE HEAD AND NECK: THE MD ANDERSON CANCER CENTER EXPERIENCE

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Background: Ewing sarcoma (ES) is the second most common malignant bone tumor found in children and adolescents, but Ewing sarcoma of the head and neck is uncommon. While there are literature noting that certain primary sites are considered high-risk, there are very little data regarding the head/neck region.

Objectives: Characterize the clinical presentation, and clinical outcome of our institutional cohort of patients treated for ES and related tumors.

Design/Method: We retrospectively reviewed patients treated for Ewing sarcoma of the head/neck from January 1, 1995 to December 31, 2013. Twelve patients were eligible for analysis. Clinical characteristics, treatment details, and clinical outcome were evaluated. EWSR1 genetic translocation was noted when available.

Results: Nine patients were male (75%) and 3 female (25%), with a median age at diagnosis of 18.5 years (range 3-27 years of age). Median follow-up was 77 months (range 29-243 months). Eight patients had parameningeal tumors as primary site (67%); 5 patients had extraosseous tumors (42%) including 2 patients with orbital tumors, and 3 patients presented with metastatic disease (25%). Seven tumors had EWSR1 translocation (58%). Initial chemotherapy regimens included VDC/IE (58%), VAI (33%) and VAC (8%). Local control consisted of surgery (17%), radiation therapy (58%), or surgery + radiation therapy (25%). Median dose of radiation therapy received was 55Gy (range 45-60 Gy). At last follow-up, 6 patients (50%) were alive with no evidence of disease (NED), while 2 (17%) patients were alive with disease. Four patients (33%) died from disease, including all 3 patients who initially presented with metastasis. In patients with parameningeal tumors, 4 were alive NED while 2 were alive with disease. Both patients with orbital tumors were alive NED at 34 and 79 months follow-up.

Conclusion: In patients with Ewing sarcoma of the head and neck, as with ES of other locations, the presence of metastasis at diagnosis is the single most important factor for overall survival. The small cohort size prevented subset analysis for prognostic factors. Treatment of H&N ES patients requires multimodal specialty care, which should be performed at treatment centers well versed in treating this rare bone tumor.

APPARENT RESOLUTION OF RECURRENT CHOROID PLEXUS CARCINOMA AFTER ANTIBIOTIC THERAPY FOR INTRACRANIAL ABSCESS

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Background: Choroid plexus carcinomas are aggressive WHO grade III tumors commonly found in children. Despite multimodal treatment, the 5-year overall survival is close to 40%.

Objectives: Describe the case of a patient with a recurrent choroid plexus carcinoma, with no evidence of disease after undergoing treatment for abscesses in the resection cavity.

Design/Method: Case Report

Results: A 3-year-old girl was diagnosed with a right parietal choroid plexus carcinoma after presenting with progressively unsteady gait. Family history was notable for breast cancer in her mother. Subsequent genetic workup was positive for the TP53 mutation, and Li Fraumeni syndrome was diagnosed. She underwent a near total resection of the tumor, followed by 6 cycles of chemotherapy of etoposide, carboplatin and cyclophosphamide. Three months after completion of treatment, she was noted to have a large recurrence in the surgical cavity. After a repeat resection, she underwent radiation therapy. Her first brain MRI after radiation therapy showed an enhancing nodule; upon resection, this was found to be recurrent/residual tumor. She started on chemotherapy with temozolomide, irinotecan and bevacizumab. Ten days after initiation of chemotherapy, the patient developed subgaleal, epidural, and intraparenchymal abscesses along the surgical tract. Operative wound cultures were positive for methicillin-sensitive *Staphylococcus aureus*, and treatment with antibiotics was initiated. Her course was complicated by recurrent wound dehiscence and unsuccessful primary closure despite multiple attempts. Due to deteriorating quality of life in the face of tumor recurrence, her parents chose to pursue palliative care, with continuation of oral antibiotic prophylaxis. After 3 months, repeat MRI of the brain showed persistence of the right parietal lobe abscess and peripheral enhancement around the surgical cavity more suggestive for an inflammatory reaction, rather than tumor. She was restarted on IV antibiotics for palliative purposes, and repeat MRI of the brain after 3 further months of antibiotic therapy showed a resolution of the abscess and no evidence of tumor.

Conclusion: This case raises interesting questions regarding the role of immunomodulation in cancer therapy, given that following the development of an inflammatory response to bacterial intracranial abscess, a tumor previously resistant to numerous resections, chemotherapeutic agents, and cranial irradiation has apparently resolved.

PRIMARY CENTRAL NERVOUS SYSTEM HISTIOCYTIC SARCOMA IN A 6 YEAR OLD MALE

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Background: Primary Histiocytic Sarcoma (HS) is a rare neoplasm that is more common in adults than children. It originates in liver, splenic, gastrointestinal, lymphoid, and cutaneous tissue. Central Nervous System (CNS) primary location is less common, and usually aggressive with poor prognosis. Few cases has been reported in children in the medical literature; and among these cases even fewer are primary CNS tumors. Currently the underlying etiology of HS is unknown and there is no standard therapy.

Objectives: We report a case of primary CNS histocytic sarcoma in a 6 year old male in order to increase the knowledge available in medical literature regarding this rare tumor.

Design/Method: A review was performed of the patient's medical record and available medical literature pertaining to pediatric HS with a focus on CNS tumors.

Results: We reviewed the English medical literature since 1970 and identified 7 pediatric patients with CNS HS. Among these patients, there was only 2 under the age of 11. Our patient is a 6 year old male with a PMH of Autism, Speech Delay, Perinatal HIV exposure, Asthma, and Sleep Apnea. He presented with visual hallucinations and new onset seizure disorder. MRI of the brain identified a left parietal dural based mass. Surgical resection of the mass was performed and pathology showed a proliferation of histiocytes with nuclear atypia consistent with HS. The patient received proton beam radiation therapy and then started ICE (ifosfamide, carboplatin, etoposide) based therapy which is ongoing, with evaluation after the third cycle.

Conclusion: Currently there is no standard therapy for HS. Treatment strategies include surgical resection, chemotherapy, and radiation. Complete surgical resection when feasible should be considered since it may provide a better prognosis. Several chemotherapy regimens have been used including ALL type therapy, high dose cytarabine, CHOP, and ICE, with reported poor outcomes. By reporting more patients and treatment regimens, we highlight the needs for collaborative efforts for international registry and clinical trial to develop a novel therapeutic approach.

CASE SERIES OF PILOMYXOID ASTROCYTOMA

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Background: Pilomyxoid astrocytoma (PMA) has similar features as pilocytic astrocytoma (PA), however has poorer prognosis. Since the original description of PMA in 1999, several case series of PMA have been published. Treatments chosen for PMA are similar to the treatments for pilocytic astrocytoma.

Objectives: To review clinical characteristics and outcome of PMA cases at University of Iowa Children's Hospital and to compare these clinical outcomes with those of PA and PMA reported in the literature.

Design/Method: A retrospective chart review of six patients diagnosed with PMA from 2003-2013 was performed. Demographics, location of the tumor, presenting symptoms, extent of initial resection, type and duration of adjuvant therapy, progression free survival, and current clinical status were collected.

Results: Age at diagnosis ranged from 9 months to 6 years. Locations of the tumors included hypothalamic and chiasmatic region, ventricle, and cerebellar hemisphere. Two cases achieved gross total resection, both of which presented in the cerebellar hemisphere. Three cases had partial resection or no surgery and progressed during an observational period. No patients with gross total resection had progression of disease. Those with progression eventually received radiation therapy, all after age 5 years, with no further progression. All patients were living with no disease or stable imaging findings at the time of our review. Endocrinopathy was present in all non-cerebellar tumors, but neurological deficits were rare and typically involved visual defects.

Conclusion: Gross total resection for cerebellar PMA prevented tumor recurrence in our cohort and was similar to findings for PA. Hypothalamic and chiasmatic lesion tumors were less apt to be completely resected and hence require different management. The hypothalamic and chiasmatic tumors also experience different late effects based on location and treatments. Our patients are all alive and hence have not revealed a poorer prognosis compared to PA although it will be important to observe these patients for a longer period of time to definitively establish progression-free survival and late effects in PMA patients compared to more mature PA patient series.

INFANT AML DIAGNOSED IN UTERO

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Background: Outcomes for children and infants diagnosed with acute myeloid leukemia (AML) have improved, however there is no literature on treatment for infant AML diagnosed in utero.

Objectives: Here we report the first case of a fetus diagnosed with AML in utero.

Design/Method: With parental consent, background clinical information, history of presenting illness, results of relevant laboratory investigations, and intended course of management are reviewed.

Results: Cordocentesis done on a 34-year-old woman at 30+4 weeks gestational age (GA) to investigate fetal hepatomegaly showed a hemoglobin of 70 g/L, leukocytosis ($166 \times 10^9/L$) and thrombocytopenia ($24 \times 10^9/L$). Further investigations, including morphologic examination and flow cytometry, confirmed the diagnosis of AML, monocytic type, in the fetus. Subsequent cytogenetic analysis showed mixed lineage leukemia (MLL) aneuploidy, but no MLL gene disruption. An exchange transfusion via cordocentesis was planned to extend gestation and optimize neonatal outcome, but the mother developed mirror syndrome, and at 30+6 weeks GA underwent an urgent caesarean section. A live female infant was born with edema, distended abdomen, petechiae, ecchymoses and no spontaneous respiratory effort. Labwork showed a hemoglobin of 66 g/L, white blood cell count of $218 \times 10^9/L$, platelets of $111 \times 10^9/L$, and abnormal coagulation profile. Resuscitation was unsuccessful and at two hours of life, parents chose to palliate their child. Autopsy demonstrated disseminated leukemia involving central nervous system, liver, bone marrow, and placenta.

Conclusion: It is possible to diagnose hematologic malignancy in a fetus, but even in neonates there is little information to direct management. We intended to begin with exchange transfusion via cordocentesis to reduce leukocytosis and thereby prolong gestation. Then, once stable after delivery, to use low dose chemotherapy until the infant was term and thought to be able to tolerate full treatment. Unfortunately the mother and infant were not well enough to pursue this course. Fetal leukemia should be considered in the differential diagnosis of a fetus presenting with hepatomegaly. As similar cases are identified, clinicians should share their experience to provide future guidance in management.

PHASE 1 TRIAL OF INDOXIMOD IN COMBINATION WITH TEMOZOLOMIDE-BASED THERAPY FOR CHILDREN WITH PROGRESSIVE PRIMARY BRAIN TUMORS (NCT02502708)

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Background: Indoleamine 2,3-dioxygenase (IDO) is a natural counter-regulatory mechanism that suppresses anti-tumor immunity. Although few clinical trials currently combine immunotherapy drugs with standard-of-care chemotherapy, our preclinical data suggest the IDO-inhibitor indoximod will synergize with chemotherapy and radiation. We therefore developed a first-in-children phase-1 trial to study indoximod. In the companion adult glioblastoma study (NCT02052648), the combination of indoximod and temozolomide was well tolerated with no dose-limiting toxicities. Six-month progression-free survival (PFS) for 12 adult phase-1b patients was 25%, compared to 15% for relapse glioblastoma historically. Two patients who had previously progressed on temozolomide, one phase-1b patient and one phase-2 patient, demonstrated partial response in month 13 and 7 of therapy, respectively, with the phase-1b patient surviving 21 months to date and continuing therapy.

Objectives: To present interim results for the ongoing pediatric phase-1 study (NCT02502708).

Design/Method: This trial assesses the feasibility, safety, and preliminary evidence of efficacy of combining indoximod either with temozolomide or with radiation therapy followed by temozolomide to treat children age 3 to 21 with progressive malignant brain tumors (excluding DIPG). Indoximod dose levels start at 80% of the adult recommended phase-2 dose.

Results: One 7 year old patient with recurrent metastatic ependymoma was treated with indoximod and stereotactic radiosurgery, which he tolerated without toxicity, and went on to receive indoximod combined with temozolomide. At the time of enrollment, he had previously received 6 separate surgeries, proton therapy to the posterior fossa (54Gy/30 fractions), cranio-spinal proton therapy (36Gy/20 fractions), proton therapy to his lower spine (20Gy/5 fractions), experimental cabozantinib, and experimental vaccine. The residual paraventricular tumor contour was extremely complex and located in a field that had previously received aggressive radiation. He started indoximod (80% dose-level) 3 days prior to receiving a multi-shot Gamma Knife® plan to target residual intracranial tumor (14Gy).

Conclusion: Indoximod may synergize with standard radiation and chemotherapy in children with brain tumors. The long-term goal is to incorporate combined indoximod, radiation, and chemotherapy in up-front treatment for pediatric brain tumors, and to re-engage aggressive local control options for partial responders in the relapsed disease setting. Sponsored by: Alex's Lemonade Stand Foundation, Cannonball Kids' cancer Foundation, NewLink Genetics Corporation.

MANAGEMENT OF METHOTREXATE-INDUCED NEUROTOXICITY IN ADOLESCENTS WITH HIGH RISK ACUTE LEUKEMIA – A CASE SERIES

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Background: Intrathecal methotrexate (IT MTX) and high dose intravenous methotrexate (HD MTX) are important components of central nervous system (CNS) prophylaxis in acute leukemia. Acute methotrexate-induced neurotoxicity can present within 5-14 days after IT MTX or HD MTX with headache, confusion, disorientation, seizures or focal deficits. There are no established guidelines for management of the acute event or subsequent CNS prophylaxis in such patients.

Objectives: To describe our management of a series of adolescents with high-risk acute leukemia with methotrexate-induced neurotoxicity.

Design/Method: Case series

Results: Patient 1- Nineteen-year-old Hispanic female with high risk B-ALL presented with paralysis of the left hand and intermittent dysarthria during delayed intensification after two doses of weekly IT MTX. Symptoms resolved spontaneously within one day. Patient 2- Nineteen-year-old Hispanic male with T-ALL presented with slurred speech, expressive aphasia, left sided facial and upper extremity weakness, and confusion during consolidation chemotherapy after three weekly doses of IT MTX. Symptoms resolved spontaneously within five days. Patient 3- Fifteen-year-old Hispanic female with mixed phenotype acute leukemia (T-Myeloid) presented with right-sided facial palsy, quadriparesis and aphasia during consolidation chemotherapy after three weekly doses of IT MTX. The patient was treated with dextromethorphan for 7 days; symptoms resolved within 48 hours. Patient 4- Twenty one-year-old Hispanic male with Philadelphia chromosome positive B-ALL presented with confusion, slurred speech, numbness, tingling of legs and tongue during consolidation chemotherapy one week after IT and HD MTX with delayed clearance. Symptoms resolved spontaneously within 9 days. A standard protocol was utilized for subsequent CNS prophylaxis. The next dose of IT MTX was omitted; and the following dose was substituted with IT cytarabine. All subsequent IT MTX doses were capped at 12 mg with leucovorin rescue 5 mg/m²/dose PO for 2 doses, 48 hours after IT MTX. Our patients have not experienced recurrent episodes of neurotoxicity or CNS relapse.

Conclusion: Continuation of intrathecal CNS prophylaxis in patients with methotrexate-induced neurotoxicity using the above protocol was safe and effective in the prevention of subsequent neurotoxicity and CNS relapse. A large series of patients with acute leukemia should be analyzed to see if Hispanic patients are at higher risk for methotrexate-induced neurotoxicity.

THE ROLE OF FINE NEEDLE ASPIRATION IN DIAGNOSING PEDIATRIC MALIGNANCIES: A SURVEY OF PEDIATRIC ONCOLOGISTS AND OTOLARYNGOLOGISTS

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Background: Fine needle aspirations (FNA) are frequently utilized to diagnose head and neck masses in adults due to fewer surgical risks, lack of requirement for sedation, and seemingly high diagnostic accuracy. Otolaryngologists have begun to perform FNAs in pediatric patients for similar reasons. In the oncology literature, the gold standard for diagnosing head and neck masses is excisional biopsy.

Objectives: To assess differences between pediatric oncologists' and otolaryngologists' views on the surgical approach to diagnosing head and neck masses in children.

Design/Method: We designed a 28-question survey consisting of 5 patient cases and sent it via electronic mail to practicing pediatric oncologists and otolaryngologists.

Results: One hundred six pediatric oncologists and forty one otolaryngologists responded to the survey. For a 15 year old girl with a 3cm firm, mobile, anterior chain mass that did not resolve after antibiotics, otolaryngologists were more likely to perform an FNA than oncologists (64.7% vs. 8.8% respectively, $p < 0.001$). Otolaryngologists were also more likely to perform an FNA in a 15-year old girl with recurrent fevers, weight loss, and a 5cm, hard, fixed supraclavicular lymph node (40.5% vs. 2.9% respectively, $p < 0.001$). Most oncologists and otolaryngologists would complete the staging work-up and begin treatment if a patient is referred with an FNA demonstrating non-Hodgkin lymphoma on pathology (78.8% vs. 78.8% respectively, $p = 1.0$). However, if the same patient was referred after an FNA that demonstrated non-specific inflammation, most oncologists and otolaryngologists would proceed by biopsying the mass (96.8% vs. 93.5% respectively, $p = 0.60$).

Conclusion: Otolaryngologists and pediatric oncologists differ in their initial approach to diagnosing head and neck masses in children. Further research is needed to understand the reasons behind these differences and to determine the potential implications of providers' initial diagnostic approach.

PREVENTION OF MERCAPTOPYRINE-INDUCED HYPOGLYCEMIA USING ALLOPURINOL TO REDUCE METHYLATED THIOPURINE METABOLITES

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Background: Hypoglycemia is an uncommon side effect of mercaptopurine (6-MP) that has been attributed to high levels of 6-methylmercaptopurine (6-MMP) in prior reports. Mercaptopurine is metabolized to 6-thioguanine (6-TGN), responsible for its anti-leukemic effect, and to 6-methylmercaptopurine (6-MMP), which appears to be hepatotoxic. Some patients preferentially metabolize 6-MP to 6-MMP. Adding allopurinol to oral 6-MP has been shown to reduce 6-MMP levels while maintaining therapeutic 6-TGN levels in patients with inflammatory bowel disease and acute lymphoblastic leukemia (ALL). We therefore reasoned that reduction of 6-MMP levels through the addition of allopurinol could prevent 6-MP associated hypoglycemia, a strategy not previously reported.

Objectives: To describe the use of allopurinol with 6-MP to successfully prevent 6-MP induced hypoglycemia by reducing 6-MMP levels in a patient with ALL and hypoglycemia.

Design/Method: Case report

Results: An 8-year old Hispanic male with T cell ALL receiving maintenance chemotherapy presented with frequent episodes of nausea/vomiting, dehydration, and blood glucoses in the 20-40 mg/dL range. Endocrine work-up, including ACTH stimulation test, was negative. 6-MP metabolites were notable for a dramatically elevated 6-MMP level of 58,667 pmol/8 x 10⁸ erythrocytes (reference range <5700). Attempted interventions included a high complex carbohydrate diet, morning dosing 6-MP and split dosing 6-MP, which only led to modest improvement in symptoms and a nadir 6-MMP level of 12,838 pmol/8 x 10⁸ erythrocytes. Allopurinol 50 mg daily was then introduced along with a 75% dose reduction of 6-MP. This led to a dramatic improvement in symptoms and stabilization of blood glucoses with a resumption of his normal diet. His 6-MMP level fell to <500 pmol/8 x 10⁸ erythrocytes while his 6-TGN level rose from 188 pmol/8 x 10⁸ erythrocytes (reference range 235-400) on split full-dose 6-MP to 705 pmol/8 x 10⁸ erythrocytes despite the dose reduction.

Conclusion: Adding allopurinol to 6-MP can optimize the balance between 6-TGN and 6-MMP metabolites and reduce hypoglycemic episodes. This finding also offers further support for elevated 6-MMP levels as the etiology of 6-MP induced hypoglycemia.

**PREDICTORS OF POOR OUTCOME AMONG CHILDREN WITH WILMS TUMOR
MANAGED AT THE ONCOLOGY DEPARTMENT OF A HAITIAN PEDIATRIC
HOSPITAL FROM 2004 TO 2015**

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Background: Wilms tumor or nephroblastoma represents about 6% of all pediatric cancers [1]. According to one study, it is the most common cancer among Haitian children [2].

Objectives: The main objective of this study is to determine the predictors of poor outcome (non-improvement, relapse, death) in children with Wilms tumor managed at a Haitian pediatric hospital.

Design/Method: This is a cross-sectional study on children diagnosed and managed for Wilms tumor at St Damien Hospital from February 2004 to April 2015. Chart reviews focused on key variables such as age, gender, geographic origin, number of kidneys affected, SIOP staging, type of treatment, metastatic disease and the occurrence of complications. Odds ratios and P-values are reported for the associations between poor outcome and each variable. The Mantel-Haenszel chi square test was used to determine statistically significant predictors of poor outcome in this setting.

Results: Sixty-seven cases of Wilms tumors were identified during the study period. 56.72% of the children were female and the age range of 1-4 years old was the most affected with a proportion of 67.16%. Mass and abdominal distension were respectively noted in 92.54% and 64.18% of the cases. 88.06% of the children had one kidney affected, and no associated malformation was found. Metastases were found in 28.36% of the cases. In terms of treatment, 61.19% of patients received the standard combination of neoadjuvant chemotherapy/surgery/adjuvant chemotherapy. 32.84% of the children achieved complete remission and the mortality rate was 22.39%. The predictors of poor outcome (non-improvement, relapse or death) were stages III to V of the SIOP classification (Odds ratio (OR)=10.35; P=0.013), bilateral Wilms disease (OR=8.4; P=0.03), the presence of metastases (OR=13.5; P=0.00038) and the occurrence of complications (OR=26.4; P=0.00000076).

Conclusion: The diagnosis of Wilms tumor in Haiti is performed at a late stage, which results to a delayed management and a poor outcome. Early diagnosis is thus the key for a better management of this childhood cancer in Haiti.[1] R. Therrien et al. Le Cancer chez l'enfant, 2013.[2] JG Lucien, J. Bernard jr, Predictors of mortality among Haitian children treated for cancer at a pediatric hospital from 2010 to 2014 (unpublished study)

VINCRIStINE TOXICITy IN A CHILD WITH ACUTE LYMPHOBLASTIC LEUKEMIA RECEIVING POSACONAZOLE

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Background: Invasive fungal infections are a major cause of morbidity and mortality in pediatric oncology patients receiving chemotherapy. Current guidelines recommend antifungal prophylaxis for high-risk patients, mainly acute myelogenous leukemia (AML) and allogeneic stem-cell transplant patients. Secondary prophylaxis is indicated if prolonged immunosuppression is expected. Posaconazole (Noxafil; Merck & Co., Inc; Whitehouse station, NJ), an oral extended spectrum triazole with a lesser drug-drug interactions profile, was shown to be safe in adults. However, few data are available regarding posaconazole safety in children.

Objectives: We report a case of vincristine toxicity in a 6 year-old boy with acute lymphoblastic leukemia (ALL) and histoplasmosis, receiving concomitant posaconazole.

Design/Method: Case report with review of medical literature.

Results: A 6-year-old Caucasian boy with pre-B-ALL on maintenance therapy (daily 6-mercaptopurine, weekly methotrexate, and monthly vincristine (1.5 mg/m²)), presented to a tertiary care hospital with febrile neutropenia and cough. Patient was diagnosed with pulmonary histoplasmosis based on the clinico-laboratory findings (diffuse reticulonodular opacities on CT scan and positive urine Histoplasma antigen). Liposomal amphotericin B and voriconazole at normally recommended doses were used and then discontinued after two and three days, respectively, due to acute kidney and hepatic injury, respectively. Patient was shifted to I.V posaconazole (20 mg/kg/day for 3 days then changed to PO form) and responded well to therapy. To avoid possible interaction with posaconazole, vincristine dose was reduced to 75% from original dose. However, 10 days later, patient presented with grade 3 (CTCAE 4.03) vincristine-induced peripheral neuropathy. Posaconazole was discontinued due to the high suspicion of posaconazole potentiated vincristine neuropathy, Peripheral neuropathy resolved within 10 days. Vincristine was restarted at reduced dose and patient continues to be neurologically intact.

Conclusion: Unlike other triazole antifungals, posaconazole interacts with fewer hepatic isoenzymes, namely CYP4503A4 that can affect vincristine metabolism. In addition, posaconazole may inhibit P-glycoprotein-mediated vincristine efflux. This may potentiate vincristine toxicity, as we speculate happened in our case. To the best of our knowledge, there are only three reported cases of posaconazole induced vincristine toxicity. We report this case to increase the awareness about this significant, yet preventable, drug-drug interaction especially that posaconazole is being increasingly used by pediatric oncologists.

LIPOCALIN 2 IS PRESENT IN PEDIATRIC HEPATOBLASTOMA

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Background: Hepatoblastoma is the most common type of pediatric liver malignancy. Signaling abnormalities in the beta-catenin pathway are associated with 90% of these tumors. In fact beta-catenin-YAP (Yes-associated protein) co-activation was observed in 80% of hepatoblastoma patients. Overexpression of YAP and beta-catenin in mice led to hepatoblastoma development. A gene array analysis of mRNA isolated from the tumor bearing livers revealed 5 genes that showed significant upregulation in the tumors and also had binding sites in their promoters of transcription factors TCF4 (which binds beta-catenin) and TEAD (which binds YAP). One of these genes was lipocalin 2, a small molecule protein with known antibacterial properties that has been found to be expressed in a variety of adult cancers.

Objectives: To determine if lipocalin 2 is expressed in human hepatoblastoma.

Design/Method: We used a tissue microarray of 74 patient hepatoblastoma samples from a tertiary care Pediatric Hospital to evaluate the presence of lipocalin 2 by immunohistochemistry. The tumors were classified by histology type and the degree of lipocalin 2 staining was graded on a 0-3 scale. Staining was further stratified as either nuclear, cytoplasmic, or both. Next, cell lysates from HepG2 cell culture (a human hepatoblastoma cell line) were tested for the presence of lipocalin 2 using western blot analysis.

Results: Lipocalin 2, which is normally not expressed in hepatocytes, was found to be present in either the nucleus or cytoplasm of 70 (95%) of the pediatric hepatoblastoma samples. The degree of staining for lipocalin 2 varied within each sample based on tumor histology. All embryonal components were strongly positive for lipocalin 2 with staining scores of 2-3. Ninety-six percent of crowded fetal histology components had positive lipocalin 2 staining, although the staining ranged from 1-2 in intensity. There was minimal to no expression of lipocalin 2 in blastema and small cell undifferentiated components. Lipocalin 2 was also confirmed to be present in HepG2 hepatoblastoma cell cultures by western blot analysis.

Conclusion: We have identified increased expression of lipocalin 2 downstream of beta-catenin and YAP activation in hepatoblastoma cells and in patient tissues. Lipocalin 2 may be playing an important role in beta-catenin-Yap driven hepatoblastoma development.

CYTOMEGALOVIRUS RETINITIS DIAGNOSED BY VITREOUS ASPIRATION IN A PATIENT WITH T-CELL ACUTE LYMPHOBLASTIC LEUKEMIA

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Background: Cytomegalovirus (CMV) retinitis is a complication of immunosuppressed hosts that is typically seen in acquired immunodeficiency syndrome and hematopoietic stem cell transplant patients. However, CMV retinitis occurring during therapy for acute lymphoblastic leukemia (ALL) without transplant is rarely described.

Objectives: Describe the case of an adolescent with T-cell acute lymphoblastic leukemia (T-ALL) in maintenance presenting with acute vision loss due to CMV retinitis.

Design/Method: Case report and review of literature.

Results: A 14-year old male with intermediate-risk T-ALL in maintenance presented with acute vision loss in the right eye. Ophthalmologic examination showed right-sided afferent pupillary defect, poor visual acuity, and large visual field deficits. Left eye vision was unaffected. Fundoscopic examination revealed bilateral optic disc edema with peripapillary hemorrhages, scattered retinal hemorrhages centrally, large areas of retinal whitening, and cotton wool spots. Differential diagnosis based on ophthalmologic examination included leukemic versus infectious retinopathy. MRI Brain/Orbit was negative for intracranial pathology, orbital masses, or optic nerve edema. Total white blood cell count was 1000 cells/ μ l with absolute neutrophil count (ANC) 400 cells/ μ l, and absolute lymphocyte count (ALC) 100 cells/ μ l. Vitreous aspiration was performed with intravitreal injection of amphotericin, vancomycin, ceftazidime, clindamycin, and ganciclovir. Vitreous fluid was positive for CMV by polymerase chain reaction (PCR). CMV DNA was also detected in serum by quantitative PCR. Vitreous cells were negative for malignancy by flow cytometry. Bone marrow and cerebrospinal fluid were also negative for malignancy. Therefore the diagnosis of CMV retinitis was made. He was treated with a three-week course of valganciclovir followed by prophylactic dosing. Visual acuity is stable with improvement in retinitis by fundoscopic exam but he remains with visual field deficits.

Conclusion: CMV retinitis has rarely been reported as a complication of ALL therapy without transplant but occurrence of CMV-reactivation should be recognized, especially in patients with cell-mediated immunodeficiencies. Our patient had an ALC of 100 cells/ μ l at time of presentation with CMV retinitis. Ophthalmologic exam findings alone may not differentiate between leukemic infiltrate and CMV retinitis, and in these cases vitreous aspiration should be considered to confirm the diagnosis.

LONG-TERM OUTCOMES OF ADVANCED HEPATOBLASTOMA WITH “INTENTIONAL” POSITIVE MARGINS- A SINGLE CENTER EXPERIENCE

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Background: Treatment of Hepatoblastoma (HB) includes surgical resection and platinum-based chemotherapy. Twenty percent of patients require orthotopic liver transplantation (OLT). Current guidelines recommend that patients should proceed to OLT if complete tumour resection with negative margins cannot be achieved.

Objectives: Our objective is to report a series of children with HB (Jan 2010-Dec 2015) treated at the Hospital for Sick Children who had to undergo a very complex hepatectomy with negative or planned microscopic positive margins and avoided OLT.

Design/Method: Demographic data, clinical characteristics, surgical and pathologic details, complications and survival information was collected by chart review.

Results: Six children with HB had a median age of 1.4 years at diagnosis (range 2 months to 3.4 years). PRETEXT classification was as follows: II, n=1 this patient had vascular involvement of the inferior vena cava (IVC) and hepatic veins; III, n=3, and IV, n=2. Synchronous pulmonary metastases were present in 3 patients. Tumour histology was epithelial-fetal (n=3), mixed epithelial and mesenchymal (n=2) and pure epithelial (n=1). Median AFP at diagnosis was 277,981 ug/Lt (range: 239-2.6 million). All patients received pre-operative chemotherapy with platinum agents with a median of 6 cycles (range: 4-7 cycles). Extended right hepatectomy was performed in 5 patients, (1 patient had two additional wedge resections in segment 2 of the left lobe), extended left hepatectomy in 1 patient. Margins were positive in 2 patients; in 4 patients, margins were negative with the closest margin ranging between 2-5 mm. Two patients required vascular reconstruction of the IVC. At 9 months, of median follow-up (range 3 months-2.8 years) none of the patients had local recurrences, 1 patient had recurrence of pulmonary disease 2 months after surgery, in this case, AFP did not fall as expected and started to rise soon after surgery.

Conclusion: Patients with advanced HB who received complex surgical resections with positive microscopic margins or close negative margins (margins ≤ 5 mm) had good outcomes. We hypothesize that planned positive microscopic margins in highly selected HB patients may spare the morbidity of OLT.

CARNITINE: AN INNOVATIVE APPROACH TO TREAT FATTY LIVER DISEASE IN PEDIATRIC ALL

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Background: There has been a dramatic increase in obesity rates among children in the United States (US). The association between obesity and cancer has been widely studied, showing that obese patients are at risk for multiple side effects and poor outcome. Nonalcoholic fatty liver disease (NAFLD) is now the most common cause of chronic liver disease in pediatric patients in the US. There is no known effective treatment of NAFLD except diet and exercise. L-carnitine has been used in prior studies to treat chemotherapy-induced liver toxicity but has not been used in pediatric oncology patients with fatty liver. We have identified a high-risk group of pediatric oncology patients at risk for developing fatty liver and its complications.

Objectives: Describe a pediatric patient with relapsed T-cell acute lymphoblastic leukemia (T-ALL) and fatty liver disease treated with L-carnitine.

Design/Method: Review of medical record.

Results: An obese thirteen year-old boy with relapsed T-ALL was found to have persistent elevations of liver enzymes (AST and ALT peaking at 2.5x and 10x normal respectively), despite breaks in chemotherapeutic regimen. Imaging performed showed changes consistent with fatty liver. Due to the risk of sinusoidal obstructive syndrome (SOS), bone marrow transplant (BMT) was held. To maintain his remission, he was given further chemotherapy and additionally started on L-carnitine 1 gram orally twice a day in an attempt to lower his liver enzymes. After three months of treatment, both AST and ALT gradually improved to near normal levels and BMT with a haplo-identical donor was pursued. Transplant regimen was overall well tolerated, without evidence of SOS. The patient continues to be in remission and continues on L-carnitine with no side effects from L-carnitine observed.

Conclusion: In this patient, L-carnitine was thought to improve the transaminitis, which enabled him to undergo BMT. Transaminitis due to fatty liver can be a significant factor leading to alterations or interruptions in chemotherapy regimens, increase transplant morbidity and thus affect overall survival and increase risk of relapse. L-carnitine supplementation along with a diet and exercise regimen may be able to improve transaminitis and reverse fatty liver. Overall, it is well-tolerated without significant toxicities. Further prospective studies are needed.

HEPATOCELLULAR CARCINOMA AND NIEMANN-PICK DISEASE TYPE C: AN INSIDIOUS MENACE WITH POTENTIAL FOR SCREENING?

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Background: Hepatocellular carcinoma (HCC), the second most common pediatric liver malignancy, has an annual incidence of 0.41 per million children in the United States. HCC associated with underlying hepatic cellular injury leading to liver cell dysplasia is described in hemochromatosis, α -1-antitrypsin deficiency, hereditary tyrosinemia, and some glycogen storage disorders. Niemann-Pick Disease type C (NPC) is an autosomal recessive liposomal storage disease characterized by dysfunctional cholesterol transport. Accumulation of sphingomyelin and cholesterol in lysosomes results in hepatosplenomegaly and hepatic dysfunction. Rare cases of HCC in NPC exist in the literature, but no clear link between the two has been established.

Objectives: We present a 12-year-old male with NPC, who presented acutely with abdominal distension and hemodynamic instability. MRI revealed a large heterogeneously-enhancing solid mass in the medial segment of the left hepatic lobe with a smaller lesion in the anterior right hepatic lobe, concerning for intrahepatic metastasis. Head and chest CT scans were negative for distant metastases. Biopsy confirmed HCC, stage III disease. Alpha fetoprotein (AFP) at diagnosis was elevated to 52,775 IU/mL. Patient underwent upfront resection of the left sided mass and biopsy of right hepatic lesion.

Design/Method: Upfront resection improved the likelihood of successful treatment, but due to residual right hepatic disease the patient received 6 cycles of cisplatin and doxorubicin administered every 3 weeks (modified PLADO regimen) with twice daily sorafenib, an FDA-approved tyrosine kinase inhibitor, at 200 mg/m²/dose. Due to vomiting and diarrhea there were compliance issues and approximately 50% of planned sorafenib doses were administered.

Results: Patient responded to treatment, with no evidence of disease on MRI imaging and AFP normalization to 2.9 IU/mL following surgical resection and 6 cycles of chemotherapy. Three months off therapy there was no evidence of disease recurrence on MRI imaging and monthly AFP remained normal, ranging 1 to 2 IU/mL.

Conclusion: HCC is a rare and challenging entity in pediatric oncology. While not classically associated with NPC, these patients can suffer hepatic damage over time and are at risk for malignant transformation. This raises questions with regard to routine screening, either radiographically or laboratory testing to monitor AFP level.

INVASIVE CONIDIOBOLUS INFECTION: MANAGEMENT DURING INDUCTION THERAPY FOR ACUTE LYMPHOBLASTIC LEUKEMIA

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Background: Invasive fungal infections in children with cancer disproportionately affect leukemia patients. *Conidiobolus* is an Entomophthoromycota found in tropical regions associated with rhinofacial infections. Although rare in pediatric oncology, it has high mortality and can spread rapidly. We report our treatment of an adolescent with acute lymphoblastic leukemia (ALL) and multidrug resistant (MDR) invasive sinopulmonary *Conidiobolus* infection.

Objectives: Describe management strategies that support neutrophil function to treat invasive *Conidiobolus* infection in a patient receiving chemotherapy for ALL.

Design/Method: Case report.

Results: A 16 year-old male presented with intermittent fever, fatigue, cough, and petechiae. He was severely neutropenic with circulating blasts, and was diagnosed with ALL. He began induction chemotherapy with concomitant antifungal prophylaxis. On day 5 of induction, he developed congestion and left-sided facial pain. Nasal endoscopy revealed pale and insensate mucosa, and imaging showed diffuse, nodular ground glass opacities throughout the lungs. Nasal biopsy revealed branching hyphae with septations, suggestive of *Aspergillus*. Voriconazole and micafungin were started empirically. On day 4 of culture, the fungus showed zygospores with a prominent beak and sporangiola characteristic of *Conidiobolus* species. The organism was resistant to all antifungal agents except terbinafine (amphotericin B and anidulafungin intermediate). Treatment was changed to liposomal amphotericin B (LAmB), anidulafungin, and terbinafine. Bone marrow aspirate was negative for leukemia at day 17 of induction. Due to progressive pulmonary and sinus disease extending to the skull base, chemotherapy was temporarily halted and neutrophil support was augmented with daily GM-CSF, granulocyte infusions and hyperbaric oxygen therapy (HBOT). Granulocyte infusions were discontinued following endogenous neutrophil recovery 30 days after ALL diagnosis, while LAmB, GM-CSF and HBOT continued for several more weeks. Imaging dramatically improved, and sinus fungal cultures became negative. After 7 weeks without neutropenia, his chemotherapy was resumed while continuing aggressive neutrophil support when severely neutropenic. His leukemia remains in remission without evidence of progressive fungal disease.

Conclusion: Multidisciplinary care is crucial for simultaneous treatment of both ALL and a life threatening fungal infection. The use of aggressive support of neutrophil function was effective in controlling disseminated MDR *Conidiobolus* infection and allowed delivery of myelosuppressive chemotherapy.

IS ADJUVANT IMMUNOTHERAPY EFFECTIVE IN PEDIATRIC MELANOMA? A NATIONAL STUDY OF 787 CHILDREN

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Background: Current treatment of pediatric melanoma is adapted from adult studies, although children with melanoma demonstrate different pathophysiology and clinical outcomes than adults. For example, adjuvant immunotherapy for melanoma has been studied prospectively in adults, but similar studies are lacking in children.

Objectives: We reviewed the National Cancer Data Base (NCDB) to understand the impact of adjuvant immunotherapy on survival in children with high-risk melanoma.

Design/Method: The 1998 – 2012 NCDB was queried for patients less than 20 years of age diagnosed with stage IIB, IIC, or III cutaneous melanoma. Patients who received adjuvant chemotherapy or radiation were excluded. Patients were grouped by whether they received adjuvant immunotherapy or not. Multivariable proportional hazards method was used to compare overall survival.

Results: In total, 787 patients met study criteria: 288 (36.6%) patients received adjuvant immunotherapy while 499 (63.4%) did not. Among children who received adjuvant immunotherapy, 268 (93.1%) had stage III disease. At baseline, children who received adjuvant immunotherapy experienced worse survival (61.8% vs. 79.3% at 15 years, $p = 0.04$). But after adjustment for patient, tumor, and treatment characteristics, children who received adjuvant immunotherapy had no significant improvement in overall survival (adjusted hazard ratio 1.56, 95% confidence interval 0.71 – 3.44, $p = 0.27$).

Conclusion: The benefit of adjuvant immunotherapy in children with high-risk melanoma remains unclear. Multi-institutional studies examining specific immunotherapy regimens would be useful in answering this important question. Ultimately, the creation of a pediatric melanoma registry would be valuable for developing evidence-based, age-specific guidelines for melanoma therapy in children.

HYPERINSULINEMIA IN A PATIENT TREATED WITH WEEKLY INTENSIVE PEG-L-ASPERAGINASE FOR RELAPSED PRE-B ACUTE LYMPHOBLASTIC LEUKEMIA

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Background: Long acting PEG-L-Asperaginase (L-ASP) is used in the treatment of Acute Lymphoblastic Leukemia (ALL), and works by inhibiting protein synthesis and increasing apoptosis. A common side effect is hyperglycemia due to either inhibition of insulin synthesis or acute pancreatitis. This is a rare case of L-ASP induced hyperinsulinemia and symptomatic hypoglycemia in the setting of weekly intensive L-ASP.

Objectives: Describe a case of symptomatic hypoglycemia/hyperinsulinemia in a patient treated with weekly L-ASP for relapsed ALL.

Design/Method: We reviewed Pubmed, Ovid, and Google Scholar for similar cases and identified 2 previously reported cases of L-ASP associated hypoglycemia on unknown cause.

Results: A 22 year old female with Trisomy 21 and relapsed pre-B ALL treated with induction chemotherapy (weekly vincristine, weekly L-ASP, TID prednisone, and weekly daunomycin) exhibited persistent hypoglycemia (serum glucose <50mg/dl) despite being on continuous IV 5% dextrose. On day 15 of induction the patient had syncope. Her blood glucose was 44mg/dl. Ionized calcium and electrolytes were normal. Fibrinogen levels were 56-103mg/dL(190-395), consistent with predicted inhibition of protein synthesis. Concurrent with glucose of 45mg/dl, insulin was 7.2uIU/ml (<2.0), betahydroxybutyrate <0.1mmol/L, free fatty acid 0.59mmol/L (0-0.72) and c-peptide 3.12ng/ml (<0.8), confirming hyperinsulinemia without exogenous insulin. The patient received 20mg prednisone TID and had normal amylase/lipase ruling out associated pancreatitis or steroid deficiency. There were no clinical signs of sepsis. The patient was treated with IV dextrose until hypoglycemia resolved 3 weeks after the completion induction and remains in clinical remission.

Conclusion: Hyperinsulinemia leading to symptomatic hypoglycemia during B-ALL induction chemotherapy with L-ASP is rare with only 2 similar reported cases. Unexpected hypoglycemia is dangerous finding, but once identified, is relatively simple to manage. A mechanism for this finding is not entirely clear at this time. We propose a mechanism that L-ASP can lead to a preferential inhibition of insulin degrading enzymes (IDE) synthesis leading to delayed clearance as opposed to inappropriate insulin synthesis in some patients. Interestingly, IDE polymorphisms have been described in Trisomy 21 individuals as a possible explanation for the well known risk of early onset Alzheimer's disease. We hope this report increases awareness and inquiry into this rare side effect. (Lucarelli, Neurosci let, 2004).

CAROTID ARTERY DISSECTION IN THE SETTING OF SEVERE IRON DEFICIENCY ANEMIA

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Background: An association between iron deficiency anemia (IDA) and cerebral vascular accidents have previously been established through a variety of case reports. Although its exact pathogenesis is unknown, severe iron deficiency anemia is associated with a near ten-fold risk of developing stroke-like symptoms as compared to patients without IDA. There is little current literature describing arterial dissection in association with iron deficiency anemia, though a recent study of older children and adults demonstrated an association between anemia and stroke with cervical artery dissection, as well as a worse outcome in stroke with concurrent anemia.

Objectives: We present the case of a child with evidence of right-sided weakness found to have arterial dissection in the presence of iron deficiency anemia highlighting an atypical presentation of severe IDA and the need for aggressive treatment and preventative care for these patients.

Design/Method: A retrospective chart review was performed on a two year old female at Texas Children's Hospital in Houston, Texas. We compare this data to previously published cases on complications of severe iron deficiency anemia

Results: The patient presented with approximately 5 days of fatigue, pallor, and progressive weakness of the right extremities. On admission, she had a hemoglobin level of 3.3g/dl, MCV of 48.7FL, ferritin of 2ng/ml, and transferrin of 264mg/dl. CT angiography of the brain identified dissection of the left internal carotid artery in the neck. There was no evidence of trauma, and comprehensive connective tissue disease and genetic workup was negative. She underwent transfusions with packed red blood cells, and was anti-coagulated with aspirin, followed by unfractionated heparin and transitioned to Lovenox. She steadily improved, and was transferred to an outside hospital near her home for long-term rehabilitation therapy.

Conclusion: While the link between iron deficiency anemia and thrombotic ischemic stroke is well-established, a link between arterial dissection and has not previously been described. Our patient's unusual presentation suggests that arterial dissection can be a life-threatening consequence of IDA. Judicious management of anemia with transfusion therapy along with anticoagulation can lead to significant clinical improvement. Our case highlights a novel complication of IDA and provides guidance in the multi-disciplinary management of such complex cases.

CASE EXAMPLE INVOLVING GERMLINE GENETIC COUNSELING NEEDS FOR 47,XXX, FAMILIAL LEUKEMIA, AND NOONAN SYNDROME FOLLOWING SOMATIC GENETIC TESTING

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Background: A previously healthy 10 year old female presented with abdominal pain, fevers, headaches, lymphadenopathy and fatigue. Her maternal family history was remarkable for a first cousin with a clinical diagnosis of familial Mediterranean fever, but no molecular MEFV testing, and grandfather with chronic lymphocytic leukemia. Serial peripheral blood cell counts showed falling hemoglobin, falling platelets, and rising monocyte and blast counts. Bone marrow analysis showed mild dysplasia and hemophagocytosis, but bone marrow blasts were not increased.

Objectives: To clarify diagnosis and treatment options, genetic testing was pursued.

Design/Method: Chromosome analysis revealed mosaic 47,XXX in 15 of 20 bone marrow cells analyzed. Mosaic 47,XXX was also detected in <10% of cultured and stimulated peripheral blood lymphocytes. Skin fibroblasts were 46, XX. A next generation sequencing panel on bone marrow detected variants in PTPN11 and RUNX1. The PTPN11 mutation had previously been reported in juvenile myelomonocytic leukemia. The RUNX1 variant had been reported in hematopoietic malignancies (COSM24756) but also as a rare single nucleotide polymorphism in the healthy population and is considered a variant of uncertain significance.

Results: A genetic counselor was involved at multiple decision points to discuss the potential for constitutional mosaic 47,XXX, familial leukemia due to a germline RUNX1 mutation, Noonan syndrome due to a germline PTPN11 mutation, and other differential diagnoses based on personal and family history. Genetic counseling was also utilized to discuss collection of appropriate specimens for genetic testing (e.g. buccal swab/saliva versus skin fibroblasts), implications of genetic test results on diagnosis and treatment options (i.e. as marker for response to therapy), selection of a bone marrow donor, and other hereditary cancer genetic counseling topics including psychosocial/ethical considerations and other medical, familial, and reproductive implications. Possible interpretations of the chromosome findings included contaminant, constitutional mosaicism that varied in different tissues, or a multilineage (myeloid/lymphoid) clonal hematopoietic malignancy. Ultimately, based on buccal cell analyses, the PTPN11 mutation appears somatic, and the RUNX1 variant appears germline.

Conclusion: This case illustrates the complexities of germline genetic counseling that can result from somatic genetic testing and the importance of having genetics professionals available for consultation when this type of testing is ordered.

COMING OF AGE IN TIME TO DIE: THE STRUGGLE TO PROVIDE EFFECTIVE PALLIATIVE CARE IN THE AYA POPULATION

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Background: Approximately 70,000 adolescents and young adults (AYAs) aged 15-39 are diagnosed with cancer in the United States yearly. Despite inferior outcomes when compared to both their pediatric and adult counterparts, integration of palliative medicine into routine care of the AYA population remains infrequent [1].

Objectives: To highlight the challenges in communication and decision-making when end-of-life occurs at the transition to legal adulthood

Design/Method: Two young people lost their lives to cancer the same year they turned eighteen: “The thespian”: 18 year-old (yo) theatre lover burdened by both osteosarcoma and bladder sarcoma. The tumor infiltrated his spine, leaving him paraplegic and completely dependent on his family at a time when independence is paramount. While he lay in a hospital bed, his twin brother searched for the college of his dreams. At the end-of-life, Mom “fired” palliative care after a frank code status discussion slapped him in the face with his own mortality. “The guardian”: 18 yo with metastatic Ewings sarcoma, who was the “ring-leader” of a gang of AYA males who carried the same diagnosis, but not the same prognosis. His mother insisted he never be told “how bad it was.” Delirium plagued his final days, and despite their desperate attempts to keep the truth from him throughout his treatment course, his parents were then devastated that he couldn’t participate in end-of-life decision making. Due to patient and family refusal, palliative care was not involved until two weeks prior to his death...and only under the guise of being called the “supportive care team.”

Results: Both of these young men died in the hospital with minimal palliative care support.

Conclusion: The unique developmental, social, emotional, ethical and existential struggles of the AYA population benefit from a highly specialized interdisciplinary approach. However, the above cases highlight conflict between autonomy and parental protection, and possible deviation from normative development as barriers to effective end-of-life care in the AYA population. Earlier engagement and education of AYA patients and families regarding palliative care may facilitate improved communication and awareness.1. (Weiner, Clin Oncol Adolesc Young Adult, 2015)

EPSTEIN-BARR VIRUS ASSOCIATED MUCOCUTANEOUS ULCER IN A PATIENT WITH T CELL ACUTE LYMPHOBLASTIC LEUKEMIA: IMPORTANCE OF ACCURATE DIAGNOSIS AND CONSERVATIVE MANAGEMENT

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Background: Epstein-Barr Virus Associated Mucocutaneous Ulcer (EBVMCU) is a recently characterized entity under EBV Lymphoproliferative Disorders (EBVLPDs). It is an EBV-driven polyclonal B-cell proliferation occurring in mucocutaneous tissues of elderly patients (immunosenescence) and patients on immunosuppressive therapy who have a limited Tcell-repertoire. The true incidence of EBVMCU is unknown due to its self-resolving nature and limited awareness amongst clinicians.

Objectives: Generate awareness about EBVMCU amongst clinicians.

Design/Method: Case report

Results: A 29 year old male with intermediate risk T-cell ALL, in maintenance phase of chemotherapy (COG Protocol AALL0434), presented with left sided throat pain with an exudative left tonsillar ulcer concerning for abscess versus leukemic infiltration. Tonsillar biopsy showed a dense polymorphous infiltrate of lymphocytes, neutrophils, plasma cells, and histiocytes. Small sheets of large atypical B-lymphoblasts, consistent with Reed-Sternberg-like cells, were prominent and raised a concern for large cell lymphoma or lymphoproliferative disorder. These cells demonstrated the following immunophenotype: CD5-, CD10-, CD15-, CD20+, CD30+, CD45+, EBER RNA+ , consistent with EBV-transformed immunoblasts. TdT immunostain was negative. EBV PCR in peripheral blood was 6200 IU/mL. Peripheral blood smear did not reveal any blasts. Peripheral blood immunophenotype showed reduction in CD4+ and absence of CD19+ cells. A whole body PET CT showed localized hypermetabolic foci in the left tonsil. Based on the clinicopathologic findings, a diagnosis of EBVMCU was made. Since the ulcer did not regress despite stopping oral chemotherapy for a week, a dose of Rituximab (375mg/m²) was tried. The tonsillar ulcer completely resolved 2 weeks after Rituximab. Presently, 3 months following the dose of Rituximab, he remains in remission.

Conclusion: Despite a striking histopathologic and immunophenotypic resemblance to B cell lymphoma and EBVLPDs, EBVMCU represents an indolent and localized variant of EBVLPD with excellent prognosis. More extensive workup including imaging, bone marrow biopsy, and serology may be needed to rule out a systemic LPD, which mandates more aggressive treatment. Appropriate diagnosis will help clinicians in making critical decisions like withholding immunosuppressive drugs necessary for immune reconstitution of T-cell repertoire to control EBV infection. Most cases resolve spontaneously or after stopping immunosuppressive therapy. Refractory or relapsing cases may require a more aggressive approach like Rituximab or radiotherapy.

BONE MARROW FAILURE IN AN INFANT WITH WILLIAMS SYNDROME CAUSED BY OSTEOPETROSIS

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Background: Background: Williams Syndrome (WS) is a genetic syndrome associated with characteristic facies, hypercalcemia, and cardiovascular anomalies but hematologic abnormalities have rarely been described.

Objectives: Objective: We present an infant with WS and bone marrow (BM) failure, found to have autosomal recessive (AR) infantile malignant osteopetrosis (OP).

Design/Method: Design/Method: Case Report A full term infant was found to have a murmur early in life. An echocardiogram showed supra-aortic and pulmonic stenosis, raising concerns for WS. Genetic testing confirmed this at 2 months of age, finding a characteristic 7q deletion. Soon after, she was evaluated for dehydration and found to be anemic and thrombocytopenic. A BM biopsy demonstrated fibrosis, and she required periodic transfusions. Further work-up for BM failure syndromes, including Fanconi Anemia and Dyskeratosis Congenita, was negative, but imaging showed bony changes concerning for OP. A repeat BM biopsy showed increased osteoclasts, and genetic testing demonstrated pathogenic TCIRG1 mutations (c.304delG and c.1887+1G>A) consistent with infantile malignant OP, AR type 1. The patient then underwent hematopoietic stem cell transplant (HSCT).

Results: Results: WS is a constellation of signs and symptoms caused by a deletion in chromosome 7. The American Academy of Pediatrics has established clinical guidelines for the care of patients with WS, including necessary surveillance, but hematologic issues are rarely associated with this syndrome, and not a part of these guidelines. OP can manifest at various ages depending on its mode of inheritance. The AR form, infantile malignant OP, presents early in life and is caused by mutations in TCIRG1, CLCN7, OSTM1, RANK and RANKL. It manifests as hypocalcemia, sclerotic bones, frequent fractures, and sometimes visual loss, hearing loss, and BM failure due to expansion of bone. HSCT can halt or slow disease progression by replacing defective osteoclasts. WS and OP have not been previously described together, although some WS mouse models have shown osteopetrosis-like features without the osteoclast dysfunction or deficiency seen in OP.

Conclusion: Conclusion: While WS and OP have been well characterized, this is the first documented case of both diagnoses in the same patient. Further research into potential genetic associations between these two diseases may elucidate the pathophysiology of both further.

PARASPINAL GANGLIONEUROMA AND SEROUS CYSTADENOMA OF OVARY IN AN ADOLESCENT PATIENT WITH PRIMARY PLEURAL SYNOVIAL SARCOMA: A MERE COINCIDENCE OR A CANCER PREDISPOSITION SYNDROME?

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Background: Primary pleural synovial sarcoma (PPSS) is an extremely rare tumor. It was first described in 1996 as a case series of 5 patients, 3 of whom were children < 18 years. We report the first case of PPSS in association with paraspinal ganglioneuroma and serous cystadenoma of ovary with a mutation in MET oncogene of unknown significance. Occurrence of multiple different tumors in a young patient with a genetic mutation suggests a possibility of a hitherto unknown cancer predisposition syndrome.

Objectives: Report a rare presentation of PPSS in association with paraspinal ganglioneuroma and serous cystadenoma of ovary.

Design/Method: Case report

Results: A 16-year-old, Caucasian female presented with 3 weeks of right chest pain in August 2013. Family history was significant for multiple solid tumors (laryngeal, thyroid, colon and renal). MRI chest showed a right pleural mass. Biopsy of resected mass was suggestive of monophasic synovial sarcoma with positive margin. Immunohistochemistry was positive for Vimentin, EMA and CK7. Cytogenetics revealed t(X;18)(p11.2-q11.2)(SYT-SSX). Metastatic workup revealed a left lumbar paraspinal lesion and right adnexal mass. Biopsy of the left paraspinal lesion revealed mature ganglioneuroma. Biopsy of resected adnexal mass was consistent with a diagnosis of serous cystadenoma of ovary. The genetic work up revealed constitutional heterozygous mutation in MET proto-oncogene- p.D208G(c.823A>G). The patient was staged as IRS Grade III, Stage III, POG Grade III. She received 6 cycles of Ifosfamide + Doxorubicin (COG Protocol ARST0332) and 55.8 Gy of radiation. Currently, patient remains in remission.

Conclusion: PPSS has never been reported in association with other tumors. Cell of origin for PPSS still remains an enigma. Based on recent demonstration of immunophenotypic overlap between SS and malignant peripheral nerve sheath tumors (Folpe et al) besides constitutive expression of SS associated fusion genes (SYT-SSX) in neuroepithelial tissue (Brujin et al) and a genetic mutation of unknown significance in our patient, we hypothesize that the constellation of tumors in our patients may not be merely coincidental. These tumors may be arising from a common pleuripotent mesenchymal stem cell. We will verify this hypothesis by further immunophenotypic and cytogenetic analysis of ganglioneuroma and cystadenoma.

A VERY RARE OCCURENCE OF SEVERE APLASTIC ANEMIA WITH A PAROXYSMAL NOCTURNAL HEMOGLOBINURIA CLONE IN AN ADOLESCENT WITH SICKLE CELL DISEASE SUCCESSFULLY TREATED WITH STEM CELL TRANSPLANT

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Background: Sickle-cell disease (SCD) is one of the most common severe genetic disorders worldwide. In SCD, individuals demonstrate an increased adhesiveness of blood cells, including red blood cells, neutrophils, eosinophils and platelets; this plays a fundamental role in the vaso-occlusive process. Aplastic Anemia (AA) is characterized by peripheral blood pancytopenia and a hypocellular bone marrow. Paroxysmal nocturnal hemoglobinuria (PNH) is an acquired hemolytic disease associated with intravascular hemolysis and thrombosis.

Objectives: We present a very rare occurrence of severe aplastic anemia (SAA) with a PNH clone in a teenager with SCD and the clinical challenges that this combination presents.

Design/Method: Case Report

Results: A 12-year old African American female with SCD was following in our comprehensive care clinic. She was initially found to have isolated thrombocytopenia which later progressed to pancytopenia. Bone marrow done was consistent with the diagnosis of SAA. She was started on cyclosporine as Immune suppressive therapy (IST) and responded transiently but eventually became transfusion dependent. 12 months later her PNH clone was increased and she declared herself with PNH. At this point she underwent transplant with unrelated donor (7/8 DRB1 molecularly matched) without any complications. Currently she is 12 months post transplant with no evidence of PNH clone, stable counts and hemoglobin electrophoresis consistent with sickle cell trait.

Conclusion: AA is a rare, life-threatening disorder, which is thought to be due to immune-mediated destruction of hematopoietic cells in the bone marrow. IST and Bone marrow transplant are the first line treatment options. About 30 % of AA children will not respond to primary IST and will require second-line therapy, 15–30% of those who respond will relapse. Clonal evolution of hematopoiesis and PNH is thought to occur in about 10–15% of AA patients, with the clonal abnormality frequently detected at diagnosis. Clonal hematopoiesis and PNH may also develop years after IST treatment. These patients require a long-term follow up by a specialized care center knowledgeable in late manifestations of disease.

SUBCUTANEOUS METASTASIS IN MEDULLOBLASTOMA – A CASE REPORT

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Background: Extraneural metastasis (ENM) in medulloblastoma is very rare. ENM usually occurs to the bone. ENM to the subcutaneous tissue is very rare and in our literature review, we came across only three such cases.

Objectives: To describe a case of medulloblastoma with subcutaneous metastasis.

Design/Method: Case report

Results: A 9 year old Indian male who presented with symptoms of obstructive hydrocephalus was found to have a large posterior fossa mass with a ‘drop lesion’ in the thoracic spine at T1 level. He had a near total resection and the pathology showed WHO grade IV medulloblastoma. He received radiation and chemotherapy with lomustine, vincristine and cisplatin. While on treatment, the patient developed an external mass over the surgical scar with associated posterior cervical lymphadenopathy. Further imaging showed a new lesion in the subcutaneous plane infiltrating the erector spinae muscles with loco-regional lymph node metastasis. There was no simultaneous recurrence in the primary tumour bed and no other metastasis. Biopsy of this lesion confirmed subcutaneous recurrence of medulloblastoma. Aggressive surgical resection combined with high dose chemotherapy and stem cell rescue was suggested as a curative option by the treating team but the family opted for a palliative approach with metronomic chemotherapy using cyclophosphamide and etoposide. He had rapid disease progression with worsening lymphadenopathy resulting in internal jugular vein compression and facial edema as well as right facial nerve palsy. Metronomic chemotherapy was withdrawn and patient ultimately succumbed to the disease five months after the recurrence was noted.

Conclusion: This report discusses the unusual subcutaneous metastasis in medulloblastoma. Subcutaneous metastasis may indicate an aggressive tumour with poor prognosis. However available literature on subcutaneous metastasis have shown that almost always the metastasis have been in the vicinity of the surgical incisions, which could imply that they were implanted during surgical procedures.

APLASTIC ANEMIA A RESULT OF TRYING TO OPTIMIZE MERCAPTOPYRINE METABOLISM THROUGH CONCURRENT USE OF ALLOPURINOL

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Background: Although it is traditional practice to avoid concurrent use of allopurinol with the administration of mercaptopurine in the world of oncology, recent literature describes the intentional use of allopurinol to “optimize” 6-mercaptopurine (6-MP) metabolism in the treatment of inflammatory bowel disease processes and even malignant processes such as acute lymphoblastic leukemia. Reportedly shown to safely shunt metabolism of 6-MP away from the hepatotoxic/myelotoxic 6-MMP metabolite and toward the more favorable/efficacious metabolite 6-TGN metabolite, the synergistic potential of allopurinol is now being employed by some cancer centers. Despite recent evidence to support the potential efficacious nature of this drug combination, users must remain cautious for possible myelotoxic and even life-threatening effects. We report a case of how such attempts at optimization of the 6-MP metabolite profile may result in aplastic anemia.

Objectives: Describe aplastic anemia as a complication of concurrent allopurinol and mercaptopurine therapies for pediatric patients.

Design/Method: Case Report

Results: 10 y.o. (TPMT*1/TPMT*1(Wild Type)) male (weight-40kg, BSA-1.27m²) with history of Crohn's disease, diagnosed at age-9 presented with progressive pancytopenia, (WBC-1600/MM³, ANC-100/MM³, Hgb-7.9g/dL, PLT-33K). He was receiving combination mercaptopurine (50mg daily) and allopurinol therapy (100mg daily). Combination therapy was initiated 1-month previously due to unfavorable 6-MP metabolite profile while on mercaptopurine monotherapy (100mg daily) (6-MMP 16,157pmol/8 x10⁸RBCs (risk of toxicity when >5,700), 6-TGN 186pmol/8 x10⁸RBCs (most therapeutic when >230<400)). This metabolite profile was associated with mild pancytopenia, (WBC-2600/MM³, ANC-1100/MM³, Hgb-11.7g/dL, PLT-143K/MM³). The addition of allopurinol, even with a concurrent 50% dose reduction of mercaptopurine, resulted in significant elevations in both 6-MP metabolites, (6-MMP 26,874pmol/8 x10⁸RBCs, 6-TGN 463pmol/8 x10⁸RBCs). Bone marrow evaluation revealed a markedly hypocellular marrow (5-10%) with panhypoplasia, most consistent with drug-induced aplastic anemia, no evidence of infectious etiology, malignancy or lymphoproliferative disorder. One month off therapy, our patient had return of peripheral blood counts, (WBC-4200/MM³, ANC-2200/MM³, Hgb-12.0g.dL, PLT-212K/MM³). While pancytopenic, our patient required one PRBC transfusion for symptomatic anemia, Hgb-6.4g/dL. He required no other interventions for his other cytopenias.

Conclusion: Optimizing mercaptopurine metabolite profiles through concurrent allopurinol therapy is a difficult balancing act with the potential for significant myelotoxic effects including aplastic anemia.

RENAL CELL CARCINOMA HARBORING SOMATIC TSC2 MUTATIONS IN A CHILD WITH METHYLMALONIC ACIDEMIA

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Background: Renal cell carcinoma, a rare malignant pediatric renal tumor, is associated with various inherited diseases including Von Hippel-Lindau and tuberous sclerosis complex (TSC). Patients with TSC are at risk for a number of renal tumors, including angiomyolipomas and renal cell carcinomas, due to germline mutations in one of two TSC associated genes (TSC1 and TSC2). Patients without TSC also rarely develop renal cell carcinoma due to somatic (tumor-specific) mutations in these same genes. Here we present a child with methylmalonic acidemia (MMA) who developed renal cell carcinoma with two somatic inactivating mutations in the TSC2 gene.

Objectives: To report a case of renal cell carcinoma with sporadic TSC2 mutations in a patient with MMA.

Design/Method: Molecular case report

Results: A 6 year old female with MMA, renal tubular acidosis, and chronic kidney disease was referred to the oncology service due to a persistently elevated PTH related peptide and hypercalcemia. Whole body PET/CT scan revealed a solitary focus of hypermetabolic uptake within a 1.5 cm left kidney lesion. A partial nephrectomy was performed and histologic examination demonstrated an encapsulated neoplasm consisting of polygonal cells with eosinophilic and vacuolated cytoplasm. Despite nuclear TFE3 expression, FISH testing for TFE3 gene rearrangement was negative, and the tumor was diagnosed as renal cell carcinoma NOS. Whole exome sequencing was performed on tumor and peripheral blood as part of the BASIC3 clinical study. Germline analysis revealed two heterozygous pathogenic variants (p.R288X, p.R108C) in the MUT gene, a known cause of MMA. Tumor sequencing identified two somatic inactivating mutations (p.A1124fs, p.W82X) in the TSC2 gene, which encodes tuberin, the principal cellular inhibitor of mTOR signaling (in complex with hamartin, encoded by TSC1).

Conclusion: While patients with MMA are prone to chronic kidney disease and eventually renal failure, there is no known association with pediatric renal cell carcinoma. This is the first reported case of renal cell carcinoma with somatic TSC2 mutations in a patient with MMA. Inhibitors of mTOR signaling are approved for the treatment of relapsed or metastatic renal cell carcinomas and might be considered in the event of tumor recurrence in this patient with known mutations activating this pathway.

AGGRESSIVE HHT DIAGNOSED IN A CHILD AFTER EXHAUSTIVE MEDICAL EVALUATION FOR SEVERE ANEMIA

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Background: Hereditary hemorrhagic telangiectasia (HHT) is an autosomal-dominant, multi-system vascular dysplasia that is characterized by telangiectasias and arteriovenous malformations (AVMs) in the nose, gastrointestinal tract, lungs, brain, and liver. HHT affects one in five thousand people. Ninety percent of affected persons are thought to be undiagnosed. This disease process often initially presents as epistaxis in adolescence.

Objectives: Discuss the presentation, diagnosis, and treatment options for a rare case of aggressive HHT in a four year-old male.

Design/Method: Case report.

Results: A four year-old male presented to his local emergency department with acute onset of emesis and fatigue. Laboratory evaluation revealed severe anemia (hemoglobin of 2.0 gm/dL) and, otherwise, normal blood counts. Stool hemoccult and urinalysis were negative. Other work-up was suggestive of concomitant iron deficiency, although the initial working diagnosis was transient erythroblastopenia of childhood (TEC). No laboratory evidence of hemolysis was noted. Bone marrow evaluation showed normal cellularity and a compensatory erythroid hyperplasia. He was transfused with an appropriate rise in his hemoglobin. A personal and family history of intermittent epistaxis was mentioned, but not thought to be contributory at that time. Two months later, he returned to the emergency department with epistaxis and rectal bleeding. Meckel's scan, upper/lower endoscopies, and tagged red blood cell scan were unremarkable. Testing for hemophilia and von Willebrand's disease was negative. Due to persistent anemia (despite frequent transfusions) and worsening epistaxis, he was referred to ENT for nasal endoscopy revealing telangiectasias throughout, consistent with HHT, confirmed with genetic testing demonstrating a heterozygous frameshift mutation in the ENG gene. Since diagnosis, endoscopies of his small and large intestines show scattered AVMs throughout. HHT rarely presents this aggressively in a child. Attempts at local control include laser, nasal bevacizumab injections, and argon beam coagulation. He is, currently, on propranolol (beta blockade), but with no significant improvement. Other, more aggressive treatment options, such as rapamycin or infliximab, may need to be considered.

Conclusion: HHT often goes unrecognized or undiagnosed. It should be considered when confronted with a suspicious family history and/or refractory epistaxis with anemia. Improved treatment options for aggressive pediatric disease need continued investigation.

A CASE SERIES OF SURVIVAL AFTER RECURRENT RENAL CELL CARCINOMA WITH CABOZANTINIB AS A SINGLE AGENT

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Background: Renal cell carcinoma (RCC) in pediatric patients carries a dismal prognosis with few curative therapeutic options for patients who cannot receive a surgical gross total resection. Cabozantinib is a small molecule receptor tyrosine kinase inhibitor against c-met, a protein known to be expressed in RCC in adults and children. It is currently FDA-approved for medullary thyroid carcinoma, but there is no data on its use in pediatric RCC.

Objectives: Describe the clinical course of two patients with metastatic RCC treated with cabozantinib at Nationwide Children's Hospital.

Design/Method: Two patients with stage IV RCC (TFE3 rearrangement +) received sunitinib following resection. Both suffered disease recurrence within 6 months of diagnosis, in, pulmonary, skeletal and nodal sites. Cabozantinib, 60mg daily, was given to both with monitoring for clinical and symptomatic response, radiographic response, adverse effects, and quality of life. Dose adjustments were made based on clinical criteria.

Results: After initiation of cabozantinib, both patients had clinical benefit, despite prior use of TKI therapy. One patient had resolution of a malignant pleural effusion, measurable reduction of an infiltrated lymph node, and reversal of cancer-related cachexia with 16lbs of normal weight gain. The other patient had improved pain control and return to normal daily activities, and qualitative improvement on MRI. Both patients remain on drug for over 12 months and 6 months, respectively, though the second patient had a dose reduction due to adverse effects (AE). Common AEs related to Cabozantinib include palmar-plantar erythrodysesthesia, loss of appetite, weight loss, diarrhea, and nausea. In the adult patient population, these are often dose limiting, however both patients tolerated it well overall. One has had mild nausea requiring no dose adjustment; the other exhibited erythrodysesthesia that required a dose reduction with resolution of the AE. Both also manifested hypothyroidism managed with levothyroxine.

Conclusion: Cabozantinib has demonstrated clinical and radiographic benefit for two pediatric patients with metastatic RCC. It presents an additional therapeutic option for this disease and further studies should examine its use more broadly in RCC and other pediatric cancers.

EARLY ONSET AND PREDOMINANT HEMATOLOGICAL PRESENTATION OF PI3KCD MUTATION

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Background: Autosomal dominant gain-of-function mutations of PI3KCD that encodes the p110 δ catalytic subunit of phosphatidylinositol-3-kinase (PI3K) are recently identified genetic causes of common variable immunodeficiency (CVID). PI3K plays a key role in activation and proliferation of cells of multiple lineages and PI3KCD mutations predispose affected subjects to autoimmune and malignant complications. However, clinical spectrum of PI3KCD mutations in early life is not known.

Objectives: To address clinical and laboratory findings in a 3 year-old male with probable PI3KCD mutation whose initial presentation was early onset hemolytic anemia in association with acute febrile illness.

Design/Method: Retrospective review of clinical and laboratory findings in the presented case whose clinical features have been dominated by hematological abnormalities.

Results: The patient initially presented with Coombs negative hemolytic anemia at the age of 6 weeks. He subsequently developed pancytopenia and hepatosplenomegaly within a few months. He had frequent episodes of febrile illnesses with worsened pancytopenia that responded to oral steroids. A gradual rise of IgM and positive family history of hyper IgM syndrome (his mother) led to immune workup, although he has maintained age-appropriate immunoglobulin levels and lacked clinical evidence of deep seated sinopulmonary infections. Eventually, his mother was diagnosed with PI3KCD mutations (P110 δ E1021K) which lead us to test him for the same (result pending). Although he never exhibited low IgG or IgA prior to starting supplemental IVIG, enumeration of T/B cell subsets revealed decreased numbers of regulatory T cells and isotype switched memory B cells (not absent) along with inverted ratio of naïve vs. memory T cells (1:2), persistent lymphopenia, and compensatory increase in NK cell numbers. It is unclear how maternal PI3KCD mutation affected his clinical features. The patient has been clinically stable with sirolimus and supplemental IVIG.

Conclusion: PI3KCD mutation can be manifested as predominant hematological abnormalities without hypogammaglobulinemia, but enumeration of T/B cell subsets may be informative before proceeding to gene mutation analysis. High index of suspicion will be required given the fact that the disease specific treatment (i.e., sirolimus) is available.

METASTATIC HEPATOCELLULAR CARCINOMA IN A CHILD WITH AUTOSOMAL RECESSIVE POLYCYSTIC KIDNEY DISEASE

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Background: Autosomal recessive polycystic kidney disease (ARPKD) is a hereditary disease that results in end-stage renal disease and congenital hepatic fibrosis in children. Common hepatic complications include portal hypertension, bile duct dilatation, and cholangitis. Hepatocellular carcinoma (HCC) has not been previously reported in this population.

Objectives: We describe the first pediatric patient reported in the literature with ARPKD and HCC.

Design/Method: An extensive MEDLINE search was performed for HCC, ARPKD, and congenital hepatic fibrosis. We also examined the literature for malignancies associated with ARPKD. Clinical exome sequencing of the patient's germline is currently pending.

Results: We report a 5-year old male with a history of kidney transplant secondary to ARPKD and known hepatic fibrosis, who was found to have biopsy proven HCC with pulmonary metastases. He is currently undergoing neoadjuvant chemotherapy with cisplatin and doxorubicin, and has had a partial response to therapy based on Response Evaluation Criteria in Solid Tumors (RECIST) criteria. Both his primary lesion and metastases have decreased in size and alpha-fetoprotein (AFP) has decreased from 263,500 to 23.9 after 5 cycles of cisplatin/doxorubicin chemotherapy. Germline patient exome sequencing results are pending and will be reported at the time of publication.

Conclusion: This is the first reported case of HCC in a pediatric patient with ARPKD. While the history of concurrent hepatic fibrosis likely contributed to progression to HCC, the extremely young age of presentation is uncommon. Exome sequencing may be helpful in determining whether the patient has a novel pathogenic variant in polycystic kidney and hepatic disease 1 (PKHD1), the ARPKD gene.

A RARE CASE OF LUPUS ANTICOAGULANT HYPOPROTHROMBINEMIA WITH ASSOCIATED THROMBOCYTOPENIA

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Background: Lupus anticoagulant-hypoprothrombinemia (LAHPS) is a rare condition resulting in hypercoagulability, which is often seen in patients with underlying autoimmune disorders.

Thrombocytopenia is found in 27% of patients with LAHPS and is associated with bleeding risk.

Objectives: Describe a case of a patient with lupus anticoagulant hypoprothrombinemia with associated thrombocytopenia presenting as protracted oral bleeding following dental extraction.

Design/Method: Medical record and literature review.

Results: A previously healthy 10-year-old boy, presented with ecchymoses, petechiae and oral bleeding ten days following a dental extraction. Initial labs were significant for a platelet count of 8 K/uL, prothrombin time (PT) 13.5 seconds with international normalized ratio 1.3, and activated partial thromboplastin time (aPTT) of 87 seconds. The aPTT 1:1 mixing study demonstrated an inhibitor but the PT 1:1 mixing study revealed a factor deficiency, later found to be lupus anticoagulant and low Factor II activity, respectively. Other autoimmune workup revealed triple antiphospholipid antibody positivity (APA), positive antinuclear antibody (ANA) and double stranded DNA (dsDNA) antibodies as well as low complement component 3 and 4 and positive direct antiglobulin test. Given the presence of the lupus anticoagulant as well as low Factor II activity, he was diagnosed with LAHPS. Initial therapy included intravenous immunoglobulin (IVIg) (1 gm/kg) and hydroxychloroquine 200 mg oral daily. The peak platelet response after IVIg was 49K/uL. A bone marrow aspirate and biopsy revealed trilineage hematopoiesis and megakaryocytic hyperplasia, normal cytogenetics, and negative myelodysplastic syndrome panel by FISH. After the third dose of IVIg, his platelet count remains above 50k/uL and all clinical signs of bleeding have resolved.

Conclusion: LAHPS is a rare phenomenon in children with predominant hematologic concern of thrombosis. A small percentage of patients can have bleeding complications typically due to thrombocytopenia. Due to these contrasting but very serious risks, patients need to be monitored closely by hematologists. Future assessments include serial monitoring of blood counts, renal function, APA, ANA, and dsDNA antibodies. Future therapies considered for LAHPS are typically chosen based on clinical symptoms and include corticosteroids and anti-CD20 monoclonal antibody therapy as well as thrombopoietin mimetics for worsening thrombocytopenia. This patient is currently stable on his single regimen of hydroxychloroquine.

NOVEL APPROACH TO LOCAL CONTROL IN AN EXTENSIVE PEDIATRIC UNDIFFERENTIATED EMBRYONAL SARCOMA OF THE LIVER

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Background: Undifferentiated Embryonal Sarcoma of the Liver (UESL) is a rare, aggressive pediatric liver malignancy characterized by frequent recurrences. Standard curative therapy involves a complete resection and systemic chemotherapy. Transcatheter arterial chemoembolization (TACE) is commonly utilized to treat liver tumors, particularly Hepatocellular Carcinoma (HCC). Y90 radio-embolization is an emerging therapy for liver tumors. Currently, there are no reports of either modality being used for local control of pediatric UESL.

Objectives: We report the case of a 17yo female with an extensive UESL with diaphragmatic invasion. After a poor response to two cycles of neoadjuvant ifosfamide and doxorubicin, two cycles of gemcitabine and taxotere were administered. While the tumor showed a moderate volumetric response, the patient experienced gemcitabine-related neurotoxicity, the tumor remained unresectable and severe tumor-related pain persisted. Therefore, Y90 radio-embolization was performed on the largest portion of the tumor followed by TACE with doxo-eluting beads to the diaphragmatic portion of the tumor via the phrenic artery.

Design/Method: This case is being reported due to the unique approach to the local control of this UESL. Y90 beads were chosen over TACE for the large inferior portion of the tumor from studies in HCC showing equivalent outcomes, but less pain with radio-embolization. TACE was chosen for the smaller superior portion in an attempt to spare healthy liver tissue that shared blood supply through the phrenic artery.

Results: The procedures were well tolerated. Within three weeks of Y90 embolization, long acting narcotics were discontinued. At the time of the TACE procedure she had decrease in tumor size, but no measurements available. TACE was also well tolerated, requiring one overnight stay for pain control. The tumor was deemed resectable within 3 weeks following her procedure.

Conclusion: Our case highlights the possible role of embolization in UESL therapy. In this case, both radio-embolization and TACE were utilized as part of a neoadjuvant regimen to facilitate surgical resection. These modalities should be considered viable options for unresectable UESL unresponsive to upfront chemotherapy.

MULTICENTRIC RETICULOHISTIOCYTOSIS IN A PEDIATRIC PATIENT

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Background: Multicentric reticulohistiocytosis (MRH) is a rare, multisystem, non-Langerhans cell histiocytic disorder. MRH is rarer in children, as the onset of disease typically occurs in the fourth decade of life. Clinical presentation includes papulonodular skin eruptions and inflammatory polyarthritis that can be debilitating. The etiology of this disorder is unknown, but an association with solid tumors or hematologic malignancies is present in 25% of reported cases. The treatment of MRH without associated malignancies includes nonsteroidal anti-inflammatory drugs, corticosteroids, and disease-modifying antirheumatic drugs.

Objectives: To report a pediatric patient with multicentric reticulohistiocytosis.

Design/Method: Single case report

Results: A 5 year old Caucasian female presented with a 1 year history of periungual papules in her hands and feet and a few months history of bilateral knee swelling and stiffness in multiple joints. Her periungual papules were initially treated as warts, but they failed to improve, and she was subsequently referred to Dermatology. A shave biopsy of one of these lesions resulted as MRH. Due to the association of MRH with malignancy, she was referred to Oncology. On our evaluation, she had no signs or symptoms of malignancy and her screening labs were normal. A CT of her neck, chest, abdomen, and pelvis was obtained to further evaluate for malignancy and was normal. Rheumatology diagnosed her with arthritis of her neck, elbows, and knees and she received methotrexate and naproxen. Three months into therapy, she has improvement of her skin lesions and arthritis. Her future evaluation for malignancy will depend on signs, symptoms and clinical exam with no plans for routine surveillance imaging.

Conclusion: There are very few pediatric cases of MRH reported in the literature. Due to the rarity, there is currently no standardized approach in surveillance for malignancy. Pediatric oncologists need to be aware of the association between MRH and malignancies. Patients with MRH need to be evaluated for malignancies prior to treatment of MRH, since it involves drugs with anti-neoplastic activity.

SORAFENIB, BEVACIZUMAB AND CYCLOPHOSPHAMIDE FOR TREATMENT OF A RESISTANT RELAPSED HEPATOBLASTOMA A CASE REPORT

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Background: Hepatoblastoma is the most common liver tumor in children. Hepatoblastoma affects mostly children under 3 years of age, Three-year event-free survival for patients with non-metastatic hepatoblastoma is 90%. However, for patients with refractory or metastatic disease, prognosis is dismal. Bevacizumab, Sorafenib and low-dose Cyclophosphamide use has not been reported in Hepatoblastoma.

Objectives: We report on a patient with recurrent resistant metastatic Hepatoblastoma treated with this combination leading to stable disease and falling AFP with excellent quality of life.

Design/Method: A 5-months-old male with right-sided abdominal mass and initial alpha-fetoprotein (AFP) of 492,894ng/ml, was proven to be pure fetal hepatoblastoma. Initial staging work-up showed no evidence of metastatic disease. However surgical resection was not possible due to compression of inferior-vena-cave. Standard adjuvant chemotherapy of cisplatin, 5-fluorouracil, and vincristine (C5V) was given for four cycle followed by complete surgical resection with negative margins, surgery was followed by two more cycles of C5V. The AFP level fell gradually to a nadir of 31ng/ml at the end of treatment. 4 months off therapy, a rise in AFP and Computed tomography of the lungs revealed two pulmonary nodules proven to be Hepatoblastoma by biopsy. Over the course of the ensuing 8 months, three distinct chemotherapeutic combinations were utilized. These regimens included: (i) Ifosfamide/Carboplatin/Etoposide, (ii) Doxorubicin / Ifosfamide (iii) Irinotecan/temodar/temsirolimus, In addition to resection of pulmonary metastases, Patient developed transthoracic mass that invaded the 6th rib causing pathologic fracture. Despite extensive exposure to multi-agent chemotherapy, AFP levels continued to rise and serial CT scans demonstrated progressive disease.

Results: Sorafenib (200 mg/m² PO daily) combined with IV Bevacizumab (15 mg/kg q2 weeks) and PO Cyclophosphamide (50mg/m² daily) were initiated. Reassessment with AFP and CT scans of lungs/abdomen were done every 1 and 2 months respectively. After 12 cycles of this regimen, patient continue to have stable disease with possible slight decrease in size, AFP fell down by 35%, patient has no side effect with normal quality of life.

Conclusion: Combination of Sorafenib, Bevacizumab and Cyclophosphamide may represent a combination with a excellent quality of life for refractory hepatoblastoma while stabilizing the disease process.

HEMOPHAGOCYTIC LYMPHOHISTIOCYTOSIS ASSOCIATED ALK-POSITIVE ANAPLASTIC LARGE CELL LYMPHOMA WITH A RARE (2;17) TRANSLOCATION

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Background: Anaplastic large cell lymphoma (ALCL) is a form of non-Hodgkin's lymphoma which represents 10-15% of childhood lymphomas. ALCL has rarely been reported in association with hemophagocytic lymphohistiocytosis (HLH). HLH is a life-threatening disorder involving macrophage and T-cell activation with cytokine release causing multi-organ dysfunction. Leukemic peripheral blood and CNS involvement in ALCL occurs infrequently. Most cases of ALCL in children are ALK positive with ALK expression as a result of translocation between chromosomes 2 and 5. Translocation between chromosomes (2;17) is extremely rare and has only been reported once in a 53 year old male patient with ALCL and rearranged ALK and RNF213 partner gene.

Objectives: To report a presentation of HLH with metabolic acidosis and hyperleukocytosis secondary to ALK positive ALCL with chromosomes (2;17) rearrangement.

Design/Method: Case Report: The patient was a 2 year old male admitted to the Pediatric Intensive Care Unit with persistent fever, respiratory distress, and massive hepatosplenomegaly. Laboratory evaluation showed lactic acidosis, leukocytosis, anemia, and thrombocytopenia. He developed respiratory failure requiring intubation and renal failure requiring dialysis. He met criteria for HLH due to absent NK function and elevated soluble IL-2 receptor. His white blood cell count increased to 102.6×10^3 mcL so bone marrow aspiration was performed. Initial pathology evaluation of the bone marrow was negative for malignancy. Chromosome analysis of bone marrow revealed main clonal (2;17)(p23;q25) rearrangement. FISH analysis confirmed ALK gene rearrangement between chromosome 2 short arm and 17 long arm in 7% of bone marrow nuclei. FISH performed on peripheral blood showed ALK gene rearrangement in 5.6% of nuclei. A subsequent bone marrow morphology re-evaluation identified a few scattered atypical cells (ALK+ and CD30+) with kidney shaped or folded nuclei and abundant cytoplasm. After one dose of etoposide, white blood cell count decreased significantly. Brain MRI showed enhancing lesions consistent with metastasis. Treatment was started per ALCL99.

Results: Patient has completed two cycles of chemotherapy and is due for brain MRI and bone marrow evaluation prior to the third cycle.

Conclusion: This case represents a unique presentation of HLH associated ALK positive ALCL with rare (2;17)(p23;q25) chromosomal translocation and with CNS and leukemic peripheral blood involvement.

BURKITT LYMPHOMA: A CASE REPORT OF DIAGNOSTIC AND THERAPEUTIC CHALLENGES

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Background: Children with bilateral renal masses carry the diagnosis of bilateral Wilms tumor in most cases. Both Wilms tumor and Burkitt lymphoma can occur in a similar age group of children, however, the initial diagnostic approaches and treatments are different. Burkitt lymphoma requires a biopsy, and nephrectomy is generally contraindicated. In contrast, bilateral Wilms tumor does not require initial diagnostic biopsy as the radiographical images show typical findings. Case reports about bilateral kidney tumors that are not Wilms tumor are also limited.

Objectives: We present a case report of 5 year old male with Burkitt lymphoma. This case posed both diagnostic and treatment challenges due to his bilateral kidney involvement that resembled bilateral Wilms tumor. We will also review relevant literature.

Design/Method: Case report and review of literature.

Results: A 5 –year- old male presented with gross hematuria followed by acute renal failure. His imaging was initially interpreted as bilateral nephroblastomatosis with Wilms tumor on the left kidney. Later, the diagnosis was changed to bilateral Wilms tumor due to tumor thrombus on the right side. The patient received treatment for Wilms tumor without a pathology diagnosis. The tumor response in his kidneys was remarkable, however, he exhibited CNS symptoms, and CSF studies revealed Burkitt lymphoma. Currently, he is receiving Burkitt lymphoma treatment according to ANHL1131.

Conclusion: Bilateral renal Burkitt lymphoma could cause both diagnostic and therapeutic challenges in younger age groups. Our case report provides a rare case of Burkitt lymphoma which was initially treated according to bilateral Wilms tumor therapy. Initial presentation with gross hematuria, renal failure, and tumor lysis syndrome may prompt pathology confirmation prior to treatment, or at an earlier point.

ACQUIRED HEMOPHAGOCYTTIC LYMPHOHISTIOCYTOSIS PRESENTING WITH PULMONARY ALVEOLAR PROTEINOSIS: A TWO CASE SERIES OF THIS UNIQUE OCCURRENCE

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Background: Hemophagocytic lymphohistiocytosis (HLH) is a rare, life-threatening hyperinflammatory syndrome caused by excessive but ineffective immune system activation. Pulmonary alveolar proteinosis (PAP) is the abnormal accumulation of surfactant in lung alveoli causing respiratory disease. We describe two cases of critically ill toddlers who presented with signs of immune-hyperactivation along with progressive respiratory compromise, and subsequently were diagnosed with acquired HLH and PAP.

Objectives: To increase index of suspicion of PAP in patients with HLH, support early and thorough evaluation in similar cases and describe available treatment options.

Design/Method: The first patient is an ex-28 weeks, 1 year old girl with chronic lung disease and the second patient is a 13 month old boy with history of failure to thrive and recurrent pneumonias. Both of them presented with persistent fevers and respiratory failure alongwith significant lymphadenopathy and hepatosplenomegaly. Workup for HLH showed a very elevated ferritin (>16,000), bicytopenia, hypertriglyceridemia, hypofibrinogenemia, hemophagocytosis in the bone marrow in both patients plus an elevated soluble IL-2 receptor in patient one. NK function was normal in both. They met 7/8 and 6/8 criteria for HLH respectively.

Results: Genetic testing for HLH was normal in patient one, but showed a compound heterozygous mutation of SLC7A7 associated with Lysinuric protein intolerance (LPI) in patient two. Lung biopsy to evaluate progressive respiratory disease showed PAP in both cases. Both patients were treated with induction chemotherapy as per HLH-2004 protocol. PAP was treated with whole lung lavages and ECMO with resolution of symptoms in patient one, however treatment options for PAP were limited for patient two due to underlying LPI. HLH and PAP have been described independently in patients with LPI. Our second patient unifies the picture of an inborn aminoaciduria leading to macrophage dysfunction and immune dysregulation causing HLH and PAP. Whole lung lavage has limited utility in this situation and bone marrow transplant has not been described.

Conclusion: Diagnosis in similar complex cases can be challenging given multi-systemic and progressive nature of the disease, broad range of differentials and time required for diagnostic evaluation. However a high index of suspicion and early thorough evaluation can be beneficial and life-saving in severe cases.

HODGKINS LYMPHOMA IN SOTO SYNDROME

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Background: Sotos Syndrome (SS) is a rare genetic condition (1 in 14,000) characterized by excessive growth, frontal bossing, downslanting of the palpebral fissures, dolichocephalic head shape, hypertelorism and prominent jaw, caused by mutation in the NSD1 gene. There is an increased risk of pediatric cancer associated with SS (3.9%), especially hematopoietic malignancies. We present a case of a 13 year old boy with SS diagnosed with classic Hodgkin's Lymphoma (HL).

Objectives: Describe a case of an adolescent with HL and SS.

Design/Method: We conducted a search of PubMed, Ovid, Google Scholar search using the terms "Sotos Syndrome" and "Hodgkin" and "lymphoma." There were 11 previously reported cases of hematologic malignancies in association with Sotos Syndrome, but none of HL. Of note, these studies indicated that males are affected much often than females. Our case increases the number of reports to 12.

Results: A 13 year old young man with SS presented with a 2x3 firm, fixed anterior neck mass, proven by excisional biopsy to be HL. Workup confirmed Stage Ia disease. Our search yielded 17 manuscripts. The patient was successfully treated with 3 cycles of doxorubicin, vincristine, prednisone and cyclophosphamide and has remained in remission now for 33 months.

Conclusion: Sotos Syndrome is a rare genetic disease that appears to have an increased risk of leukemia and lymphoma. Our case is the 12th such case and the first HL. We hope that this will increase awareness of the possible association of SS and HL and further research of this condition. (Kurotaki, Nature Genetics 2002; Cohen. Am J Med Genet. 1999)

PNEUMOCYSTIS JIROVECI PNEUMONIA DIAGNOSED VIA RT-PCR FROM INDUCED SPUTUM IN PEDIATRIC ONCOLOGY PATIENTS

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Background: Pneumocystis jirovecii pneumonia (PJP) is a common cause of pneumonia in oncology patients with chemotherapy-induced immunosuppression. A high index of suspicion for PJP should be maintained in oncology patients undergoing active chemotherapy who present with fever, dyspnea, cough and hypoxia. Bronchoalveolar lavage (BAL) is the recommended method for specimen collection to diagnose PJP. However, the risks associated with performing BAL in an immunosuppressed oncology patient must be carefully weighed with the benefits. Less invasive diagnostic approaches such as induced sputum are not routinely used for PJP diagnosis in oncology patients as the low burden of organisms in these samples leads to low test sensitivity and there is scant data to support use of induced sputum for the diagnosis of PJP in pediatric oncology patients. Three pediatric patients with acute lymphoblastic leukemia (ALL) undergoing active chemotherapy presented with fever, cough, respiratory distress and hypoxia. Induced sputum was sent on all three patients for PJP real-time polymerase chain reaction (RT-PCR), and one patient underwent a BAL when he was clinically stable.

Objectives: To demonstrate the utility of PJP RT-PCR from induced sputum in immunosuppressed pediatric patients with ALL.

Design/Method: A retrospective chart review of three pediatric patients with ALL diagnosed with PJP via RT-PCR from induced sputum was performed. PJP RT-PCR was performed at Focus Diagnostics.

Results: Induced sputum from all three patients and the BAL specimen from one patient who underwent bronchoscopy were positive for PJP via RT-PCR. All patients were treated with trimethoprim-sulfamethoxazole and demonstrated clinical improvement.

Conclusion: Sending induced sputum for PJP RT-PCR is a less invasive and potentially useful approach to diagnose PJP in immunosuppressed pediatric oncology patients who are unable to undergo bronchoscopy and BAL.

SINUSOIDAL CD30+ DIFFUSE LARGE B-CELL LYMPHOMA MIMICKING ANAPLASTIC LARGE CELL LYMPHOMA: A RARE TYPE OF MONOMORPHIC POST-TRANSPLANT LYMPHOPROLIFERATIVE DISORDER

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Background: Incidence of Post-Transplant Lymphoproliferative Disorders (PTLD) has increased with rise in solid organ transplants in children. Higher levels of immune suppression, negative EBV serostatus at transplant with subsequent seroconversion, and early age at transplant are major risk factors. The World Health Organization (WHO) classifies PTLD into four types: early lesions, polymorphic, monomorphic, and Hodgkin Lymphoma. A majority of monomorphic PTLD are of B-cell origin. We describe a rare histologic variant of Diffuse Large B-Cell Lymphoma (DLBCL) in a child with PTLD showing sinusoidal invasion of B-cell lineage malignant cells.

Objectives: To describe the unique histology and treatment outcome in a child diagnosed with sinusoidal CD30+ DLBCL post heart transplant

Design/Method: Single case report

Results: A 9 year old female received a heart transplant (EBV: donor positive; recipient negative) at 3 weeks of age due to pulmonary atresia with intact ventricular septum. Tacrolimus and Mycophenolate were used as immune suppression. She presented with a 2 week history of left neck mass and fever. Imaging showed extensive lymphadenopathy above and below the diaphragm. Interval increase in blood EBV DNA (<200 --> 12211 IU/ml) was noted. An excisional lymph-node biopsy was performed and histology showed large pleomorphic lymphoid cells with sinusoidal pattern of invasion. Differential diagnosis included Hodgkin Lymphoma (HL), Anaplastic Large Cell Lymphoma (ALCL) and sinusoidal variant of DLBCL. Immunohistochemistry verified B-cell lineage of the sinusoidal cells (positive for CD20, CD30, CD45, and PAX-5). ALK-1 and CD15 were negative. In situ hybridization for EBV (EBER) was positive in numerous malignant nuclei. Focal bone marrow invasion was also noted. Based on these findings, a final diagnosis of stage IV sinusoidal CD30+ DLBCL was made. She completed treatment with Rituximab and chemotherapy (ANHL01P1 group B arm) and currently remains in remission.

Conclusion: Sinusoidal CD30+ DLBCL has not been reported in pediatric PTLD setting. It can mimic HL or ALCL based on similarities by morphology and immunohistochemistry. A high degree of suspicion and an extensive immunohistochemical panel is necessary to reach the diagnosis of this rare entity. Accurate histological diagnosis is important in patients with PTLD in order to make appropriate treatment decisions.

ELANE MUTATIONS DO NOT PORTEND NEUTROPENIA: REPORTS OF A KNOWN MUTATION AND A NOVEL MUTATION WITH VARIABLE PHENOTYPES

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Background: Two forms of hereditary neutropenia, cyclic neutropenia (CyN) and severe congenital neutropenia (SCN), are attributed to mutations in the ELANE gene. The distinction is clinically relevant, as patients with SCN have increased infectious complications and heightened risk of developing myelodysplasia or myeloid leukemia. Autoimmune Neutropenia is an acquired neutropenia, secondary to antibodies directed against granulocyte precursors; infections are less frequent than in inherited causes of neutropenia.

Objectives: To describe genotypes and phenotypes of 2 mutations/variants identified within the ELANE gene that have been associated with SCN and CyN.

Design/Method: Review clinical course and laboratory findings of two unique patients with ELANE mutations/variants.

Results: Case 1 is a 4 year old Caucasian female with history of recurrent fevers associated with oral ulcers and abdominal pain. A genetic panel showed V186I mutation of ELANE gene associated with SCN. Serial labs did not show neutropenia. Her mother had no clinical history for neutropenia or infections, yet, she too carries the mutation. Our patient responded to colchicine for Familial Mediterranean Fever; they each were additionally noted to be heterozygous for E148Q mutation in the MEFV gene. Case 2 is a 2 year old Caucasian male who presented with fatigue, poor oral intake, diarrhea and bruising; infection history was significant for a single staph infection of a wound that responded to outpatient antibiotics. Severe persistent neutropenia was noted on serial testing. A novel ELANE variant H39Q was identified in both the child and his mother. His mother reported episodes of cellulitis and abscess at the site of her cesarean section, and inguinal lymphadenitis, although she reported being healthy prior. His mother is without neutropenia on serial testing. Our patient also demonstrated positive testing for anti-neutrophil antibodies.

Conclusion: Mutations or variants within the ELANE gene are associated with SCN and CyN in majority of cases, yet modifying genes and autoimmune neutropenia can confound the diagnosis. Caution should be used when attributing neutropenia or clinical symptomatology solely to genetic etiology, given the phenotypic variability of ELANE mutations. Genetic counseling should be sought when genetic testing is requested.

PAROTID EXTRANODAL MARGINAL ZONE B CELL LYMPHOMA IN A CHILD WITH SJÖGREN SYNDROME

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Background: Extranodal marginal zone B cell lymphoma of mucosa-associated lymphoid tissue (EMZL) is predominantly seen in adults (median age 60 years), and comprises only 5% of non-Hodgkin lymphoma diagnoses. EMZL is rare in children, often secondary to underlying immunodeficiency. In adults, MZL is associated with chronic infections and autoimmune diseases, such as Sjögren syndrome (SS). EMZL due to SS has not previously been described in childhood.

Objectives: To describe the clinical and pathological features of a teen with EMZL subsequently diagnosed with SS.

Design/Method: Case report and related literature review were performed.

Results: A 16-year-old boy presented with right pre-auricular mass. There was a long history of intermittent cervical lymphadenopathy and bilateral parotid swelling for more than 5 years. Fine needle aspiration showed benign lymphoid tissue with no evidence of malignancy. Serologic testing for CMV, EBV, HIV, toxoplasmosis, tuberculosis, cat scratch disease, syphilis, and streptococcus showed only remote infection by CMV and EBV (positive IgG, negative IgM). Erythrocyte sedimentation rate (ESR) was 122 mm/h. Near-total parotidectomy was performed, diagnostic of EMZL with unclear surgical margins. 30.6 Gy radiotherapy was delivered. There is no evidence of recurrence after 14 months follow-up. Further testing for Chlamydia psittaci, hepatitis B virus, and hepatitis C virus infection was negative. However, there were significant elevations in the antinuclear antibody (>1:640 dilution, speckled pattern), rheumatoid factor (106 IU/mL), SSA antibody (>8 antibody index), SSB antibody (>8 antibody index), and total IgG (3230 mg/dL). Testing for systemic lupus erythematosus was negative. Despite only vague sicca symptoms, ophthalmology exam revealed corneal and conjunctival erosions, and the patient was given a diagnosis of SS. Hydroxychloroquine and rituximab were prescribed, with reduction in the ESR to 14 mm/h, and there has been no subsequent parotid swelling. No similar published cases of EMZL occurring in pediatric SS patients were reported to date.

Conclusion: EMZL occurring in pediatric SS patients has not previously been described.

Because of the potential paucity of clinical symptoms, evaluation for SS or other autoimmune disease should be undertaken in children with EMZL.

THE USE OF SUNITINIB AS MAINTENANCE CHEMOTHERAPY IN A PEDIATRIC PATIENT WITH A POORLY DIFFERENTIATED THYMIC CARCINOMA

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Background: Thymic carcinomas (TC) are rare in adults and less common in children, accounting for less than 1% of childhood mediastinal tumors. In adults, the first treatment is usually surgical resection. Approximately 30% of TC are metastatic at diagnosis and are unresectable. The median survival with current platinum-based chemotherapy regimens is approximately 2 years. There are ongoing studies of tyrosine kinase inhibitors (TKI) for advanced thymic tumors, but no reports of their use in maintenance therapy in metastatic TC in children.

Objectives: We report the use of cisplatin and docetaxel followed by sunitinib as maintenance chemotherapy in a pediatric patient with metastatic TC.

Design/Method: A 13 year old male with autism, who presented with a mediastinal mass, was diagnosed with stage IV TC. The tumor was unresectable and there were multiple metastatic lung lesions. The patient was treated with cisplatin 75mg/m² and docetaxel 75mg/m² every 3 weeks. To prevent regrowth, we initiated maintenance therapy with sunitinib, a drug reported to stabilize disease in adults with advanced thymic malignancies.

Results: After 4 cycles of chemotherapy, imaging revealed reduction of the anterior mediastinal mass (36% reduction) and decreased pulmonary metastases. Following 8 cycles of chemotherapy, repeat imaging showed further decrease in size (76% reduction) and number of pulmonary metastases. Due to the aggressive nature of the disease, he was started on sunitinib 25mg oral daily. Side effects included discoloration of skin surrounding his g-tube which was used for administration and a faint, erythematous rash on his chest. Since starting sunitinib, the patient continues to have reduction in the primary tumor size. Most recent chest CT performed 22 months after initiation of sunitinib showed an 88% reduction from the original mass and further resolution of lungs metastases.

Conclusion: Thymic malignancies are rare tumors that are aggressive and difficult to treat in advanced stages. We demonstrate disease response using sunitinib, a multi-TKI, as maintenance therapy to prevent regrowth. While on sunitinib, the patient continues to have disease reduction with minimal side effects. Given the rarity of these tumors, this is a promising therapeutic approach for an advanced-stage tumor in a pediatric patient.

MATURE B-CELL LYMPHOMA IN A PEDIATRIC PATIENT WITH ATAXIA-TELANGIECTASIA: AN UNCERTAIN FRONTIER

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Background: Ataxia-Telangiectasia (A-T) is an autosomal-recessive DNA-mismatch repair disease causing predisposition to malignancies. Up to 30% of A-T patients will develop cancer, mostly of lymphoid origin. These patients pose a unique challenge due to their sensitivity to radiation and increased risk of chemotherapy complications such as hemorrhagic cystitis and severe infection.

Objectives: We discuss a 12-year-old female with A-T who presented with two weeks of neck swelling. Excisional biopsy revealed mature B-cell lymphoma. Staging PET/CT scan showed localized disease.

Design/Method: The patient's treatment was based on the successful treatment of elderly patients with high-grade non-Hodgkin lymphoma with 6 cycles of CHOP (cyclophosphamide, doxorubicin, vincristine, and prednisone) combined with rituximab (375 mg/m²), which resulted in complete response (CR) rate of 85% which was modified therapy to limit toxicity. She received one cycle of COP (cyclophosphamide, vincristine, and prednisone) with near CR on MRI. For her first cycle of R-CHOP, cyclophosphamide dose was reduced and she remained hospitalized for count nadir and recovery due to risk of infection. She did not have a significant nadir so cyclophosphamide was escalated to full dose for subsequent cycles. Complications included prolonged (culture-negative) febrile neutropenia, *C. difficile* colitis, and right intra-atrial thrombus requiring anticoagulation.

Results: Following four cycles of R-CHOP, MRI showed CR. Following her fifth cycle she was admitted with fever, neutropenia, and hypotension requiring vasopressor support. Echocardiogram revealed ejection fraction of 22% following a cumulative anthracycline dose of 250 mg/m². She was intubated, and developed worsened hypotension and desaturation, progressing to cardiac arrest. Despite cardiopulmonary resuscitation, spontaneous cardiac function did not return, and patient died. Signs of heart failure were evident on limited autopsy of chest, however underlying etiology remained unclear.

Conclusion: Despite superior treatments for many non-Hodgkin lymphomas, patients with A-T continue to present obstacles due to their exquisite sensitivity to commonly employed anti-cancer therapies. R-CHOP may be an acceptable regimen for these patients, but may still be too toxic. Increased risk for cardiac toxicity has not been reported, and may be another sensitivity in A-T patients. Additional studies are warranted to further understand this special patient population, leading to adaptation of treatments or improved protection from toxicities.

THE USE OF MODIFIED HEAD START II CHEMOTHERAPY IN GERM CELL TUMORS WITH SOMATIC MALIGNANT TRANSFORMATION: A REPORT OF TWO CASES

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Background: Pediatric germ cell tumors (GCT) are rare, accounting for only 3-5% of all pediatric malignancies. Somatic malignant transformation (SMT) of a GCT is therefore an extremely unusual event, and hence there are no standard treatment guidelines. Consensus is that treatment should be directed at the malignant component that has undergone somatic transformation. Prior reports of prognosis have been guarded. We report the successful treatment of 2 extracranial central PNETs which arose from a GCT.

Objectives: To report the treatment of two GCTs that underwent SMT into a PNET with a modified Head Start II regimen followed by high dose chemotherapy with stem cell rescue.

Design/Method: A 12 month old female (A) and a 23 month old male (B) both presented with abdominal distension, urinary retention and constipation and were found to have sacrococcygeal teratomas (SCT) with somatic transformation to central PNET. In case A, upfront resection was not possible due tumor encasing the rectum. In case B, upfront surgical resection was complicated by tumor rupture. Both were treated with a modified Head Start regimen which consisted of vincristine (VCR) 0.05 mg/kg, cisplatin 3.5 mg/kg, etoposide (VP-16) 4 mg/kg and cyclophosphamide (CTX) 65mg/kg. High-dose methotrexate was excluded from the regimen to avoid additional toxicity since the tumors were extracranial. In case A, chemotherapy was followed by gross total resection with positive margins. Both patients underwent consolidation with high-dose chemotherapy (HDCT) with carboplatin 16.7 mg/kg, thiotepa 10 mg/kg and etoposide 8.3 mg/kg followed by autologous peripheral stem cell rescue. Neither patient received radiation therapy.

Results: The chemotherapy regimens were tolerated well. Patient A developed post-operative wound dehiscence. Patients A and B are currently without evidence of disease after a follow-up period of 18 months and 12 months respectively.

Conclusion: We present two cases of SCTs that underwent SMT into central PNET treated with the same modified Head Start regimen followed by HDCT. High-dose methotrexate was excluded from the regimen since there was no need to penetrate the blood-brain barrier. GCTs with SMT are treatable with aggressive therapy targeted at the somatic malignant component.

USE OF ADJUVANT PEGYLATED INTERFERON ALFA-2B FOR ULCERATED STAGE IIIB MELANOMA IN AN 8 YEAR OLD GIRL

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Background: Ulcerated primary melanoma is associated with a poor prognosis. Studies show that ulcerated melanoma treated with adjuvant pegylated interferon alfa-2b (PEG-IFN- α -2b) has improved recurrence-free survival in adults with cutaneous melanoma.

Objectives: To report our experience using pegylated interferon alfa-2b in a pediatric patient with ulcerated stage IIIB Melanoma.

Design/Method: Case report

Results: An 8-year-old girl presented with a right lower extremity lesion with pathology revealing a malignant melanoma with spitzoid features invasive to at least Clark level IV, Breslow depth of at least 1.4 mm with a microscopic focus of ulceration, and a mitotic rate of 3/mm². A PET scan showed increased uptake in a right inguinal lymph node with no distant metastasis. She underwent a wide local excision with full-thickness skin grafting and a sentinel lymph node biopsy. Pathology was negative for residual disease with a 1.5 cm margin. One lymph node was focally involved by metastatic melanoma (0.7 mm). A radical inguinal lymph node dissection was performed and negative for disease. Given the presence of high-risk disease with ulceration, she was started on PEG-IFN- α -2b induction therapy for 8 weeks. With limited pediatric data she was started at the maintenance adult dose of 3 mcg/kg/dose by weekly subcutaneous injection. The dose was increased by 1 mcg/kg each week to the full induction dose of 6 mcg/kg. Following induction she continued on maintenance therapy, 3 mcg/kg/week for 52 weeks. Side effects and organ toxicity were monitored monthly throughout her course. Despite premedication with acetaminophen, the patient experienced a low-grade fever with chills and myalgias following the first dose. Subsequent injections were followed with scheduled acetaminophen for 24 hours, which prevented symptoms. She reported mild fatigue for one to two days following each injection, but denied symptoms of depression, headache, and nausea or vomiting. Monthly laboratory monitoring for myelosuppression, hepatic and renal dysfunction was performed along with a TSH and triglyceride level every three months. No persistent abnormalities were seen.

Conclusion: Our patient tolerated pegylated interferon alfa-2b with no significant adverse side effects or organ toxicity. This is the first reported pediatric patient with melanoma treated with this therapy.

PERICYTOMA t(7:12) WITH ACTB-GLI1 FUSION IN A PEDIATRIC GASTRIC TUMOR

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Background: Tumors with the t (7;12) and ACTB-GLI1 fusion are a recently described entity, usually arising in the soft tissue. Two prior published articles reported six cases, two of them in children, both arising in the tongue.

Objectives: To report an unusual gastric tumor arising from the pyloric wall of the stomach in a 9-year old child harboring the exceptionally rare translocation t(7;12) resulting in ACTB-GLI1 gene fusion.

Design/Method: Case report

Results: A 9-year-old previously healthy female, presented with one episode of abdominal pain and vomiting. An epigastric mass was palpated. Computed tomography scan of the abdomen showed a localized 6cm X 7cm X 6cm solid and cystic mass arising from the distal stomach. Preoperative differential included gastrointestinal stromal tumor and inflammatory myofibroblastic tumor. The child underwent an exploratory laparotomy, which revealed a mobile mass attached to the anterior portion of pylorus. The mass was completely resected, and a Heineke-Mikulicz pyloroplasty was performed. Microscopic examination of the mass revealed a spindle cell proliferation diffusely positive for CD56 and vimentin and focally for EMA and CD10. Initially the pathology was reported as angiomatoid fibrous histiocytoma. Cytogenetic studies showed a balanced translocation involving the short arm of chromosome 7 at p22 and the long arm of chromosome 12 at q13 [46,XX,t(7;12)(p22;q13)]. The diagnosis was changed to pericytoma t(7:12). The presence of ACTB-GLI1 fusion transcripts was confirmed by RT-PCR and genomic DNA amplification. The child was in remission at 6 months follow-up.

Conclusion: Our case is the first report of a gastric tumor with the translocation t(7;12)(p22;q13) and confirmed ACTB-GLI fusion gene, in a pediatric patient. The unusual location and morphology made the differential diagnosis quite difficult, making genetic and molecular analyses imperative for the correct diagnosis. No evidence of recurrence or metastasis has been documented in the prior reported cases and resection seems to be the treatment of choice.

PREMATURE PHYSEAL CLOSURE FOLLOWING PROLONGED FENRETINIDE ADMINISTRATION IN NEUROBLASTOMA

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Background: Despite advances in multimodal therapy for high risk (HR) neuroblastoma, survival remains suboptimal. Retinoid therapy with 13-cis-retinoic acid (13cisRA) has contributed to improved outcomes. The synthetic retinoid fenretinide has demonstrated in vitro toxicity against neuroblastoma cells that have developed resistance to other retinoids, and has a favorable toxicity profile in Phase I trials. Skeletal effects, including premature physeal closure, have been described with other retinoids, but have not been described in children treated with fenretinide to date.

Objectives: To report two patients with neuroblastoma who developed premature physeal closure following protracted fenretinide therapy.

Design/Method: Retrospective chart review

Results: Patient 1 (Caucasian girl), and Patient 2 (African American boy) were diagnosed at ages 6 and 5 years respectively with HR stage 4, single copy MYCN neuroblastoma. Both failed induction therapy and received investigational ¹³¹I-MIBG followed by consolidation chemotherapy and stem cell rescue, local radiation therapy, and 13cisRA. Due to persistent metastatic disease, both received oral fenretinide (capsular formulation, 800 mg PO TID) for a total of 70 and 61 cycles, respectively, and ultimately achieved complete remission. During treatment with fenretinide, both developed asymmetric premature physeal closure of multiple long bones, resulting in limb length discrepancies and angular deformities. Nearly a decade off therapy, both are alive and in remission from neuroblastoma.

Conclusion: Phase I and II studies of fenretinide in children have not reported skeletal toxicity as a late effect of therapy. The unusual and strikingly similar radiographic and clinical findings strongly suggest that the skeletal abnormalities may be a consequence of protracted fenretinide exposure. Further study of potential skeletal toxicity in neuroblastoma patients receiving retinoid therapy is indicated to better understand the mechanism and risk factors of retinoid bone toxicity.

A NOVEL PMS2 MUTATION IN A YOUNG ADULT WITH KCNT1 POTASSIUM CHANNELOPATHY AND COLORECTAL CARCINOMA IN SITU (CIN): A CASE REPORT AND REVIEW OF LITERATURE

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Background: Pediatric colorectal cancer (CRC) accounts for 2.1% of all cancers in patients aged 15–29 years. Lynch syndrome (LS), a cancer predisposition syndrome caused by mutations in one of the mismatch repair (MMR) genes, occurs in 3 – 5% of adults with CRC but is rarely seen in pediatrics. Mutations in MLH1, MSH2, MSH6 or PMS2 genes result in defective surveillance/repair during DNA replication, resulting in microsatellite instability. If a second hit occurs due to acquired local stresses, malignant transformation may result. PMS2 mutation is more represented in biallelic germline mutations of MMR (>50%), though it accounts for only 2% of LS mutations.

Objectives: Report a novel PMS2 gene mutation in a young adult with CIN. Examine the ethical and therapeutic dilemmas highlighted by this case and discuss potential mechanisms of malignant evolution.

Design/Method: A 21-year-old male, conceived via sperm donation from a male of Ashkenazi-Jewish descent, presented with persistent rectal bleeding. His maternal family history is significant for CRC in grandmother, bladder cancer in uncle and relatives with skin cancer. He has a history of refractory epilepsy, severe intellectual disability and was diagnosed using whole exome sequencing with a very rare potassium channelopathy due to a heterozygous mutation in the KCNT1 gene. He also has a history of recurrent volvulus with significant colonic resection, pseudo-obstructive syndrome with colonic neuropathy and TPN-dependent intestinal malabsorption.

Results: Colonoscopy revealed a tubular villous adenoma with high-grade dysplasia consistent with CIN. Staging workup, including CEA and CA19-9 evaluation was negative. Reanalysis of the exomic data for 56 known cancer-related genes revealed a heterozygous c.851C>G mutation resulting in a stop codon p.Ser284X in the PMS2 gene, not present in his mother's exome sequencing.

Conclusion: This case report presents a novel PMS2 mutation, uniquely observed in a patient with a known channelopathy. The emerging role of PMS2 mutation in pediatric cancer, possible mechanisms of a second hit and the therapeutic dilemma of CIN in patients with LS are important considerations illustrated by this unique case. We will also highlight the ethical dilemmas surrounding reporting of incidental findings in whole exome sequencing in the context of detection of clinical oncogenetic potential.

MULTIPLE METASTATIC SOMATIC TISSUE GANGLIONEUROMA FROM A PRIMARY ADRENAL GANGLIONEUROBLASTOMA IN A PEDIATRIC PATIENT

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Background: Neuroblastic tumors have an age-linked classification that is dependent on the differentiation of the neuroblast and the presence or absence of Schwannian stromal development. They fall along a spectrum of tumor maturity, which dictates tumor aggression and course. Ganglioneuromas and intermixed ganglioneuroblastomas are the most mature subtypes that tend to present with unifocal disease and have a benign course.

Objectives: We present a unique case of a 3-year-old boy with multiple tumors identified at initial presentation, with histology consistent with multiple soft tissue ganglioneuromas and an abdominal intermixed ganglioneuroblastoma.

Design/Method: Our patient is a previously healthy boy who presented with a mass on the posterior aspect of his right thigh that was increasing in size over a 1-month period. An MRI of his thigh revealed 3 well-circumscribed lesions within the muscle. The biopsy of these lesions was in keeping with a ganglioneuroma. An abdominal MRI performed as part of a staging work-up revealed a mass in the right adrenal fossa. The biopsy of this mass was consistent with an intermixed ganglioneuroblastomas. N-MYC was not amplified in either lesion. The remainder of the staging work-up including urine vanillylmandelic acid (VMA) and homovanillic acid (HVA), a bone scan, bilateral bone marrow aspirates and biopsies, and a MIBG scan were unremarkable. Although metastatic disease was present upon presentation, based on the histological subtypes of his tumors, the likelihood of progressive disease was low. Therefore, he was observed without active treatment.

Results: He remains well without disease progression almost 1-year following diagnosis.

Conclusion: Reports of metastatic ganglioneuromas and intermixed ganglioneuroblastomas in the literature are limited. To our knowledge, this is the first pediatric case with concurrent adrenal ganglioneuroblastoma and multiple soft tissue ganglioneuroma metastases present at the initial diagnosis. This rare presentation of multifocal soft tissue ganglioneuromas, with an abdominal intermixed ganglioneuroblastoma, raises the possibility that these lesions were once less mature neuroblastic tumors that underwent maturation. Given the distribution of disease in our patient, it is possible that our patient once had a stage IV-S neuroblastoma, with subsequent maturation of the primary tumor and metastases.

NEUROMUSCULAR SYMPTOMS AS A RARE PRESENTATION OF ADRENOCORTICAL CARCINOMA

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Background: Adrenal cortical carcinomas (ACC) are rare aggressive malignant neoplasms with a reported incidence of 1-2 cases per 1 million population and account for 0.05-0.2% of all malignancies. The majority of these tumors are functional with approximately 60% of patients experiencing endocrine symptomatology typically characterized by Cushing's syndrome (40%) or a mixed hormonal picture of Cushing syndrome seen in association with virilization. Rarely, patients present with a pure hormonal syndrome of feminization or hyperaldosteronism, 6% and 2.5%, respectively.

Objectives: To report a rare case of primary hyperaldosteronism associated to ACC.

Design/Method: Case report

Results: A 16 year old girl presented with neuromuscular symptoms (inability to rise her arms above her head), severe hypokalemia (1.6mmol/l), hyponatremia (147mmol/l) and borderline hypertension (131/70 mmHg). No signs of virilization were noted. Laboratory evaluation showed hyperaldosteronism with plasma aldosterone 69 ng/dL and plasma renin activity 0.4 ng/mL/h. A CT of the abdomen showed a 5.8 cm noncalcified vascular mass arising from the right adrenal gland, impinging on the posterior inferior vena cava. The patient underwent open adrenalectomy and a diagnosis of stage 3 ACC was made due to the presence of tumor thrombus on the adrenal vein. Pathology report revealed poorly differentiated (grade III) adrenal cortical carcinoma. A strong family history of cancer was noted: mother died at the age of 25 of breast cancer, maternal grandfather had testicular cancer and died of lung cancer at age 47. Maternal great-grandmother died of skin cancer at 29 years old. Maternal great-great grandmother died of breast cancer at the age of 20. A maternal great-aunt died of abdominal organ cancer at 51. This prompted genetics testing that revealed a heterozygous mutation, c.154_157delinsGACCTG in the P53 gene, which is known to be associated with Li-Fraumeni syndrome. The patient's biochemical laboratory data normalized postoperatively. She was enrolled on a COG clinical trial for ACC and completed therapy with mitotane, etoposide, cisplatin, doxorubicin in December 2009. She is currently alive without evidence of disease, but the long-term side effect of adrenal insufficiency.

Conclusion: While rare, aldosterone-secreting adrenal cortical carcinomas may occur and should be considered in the differential diagnosis of adrenal tumors in children.

PTPN11 MUTATION IN A CHILD WITH NEUROBLASTOMA AND PROTEIN LOSING ENTEROPATHY: THE MISSING LINK?

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Background: Neuroblastoma is the most common extracranial solid tumor in children, and the most common cancer in infancy (1). It is a tumor which may present with a spectrum of paraneoplastic syndromes. Protein losing enteropathy (PLE) has been described in a small number of children with neuroblastoma unrelated to the gastrointestinal involvement by cancer, and has been thought to be either a rare paraneoplastic syndrome due to catecholamine effects on the gut or to lymphatic obstruction from mass effect (2). Noonan Syndrome has been associated independently with neuroblastoma and with PLE (3).

Objectives: To describe the clinical course of phenotypically normal baby with concurrent neuroblastoma and PLE whose tumor DNA was found to have a mutation in the PTPN11 gene.

Design/Method: A 6 month old Caucasian female with PLE was referred for evaluation of a retroperitoneal mass. Laparoscopic biopsy confirmed diagnosis of favorable histology neuroblastoma. It was the unusual constellation of clinical abnormalities which raised concerns about our ability to predict how either the tumor or the PLE would respond to first-line anti-neuroblastoma treatment. This led us to have her tumor evaluated for actionable mutations which might provide treatment options if needed.

Results: Next generation sequencing of the tumor identified a mutation in the PTPN11 gene. PTPN11 was normal in her DNA from peripheral blood. Thus, she did not have Noonan Syndrome, the most common form of which results from an autosomal dominantly inherited constitutional PTPN11 mutation. The possibility of mosaicism as an explanation for these comorbidities remains to be evaluated.

Conclusion: We conclude that the finding of PLE in children should raise consideration of PTPN11 mutations. Identification of mutations of PTPN11 in tumors of patients with neuroblastoma should prompt consideration of study of constitutional and other tissue for evidence of full blown or mosaic Noonan Syndrome. Rare pediatric cancers and increasing capabilities for genetic analysis provide an opportunity to decipher the missing links which explain unusual case presentations including paraneoplastic syndromes. 1. Howlander, SEER Cancer Statistics Review, 2012. Citak, Pediatric Blood & Cancer, 2006. Ekvall, Clinical Genetics, 2011

A CASE REPORT OF AN INOPERABLE INFLAMMATORY MYOFIBROBLASTIC TUMOR RESPONSIVE TO CHEMOTHERAPY AND A NONSTEROIDAL ANTI-INFLAMMATORY DRUG

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Background: Inflammatory myofibroblastic tumor (IMT) is a rare benign neoplasm of unknown origin that can be associated with malignant features such as local invasiveness and recurrence. Complete surgical resection is the treatment of choice; however, this is not always feasible due to anatomical challenges. Case reports have demonstrated tumor reduction of inoperable IMT's with the use of anti-inflammatory agents, a variety of chemotherapy drug combinations, and targeted therapy with crizotinib for IMT's with ALK-1 gene rearrangement. Currently, a standardized approach for inoperable IMT's has not been established.

Objectives: To describe a case of inoperable ALK-1-negative, pelvic IMT treated with vincristine, dactinomycin, and cyclophosphamide (VAC) in combination with celecoxib.

Design/Method: Single case report

Results: A 7-month-old Caucasian female presented with a 2-week history of poor oral intake, constipation, and abdominal distention. Imaging demonstrated a large presacral mass measuring 8.1 X 8.4 X 15.8 cm. A biopsy was performed, due to tumor unresectability, which noted myofibroblastic proliferation with marked inflammation consistent with IMT. Next-generation sequencing revealed an alteration in the CPS1 (A347S) gene, previously reported as a poor prognostic marker in rectal cancers, and a normal ALK-1 gene. Initially, she was treated with celecoxib and methylprednisolone; however, the tumor ruptured and resulted in abdominal compartment syndrome with hypertension, obstipation, bladder outlet obstruction, and bilateral hydronephrosis. She was then transitioned to VAC chemotherapy, which consisted of a 21-day cycle of vincristine (0.025 mg/kg/dose) weekly, dactinomycin (0.025 mg/kg/dose) on day 1, and cyclophosphamide (40 mg/kg/dose) on day 1, in addition to daily celecoxib therapy. She has tolerated 5 cycles of therapy with minimal side effects and occasional growth factor support. The most recent imaging reveals tumor measurements of 3.7 X 4.2 X 6.7 cm. She has had complete resolution of her hypertension, obstipation, bladder outlet obstruction, and marked improvement of her bilateral hydronephrosis. She will continue this regimen until complete resection is feasible.

Conclusion: VAC used in combination with celecoxib may be a therapeutic option for inoperable ALK-1-negative IMT.

MINIMALLY INVASIVE SURGICAL RESECTION AND BUCCAL GRAFT VAGINOPLASTY WITHOUT RADIOTHERAPY (RT) FOR DEFINITIVE LOCAL CONTROL IN GIRLS WITH VAGINAL BOTRYOID RHABDOMYOSARCOMA (RMS)

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Background: Vaginal RMS is associated with a favorable prognosis, although the optimal local control approach is controversial due to the long term reproductive, musculoskeletal, and psychological sequelae of RT. A response-based local control approach has been attempted in patients with group III vaginal RMS, eliminating the need for RT.

Objectives: To describe a new surgical approach for localized vaginal RMS using minimally invasive surgical resection followed by autologous buccal graft vaginoplasty reconstruction.

Design/Method: Case series of 3 patients with localized vaginal botryoid RMS from 3 institutions who were treated with chemotherapy as per ARST0331, subset B.

Results: All 3 patients were under 3 years of age (range 11-30 months) and had botryoid RMS. All patients received a maximum of 4.8 g/m² of cyclophosphamide followed by vincristine/dactinomycin therapy. Surgery was performed at different times (weeks 0, 12, and 16), and all patients underwent a subtotal or total vaginectomy with autologous buccal graft vaginoplasty reconstruction. In one patient the surgical margins were positive, and in the other two the closest margins were 1 and 2 mm. No patient received RT. At a median length of follow-up of 25 months, all 3 patients remain disease-free.

Conclusion: Herein we report 3 cases of vaginal RMS successfully treated without RT. Our preliminary data suggests that surgical local control and immediate reconstruction is feasible and can spare these young patients the long-term complications associated with RT. Longer follow-up is critical to secure disease free survival with a functional neo-vagina.

MALIGNANCY VS SCURVY; SIMILAR MANIFESTATION DIFFERENT PATHOPHYSIOLOGY - CASE SERIES

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Background: Scurvy, thought to be of historical significance, is commonly misdiagnosed in developed countries. 15-20% of children in the United States consume less than 30mg of vitamin C per day (1) and can present with anemia, petechial rash, bone pain and gingival bleeding, leading to extensive hematology workup.

Objectives: Three cases of scurvy presenting with hematological complications.

Design/Method: Retrospective review of three cases of scurvy presenting to a pediatric hematology/oncology center.

Results: Seventeen year-old with gingival hyperplasia, presented with subungual hemorrhages, lower extremity ecchymosis and swelling. Bloodwork revealed hemolytic anemia, hemoglobin of 8 g/dL, total bilirubin 2.5 mg/dL and PT/INR 17.1/1.4. Physical exam revealed perifollicular hyperkeratosis with corkscrew hair. Dietary history revealed 1-2 liters of diet Pepsi per day, bread, peanut butter and jelly; devoid of vitamin C containing foods. After ruling out coagulation deficiencies; Vitamin K, Cholecalciferol, and Ascorbic Acid were started empirically, to which he responded remarkably. Five year-old with tuberous sclerosis (TS), on ketogenic diet for epilepsy, presented with difficulty ambulating secondary to bone pain, anemia and petechial rash. CT scans were normal; X-rays of knee, wrist and ankle demonstrated metaphyseal lucency with soft tissue swelling, seen with salter 1 fractures or inflammatory conditions. Bloodwork revealed hemoglobin of 5.6 gm/dl, thrombocytopenia (135,000/mcl) and coagulopathy (PT/INR 16.6/1.4). Inappropriate reticulocyte response prompted bone marrow biopsy which ruled out malignancy. Physical exam, dietary history and negative marrow raised concerns for scurvy and Vitamin C was initiated. She demonstrated immediate clinical improvement. Twelve year-old presented with a year long history of left knee pain, and recent leg limp. MRI and bone scan revealed chronic relapsing multifocal osteomyelitis (CRMO) versus bone malignancy. Bone biopsy showed osteonecrosis with new bone formation and marrow fibrosis, consistent with CRMO or “metabolic” bone disorders. Dietary history revealed a restrictive diet, devoid of fruits and vegetables. All three patient’s had vitamin C level <0.1mg/dL

Conclusion: Restrictive diets can lead to multiple nutritional deficiencies. Avoidant/Restrictive food intake disorder (ARFID), a published DSM V disorder, highlights associations of restrictive diets, pediatrics and nutritional deficiencies (2). Scurvy often presents with bleeding manifestations and bone pain resulting in a referral to pediatric hematologist/oncologist.

RARE CASE OF CONGENITAL EMBRYONAL RHABDOMYOSARCOMA OF THE HAND

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Background: Rhabdomyosarcoma (RMS) is the single most common type of soft tissue sarcoma in children and adolescents. Two-thirds of cases are diagnosed in children younger than six years of age but it is rare in neonates. Extremity tumors present more commonly in adolescents and are frequently of the alveolar type. The presence of a congenital extremity RMS is extremely rare but should be considered in such presentation.

Objectives: To increase the clinical suspicion of the congenital embryonal RMS in neonates who present with extremity soft tissue mass.

Design/Method: We report a unique case of congenital embryonal RMS of the hand.

Immediately after birth, a term neonate was noticed to have an approximately 1cm x 2cm soft mass over the left thenar eminence. There was no overlying skin discoloration noted. The mass size progressively increased over a period of two weeks with dorsal extension, and concomitant change in the mass consistency from soft to hard. On day of life 19, MRI scan of the left hand showed a T2 hyperintense mass that had interdigital extension to the second, third, fourth metacarpals. Surgical biopsy was obtained on day of life 34. The pathology report was consistent with an embryonal rhabdomyosarcoma, spindle cell variety. Tumor cytogenetic was normal. A clinically non-palpable left axillary lymph node was noticed to be enlarged on staging imaging CT scan. Subsequent biopsy of the left axillary lymph node was negative for metastatic disease. A whole body PET scan showed no evidence of metastatic disease. According to the Soft Tissue Sarcoma Committee of the Children's Oncology Group (COG), Pretreatment Staging System our patient disease was stratified as non-metastatic group III intermediate risk RMS.

Results: The RMS was treated as per the COG protocol ARST0531 regimen A (VAC only) with multi-agent chemotherapy consisting of cyclophosphamide, vincristine and dactinomycin. Local control obtained at with radiocarpal disarticulation. Patient is now 20 months from completion of treatment without evidence of disease relapse.

Conclusion: This is the third case in medical literature describes congenital RMS of the hand. Clinicians should be aware of such rare presentation to establish diagnosis and start early treatment.

A UNIQUE CASE OF METASTATIC TESTICULAR PURE CHORIOCARCINOMA IN A PERI-PUBERTAL MALE WITH A REVIEW OF THE LITERATURE

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Background: Pure choriocarcinoma of the testis is a highly malignant tumor derived from trophoblastic cells with the potential for early metastasis. It accounts for 0.3% of all primary testicular germ cell tumors. Given its rarity and propensity in older patients, pure choriocarcinoma is often not in the differential for patients who present at pediatric oncology services.

Objectives: To describe a case of pure choriocarcinoma in a peri-pubertal male patient, review pediatric/adolescent cases, and discuss the use of pubertal status in testicular tumor work up.

Design/Method: We report a case of a previously healthy, normally developing, Tanner IV, 14-year-old male patient who presented with an asymmetrically enlarged right testicle following blunt trauma with subsequent right-sided chest pain, fever, and emesis. A right radical orchiectomy was performed and pathology showed pure choriocarcinoma. Imaging revealed extensive metastatic disease including to the lungs and brain. A literature search on PubMed identified previously reported cases of testicular pure choriocarcinoma in adolescents.

Results: Due to its rarity, pure choriocarcinoma of the testis mostly appears as case reports within current literature. The patients in reported cases (n=17) range from age 18 to 63 years (mean age 31.3). Our patient is the youngest known reported case. Pure choriocarcinoma is often initially misdiagnosed given its tendency to present with symptoms secondary to lung, skin, and/or brain metastasis, as opposed to testicular swelling like other testicular tumors. Its misdiagnosis may be related to the gap in knowledge regarding peri-pubertal testicular tumor differential and workup. While puberty plays an important role in the frequency of testicular tumor types, teenage and adolescent patients, like the presented patient, often fall between pre- and post-pubertal studies in the literature. Research studies often use age cut-offs when studying pre- versus post-pubertal testicular tumors; yet, the variability of age of puberty onset and the variety of puberty stages suggests that age-defined cut-offs are suboptimal.

Conclusion: Peri-pubertal boys are at risk for testicular cancers that are typically identified in the 15- to 35- year-old cohort. Our report of testicular pure choriocarcinoma in a 14-year-old highlights unique characteristics of this tumor and the importance of puberty status in pediatric oncology workup algorithms.

MANAGEMENT OF LOCALISED PERIANAL EMBRYONAL RHABDOMYOSARCOMA IN A THREE YEAR OLD CHILD

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Background: Rhabdomyosarcoma (RMS) is the most common sarcoma in children. The perianal site is unusual in occurrence and associated with lower cure rates. Cases treated with gross total surgical resection and conventional radiotherapy have been reported to be associated with sphincter dysfunction and anal ulcerations.

Objectives: To describe a case of localised perianal embryonal RMS and its management using neoadjuvant chemotherapy and stereotactic radiosurgery.

Design/Method: Single case report

Results: Three year old boy presented with painful swelling over the right perianal region since two months. Examination revealed a 2.5 cm soft, tender, diffuse swelling over the right perianal region. Open wedge biopsy of the lesion was suggestive of embryonal rhabdomyosarcoma and immunohistochemistry was positive for desmin, Myf4, CD99 (focal), WT1, CD 56 and negative for S-100, pan, CK, CD45. FDG PET CT scan showed 2.7 x 1.5 cm metabolically active enhancing soft tissue mass in the right perianal region extending to perineum and right half of the gluteal cleft, with no evidence of distal metastases. He received four courses of neoadjuvant chemotherapy with IVA (Ifosphamide, Vincristine and Actinomycin D). The child was treated with stereotactic radiosurgery to a dose of 19.8Gy /3 #to CTV, 23.1Gy/ 3#to GTV to the perianal area. Subsequently he received five more courses of IVA based chemotherapy. Thirty nine months post completion of treatment, the child is in complete remission with normal sphincter function.

Conclusion: Perianal RMS is a rare tumor associated with poor outcomes. Delay in diagnosis worsens the chances of cure. The lack of definite guidelines makes managing these cases a challenge. Surgical management for this tumor is involved with risk of life long rectal incontinence and sphincter dysfunction. Multimodal treatment including stereotactic radiosurgery offers better results while minimizing complications and thereby a better quality of life.

A NOVEL P53 MUTATION WITHIN THE DNA BINDING HOTSPOT

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Background: A 17 y/o fraternal twin male, product of IVF, presented with hematuria and diagnosed with pleomorphic sarcoma of the pelvis invading his bladder (favoring leiomyosarcoma) was found to have a left humeral mass, biopsied, and diagnosed as telangiectatic osteosarcoma. He completed five cycles of ifosfamide/doxorubicin and local radiation followed by surgical resection of pelvic tumor. His disease continued to progress, and he died 13 months from diagnosis. There was no significant family history of cancer. Sequencing from peripheral blood lymphocytes revealed a de novo germ line TP53 synonymous mutation G>A at position 672, within the DNA binding domain of p53. That is, sequencing in mother and father revealed wild-type TP53.

Objectives: Relevance of the mutation

Design/Method: Review literature on the structure of p53 and its DNA binding site. Review TP53 database (<http://p53.iarc.fr/>).

Results: Most p53 mutations result in amino acid substitution in the DNA binding domain. The mutations result in a full length protein produced with a gain of function. We are presenting a case of a novel p53 mutation c.672 G>A. Mutations in this hotspot are associated with the DNA binding site resulting in a gain of function of p53. These are associated with altered cancer spectrum, deregulated metabolic pathways, increased metastases, enhanced chemotherapy resistance, and binding of ETS and MOZ involved in histone methylation and acetylation. We found no reports of this mutation but have found a missense mutation resulting in a splicing variant as well as a number of indels occurring at c.672. Synonymous mutations may play a part in cancer biology, by affecting cryptic and non-cryptic alternative splice sites, including those in TP53 (Supek et al, Cell 156:1324, 2014). They found that TP53-synonymous mutations were extremely recurrent and affected nucleotides directly adjacent to splice sites.

Conclusion: There is no documentation of this mutation in the literature, and further work must be done to determine its relevance. One such experiment would be creating a mini gene construct to evaluate TP53 splicing and analyze cell activity. We hypothesize this synonymous mutation may affect TP53 splicing, RNA folding or codon usage and serves as a driver for the two concurrent and aggressive primary tumors.

EMBRYONAL RHABDOMYOSARCOMA IN A PATIENT WITH FREEMAN SHELDON SYNDROME

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Background: Freeman-Sheldon Syndrome (FSS) is a rare distal arthrogryposis characterized by contractures of face and distal extremities. The main cause is mutations in the embryonic skeletal myosin (MYH3) gene that lead to altered muscle physiology. Most patients have one of the three mutations: R672C, R672H, and T178I. Although the incidence of soft tissue sarcomas, especially embryonal RMS (eRMS), is higher in children with abnormal muscle development, it is not reported with FSS.

Objectives: We report a case of orbital embryonal rhabdomyosarcoma in a child with FSS and discuss a possible association in this population.

Design/Method: A five-year-old Caucasian male, with a known diagnosis of FSS, was diagnosed with right orbital eRMS after presenting with five days of progressive right eye swelling. Family history is positive for FSS in mother. His FSS course involved G tube placement, bilateral hearing aids and multiple surgical procedures for marked contractures.

Results: Metastatic work up was negative. A microarray (CMA) on the orbital mass revealed cytogenetic heterogeneity, with near triploid chromosomes, with gains, losses, and uniparental disomy. A CMA of the blood showed a normal male karyotype. MYH3 testing on peripheral blood confirmed mutation of C.2015 G>A resulting in amino acid substitution of arginine with histamine p.R672H. He was treated per COG protocol ARST 0031 with chemotherapy and radiation therapy. He remains in remission 8 months after completion.

Conclusion: MYH3 is important for normal development and expressed mainly in utero but may persist through adult stages, especially in extra-ocular muscles. Mutations in MYH3 lead to aberrant muscle development and possible block in differentiation that predisposes to tumorigenesis. Development of eRMS in our patient could suggest mutated embryonic myosin continues to influence contractile function postnatally and leads to permissive environmental changes for spontaneous development of eRMS. Fernandez et al demonstrated a similar concept with the spontaneous development of muscle derived eRMS after one year of age in mouse models of Duchenne Muscular Dystrophy and Limb Girdle Muscular Dystrophy 2D. Further reporting of similar cases and histologic studies may enhance our understanding of the underlying mechanism.

GEMCITABINE INDUCED RADIATION RECALL MYOSITIS IN A PATIENT WITH RELAPSED NASOPHARYNGEAL CARCINOMA

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Background: Background: Radiation recall is characterized by inflammation of the skin and superficial tissue in the radiation field following administration of chemotherapy agents such as doxorubicin and taxane. Involvement of the skeletal muscle in radiation recall is rare.

Objectives: To report on a patient with relapsed nasopharyngeal carcinoma who developed radiation recall myositis following administration of gemcitabine containing regimen.

Design/Method: Case report.

Results: A 16-year-old female with stage III (T2, N2, M0) nasopharyngeal carcinoma was treated as per Children's Oncology Group protocol ARAR0331. She received 61.2 Gy radiation to the nasopharynx and bilateral neck. At the end of therapy, she developed a new right hip pain. Positron emission tomography scan showed multiple bone metastases along the axial skeleton and a left 9th posterior rib bone and soft tissue lesion. She was started on gemcitabine (1000 mg/m²) and oxaliplatin (100 mg/m²) every 2 weeks. After 4 cycles, she had complete resolution of all lesions. At the end of 7th cycle, she developed bilateral neck swelling and pain. Magnetic resonance imaging of the neck showed diffuse muscle swelling consistent with myositis. The neck swelling resolved spontaneously. After the 8th and final cycle of chemotherapy, the neck swelling recurred. The area of myositis corresponded to the radiation field. She was started on steroids with immediate improvement. Since then she has required multiple courses of steroids, and is currently on a low-dose maintenance steroid regimen with good control of symptoms for 3 months.

Conclusion: Unlike other radiation sensitizing agents, gemcitabine may induce radiation recall injury to deeper tissues. With increasing use of gemcitabine in pediatric salvage regimens, pediatric oncologist should be aware of this rare side effect in patients who have received prior radiation therapy. Steroids can provide symptomatic relief for gemcitabine induced radiation recall myositis.

LOCAL CONTROL OF UNRESECTABLE RELAPSED SARCOMA WITH MINIMALLY INVASIVE ABLATIVE THERAPIES IN CHILDREN AND YOUNG ADULTS: SEVEN CASES

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Background: Relapsed Osteosarcoma (R-OS) or Relapsed Ewing Sarcoma (R-EWS) has a poor prognosis with a 20-30% 5-year survival. Re-inducing remission with aggressive systemic and local control provides the best chance of survival. When surgery or radiation is not possible, minimally invasive ablative therapies such as Irreversible Electroporation (IRE), Radiofrequency Ablation (RFA) or Microwave Ablation (MWA) may offer promising alternatives for local control. IRE has been described for solid tumors, while unreported in primary bony sarcoma. RFA has been described only rarely in pediatric EWS/OS.

Objectives: We report outcomes of cases of R-EWS/R-OS treated with minimally ablative therapies for local tumor control.

Design/Method: We collected retrospective data on 7 patients with R-EWS/R-OS treated with IRE, RFA and/or MWA in the last 3 years at our institution.

Results: Seven patients (median age 19, age range 11-29, 2 R-EWS, 5 R-OS) were treated 13 total times (IREx4, RFAx6, MWAx3). From first intervention, 2 patients are in remission (CR), 2 have stable disease (SD) and 3 had progression and death (PD). The patients included: (1) 12 year-old female with R-EWS of sacrum treated with IRE, CR at 27 months; (2) 29 year-old male with R-EWS of T10 vertebrae and lung treated with RFA of T10 lesion, CR at 23 months; (3) 21 year-old female with R-OS of femur and lung treated with RFAx2 of lung lesions, PD at 11 months; (4) 29 year-old male with R-OB of pelvic bone, spine and lung treated with IREx2 of lung and paraspinal lesions, PD at 6 months; (5) 11 year-old male with R-OS of femur, lung and heart treated with RFA of lung lesion, PD at 2 months (6) 17 year-old male with R-OS of fibula, femur and lung treated with RFAx1/MWAx2 of lung/paramediastinal lesions, SD at 2 months; (7) 17 year-old male with R-OS of femur, humerus and lung treated with RFAx1/MWAx1/IREx1 of lung lesions, SD at 1 month. Complications included a spinal cord infarction post-operatively (patient 2) and recurrent pneumothorax (patient 6).

Conclusion: IRE, RFA and MWA may be promising alternatives to achieve local control of select tumors in children and young adults with metastatic R-EWS/R-OS. Additional research is warranted.

REPORT OF A RARE CASE OF PLEUROPULMONARY BLASTOMA WITH DICER1 GENE MUTATION

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Background: Pleuropulmonary Blastoma (PPB) is a rare pediatric lung tumor typically composed of primitive lung mesenchyme. Studies have reported that familial cases of PPB are associated with DICER1 gene mutations (1).

Objectives: Although most congenital lung cysts are benign and require no further intervention, it is important to consider rare entities such as PPB. For patients with PPB, their prognosis is impacted by prompt evaluation, intervention, and histological classification (2). We also aim to stress the importance of DICER1 gene mutation analysis for patients diagnosed with PPB and their families.

Design/Method: We report a previously healthy two-year-old girl who presented with a several week history of fever and intermittent cough. Review of family history revealed the patient's father was diagnosed with a right lower lobe lung cyst and underwent surgical resection during adolescence. In addition, the father is currently undergoing evaluation of new thyroid nodules. Computed Tomography of the patient's chest demonstrated a large cystic mass with a solid mural nodule in the anterior segment of the right upper lobe. The patient underwent resection of the cyst with corresponding lobectomy. Histological diagnosis was consistent with Type II PPB with negative margins. No evidence of metastatic disease was identified.

Results: Through genetic investigation, the patient was found to be positive for DICER1 gene mutation. She is currently receiving adjuvant chemotherapy with ifosfamide, dactinomycin, doxorubicin and vincristine. She remains free of tumor and plans for follow-up include surveillance for malignancies associated with DICER1 gene mutations.

Conclusion: The association of this autosomal dominant mutation with PPB has prompted genetic counselling for our patient and others, in order to identify at-risk relatives of all ages with the mutation who may benefit from surveillance (3). Our recommendations include: 1. Increased awareness of this rare tumor among Pediatric Oncologists, Pathologists and Surgeons. 2. Encourage appropriate clinical evaluation of all pediatric lung cysts and surgical resection aimed towards securing negative margins, given that recurrent and metastatic PPBs are associated with poor outcome (2). 3. Stress the need for multi-institutional collaborative research to improve our understanding of DICER1 gene mutations and familial manifestations of PPB.

A RAPIDLY PROGRESSIVE MALIGNANT RHABDOID TUMOR (MRT) WITH A NOVEL SOMATIC MUTATION IN A THREE-MONTH OLD INFANT

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Background: The differential diagnosis for a soft tissue mass in an extremity of an infant can span the spectrum of benign, e.g. vascular malformations, fibroblastic tumors, to malignant, e.g. rhabdomyosarcomas. MRT is a very rare and extremely aggressive cancer with a 5-year overall survival of 24% (SEER database). Most occur in the central nervous system and kidneys, and less frequently in soft tissues.

Objectives: We present the case of a three-month old previously healthy male who developed a rapidly growing mass within the left axilla. Initial biopsy resulted in the diagnosis of primitive sarcoma, but the tumor exhibited interval growth despite standard chemotherapy. Further pathologic review of the primary biopsy was suspicious for MRT. The tumor continued to progress, and the patient was taken to surgery, requiring extremity amputation due to the extent of neurovascular involvement. A chest CT revealed pulmonary metastasis and the disease progressed rapidly with the patient succumbing to his disease five months after diagnosis.

Design/Method: Case Report.

Results: Subsequent evaluation of the patient's tumor by whole exome sequencing and SMARCB1 mutation analysis revealed a mutation of the hSNF5/SMARCB1/INI1 gene in exon2, c.118C>T. The mutation is predicted to result in the insertion of a novel stop at codon40 in exon2 (p.Arg40*) resulting in the loss of expression of the INI1 protein. MRTs typically have loss of heterozygosity of SMARCB1, a member of the SWI/SNF chromatin-remodeling complex that drives tumorigenesis by epigenetic dysregulation. Mutations are frequently detected in the germline; our patient is the first to have a somatic mutation of its kind. Epigenetic targeted therapies for SMARCB1 mutations hold promise in the treatment of MRTs. Potential therapeutic agents include inhibitors of histone deacetylation, DNA methylation, histone methylation, cyclin-dependent kinases, and Aurora A kinase. Pre-clinical animal models show promising results in MRT response, and pediatric phase I/II clinical trials are currently underway for several of these agents.

Conclusion: This case illustrates the occurrence of a rare malignancy in an infant, the dismal prognosis of MRTs, and the need to pursue improved targeted treatments. Earlier identification of actionable mutations, particularly for SMARCB1, can lead directly to targeted therapies.

RECURRENT, SEVERE HYPERCALCEMIA UPON DISCONTINUATION OF LONG-TERM DENOSUMAB FOR TREATMENT OF PEDIATRIC METASTATIC GIANT CELL TUMOR

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Background: Giant Cell Tumor of Bone (GCTB) is a rare diagnosis in pediatrics, accounting for 1-2% of GCTB diagnoses. Histologically benign, 2% of tumors metastasize. Recent studies have shown response with denosumab, however little long-term data is available. Here we describe severe, recurrent hypercalcemia responsive to denosumab after discontinuation of denosumab for metastatic GCTB in a child.

Objectives: Discuss the complications associated with discontinuation of denosumab for GCTB in a child and its utility in treating recurrent, post-therapeutic episodes of hypercalcemia.

Design/Method: A twelve year-old male presented with episodic left-sided hip pain and difficulty weight-bearing. MRI revealed a cystic lesion in the left ischium. Treatment with monthly denosumab 120mg was initiated. Dramatic improvement was noted clinically and radiographically. After forty months asymptomatic and stable, denosumab was discontinued. One month later, he presented with nausea and vomiting, hypercalcemic at 15.5 mg/dL with acute kidney injury (serum creatinine 2.4 mg/dL). Calcitonin, hyperhydration and lasix were unsuccessful. He was treated with denosumab with rapid resolution of hypercalcemia. In the following five months, hypercalcemia recurred twice, both with resolution within 48 hours of treatment with denosumab 20mg and 10mg, respectively.

Results: While GCTB is a benign histologic diagnosis, its locally aggressive nature complicates treatment. Definitive management is often surgical, which was precluded by our patient's metastatic disease. Tumor cell expression of receptor activator of nuclear factor- κ B ligand (RANKL) interacts with RANK on monocytes, activating osteoclasts, their precursors and giant cells, promoting bone resorption. Denosumab, a human monoclonal antibody, binds and inhibits RANKL, suppressing bone turnover. Upon discontinuation of denosumab's inhibitory effects, osteoclast hyperactivity may cause rebound hypercalcemia. This phenomenon may be more pronounced in a skeletally immature child with increased rate of bone metabolism. Treatment with denosumab resolves these episodes of hypercalcemia.

Conclusion: This patient highlights the utility of low dose denosumab in managing severe hypercalcemic episodes following long-term treatment with denosumab. Further research is needed to determine ideal dosing, effects of recurrent treatment, recommended monitoring and the potential need for gradual discontinuation of therapy.

INTERDIGITATING RETICULUM CELL SARCOMA IN A PEDIATRIC PATIENT

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Background: Interdigitating reticulum cell sarcoma is a rare spindle cell sarcoma of the lymph node stromal cells known as interdigitating reticulum cells. Tumor cells are positive for S-100 protein, CD 68, HLA-DR and CD45RB. Treatment regimens have been varied, with a poor overall prognosis. We were able to identify 5 cases reported in the literature from the adult population and none from the pediatric population.

Objectives: To introduce a pediatric case of Interdigitating reticulum cell sarcoma

Design/Method: Clinical case report

Results: Our patient is a 4 year old male adoptee brought to the U.S. from an industrial region of China. He was 9 months old and still living in China when he was diagnosed with a Fibrosarcoma of his lower back. He underwent complete resection with wide margins and was treated with Vincristine and Dactinomycin adjuvant chemotherapy prior to moving to the U.S. reportedly in remission. At a follow-up visit at 3 years of age in the U.S., a right axillary mass was noted on CT scan. He underwent complete resection of this mass, as well as wedge resection of 2 left lower lobe pulmonary nodules that had been stable since age 2. Final pathology from all sites revealed an atypical spindle cell sarcoma, mostly suggestive of an Interdigitating reticulum cell sarcoma. He was treated with Ifosfamide and Doxorubicin off-study per Children's Oncology Group protocol ARST1321. Six weeks after the completion of therapy, scans remain stable from prior to therapy. He continues to have 2 sub-centimeter right upper lobe pulmonary nodules of uncertain etiology that have been stable since 2 years of age. Since his disease has been very slow growing, parents opted to observe with scans for 3 months prior to proceeding with resection of these remaining nodules in the next month.

Conclusion: This is an exceedingly rare case of Interdigitating Reticulum Cell Sarcoma in a pediatric patient from an industrial region of China. An optimal treatment regimen is yet to be determined. The impact of exposure to this industrial region on cancer incidence is unknown.

SIMULTANEOUS DIAGNOSIS OF IMMUNE THROMBOCYTOPENIA AND TYPE 1 DIABETES MELLITUS IN A PEDIATRIC PATIENT

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Background: Type 1 diabetes (T1DM) is associated with other autoimmune diseases, namely thyroiditis, celiac disease and autoimmune gastric disease. Two conditions at initial presentation, however, is exceedingly rare. Here we describe a child with novel, simultaneous presentation of thrombocytopenia and hyperglycemia, leading to concurrent diagnoses of immune thrombocytopenia (ITP) and T1DM.

Objectives: Describe a child with severe thrombocytopenia and hyperglycemia, leading to new diagnoses of both ITP and T1DM. Explore known co-morbid autoimmune diagnoses, and the significance behind less commonly reported pairs.

Design/Method: A five year-old male presented with bruising. He had a viral URI one week prior. CBC and CMP revealed thrombocytopenia of 2 K/cmm and hyperglycemia to 457 mg/dL. Urinalysis was positive for glucose, negative for ketones. Bleeding history was negative. Physical exam revealed wet purpura and scattered bruises. Presentation was consistent with ITP, and his hyperglycemia was attributed to an acute illness stress response. He received IVIG with platelet improvement to 83 K/cmm. Elevated serum glucose persisted overnight. Hemoglobin A1c was elevated at 7.8%, indicating chronic hyperglycemia. Autoantibody testing obtained prior to IVIG demonstrated an elevated anti-glutamic acid decarboxylase antibody, diagnostic for T1DM. He started insulin therapy with stabilization of serum glucose.

Results: Pleomorphic by nature, with non-specific symptomatology, autoimmune diseases can be challenging, confounded by associated conditions. Genetic and immune dysregulation disorders are considered when presented with associated conditions. Thrombocytopenia and T1DM are an unusual pair. To our knowledge, only five pediatric cases have described this association, none with simultaneous presentation. T1DM results from T cell destruction of insulin-producing pancreatic beta-cells. ITP is mediated by circulating autoantibodies to platelets. Both conditions share a basis in autoimmune dysregulation, but by independent mechanisms. These associations may have significant implications for treatment. Recent studies suggest when traditional treatments fail, rituximab (anti-CD20) therapy targeting B lymphocytes may prove beneficial for many autoimmune disorders, including T1DM and ITP.

Conclusion: Complex autoimmune disorders should be considered in patients who develop multiple autoimmune conditions. In less commonly recognized associations like ITP and T1DM, early recognition and management is critical to patient success. Response to conventional treatments, and the utility of antibody therapy in resistant cases should be considered.

PRIMARY SYNOVIAL SARCOMA OF THE SPINE WITH TUMOR THROMBUS EXTENDING INTO THE RIGHT VENTRICLE

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Background: Synovial sarcoma is a malignant mesenchymal malignancy that most commonly originates in the deep soft tissue of the extremities, with < 3% being reported in the head and neck region.

Objectives: We present a 16-year-old male with a several-month history of progressive left upper extremity pain and weakness, exacerbated after slipping and falling on his left elbow.

Design/Method: MRI demonstrated an intraspinal extradural tumor involving the left aspect of the spinal canal, neural foramina and paraspinal soft tissue from the C2 to T2 levels. Biopsy revealed a malignant mesenchymal neoplasm with negative immunohistochemical markers for rhabdomyosarcoma and Ewing sarcoma. Molecular studies were positive for a SS18/SSX2 fusion transcript, conferring the diagnosis of synovial sarcoma. Positron emission tomography scan was negative for metastatic disease. While awaiting diagnostic biopsy results, the patient developed worsening left arm pain and swelling accompanied by increasing facial edema.

Venous Doppler ultrasound revealed extensive deep vein thromboses spanning from the internal jugular vein to the proximal brachial vein. Transthoracic echocardiogram revealed an echogenic mass in the right atrium extending through the tricuspid valve into the right ventricle. Computed tomography cardiac angiogram demonstrated contiguity between the intra-cardiac mass with the superior vena cava and left brachiocephalic and internal jugular veins. He underwent urgent surgery due to impending hemodynamic deterioration and pathology of the resected specimens from the left brachiocephalic vein and right atrium/tricuspid annulus were consistent with synovial sarcoma.

Results: He subsequently received neoadjuvant treatment with chemotherapy and conventional radiation, followed by surgical resection, postoperative proton radiation boost, and adjuvant chemotherapy. He had no evidence of disease upon completion of therapy and is being monitored under regular surveillance.

Conclusion: Primary synovial sarcoma involving the spine is rare, and while tumor thrombi have been described with synovial sarcoma, this is the first known report of extension into the right side of the heart. Multidisciplinary care between neurosurgery, cardiothoracic surgery, otolaryngology, oncology and radiation oncology was key in rendering this patient free of disease.

A RARE CASE OF POLYCYTHEMIA: CHUVASH POLYCYTHEMIA

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Background: Chuvash Polycythemia is a rare form of congenital polycythemia caused by an altered oxygen-sensing pathway. It was recognized in the 1970s in the Chuvash Republic of the Russian Federation as a clinically distinct entity from polycythemia vera and has an autosomal recessive inheritance pattern. A specific mutation in the Von Hippel-Lindau (VHL) gene results in an R200W amino acid substitution leading to an upregulation of hypoxia inducible factors (HIF-1, HIF-2) despite normal oxygen levels. This leads to a chronic increase in red blood cell production. The mutation is in the VHL gene on chromosome 3p25.4. This mutation was subsequently found in people of European, African-American, and Pakistani/Bangladeshi ethnicities. Our patient is a 9 year old female of Pakistani descent who presented to a neurologist with a longstanding history of headaches. Lab evaluation revealed a hemoglobin level of 20.5 and hematocrit of 60.6. Family history is positive for father having an undiagnosed polycythemia for which regular phlebotomies are performed, and parents are cousins.

Objectives: Describe a rare case of Chuvash Polycythemia, diagnosis, treatment, and outcomes in a pediatric patient.

Design/Method: Case Report

Results: An extensive workup for polycythemia was conducted after confirming the hgb and hct levels for primary and secondary polycythemia. Work up for polycythemia vera (JAK2, Exon 12&14) was negative and erythropoetin levels were normal. Additionally, P50 (oxygen affinity) studies were found to be normal. Gene testing was performed and revealed a homozygous R200W mutation on the VHL gene, confirming the diagnosis of Chuvash Polycythemia. To date, there is no treatment for Chuvash polycythemia. However, symptom management with phlebotomy is thought to be acceptable. Phlebotomy can help with headaches, ruddy complexion and other morbidity but may lead to iron deficiency anemia. There is also a significant increase in stroke and other thrombotic events in these patients. Paradoxically, there is an increase in bleeding events as well, and some of the strokes are hemorrhagic. Other complications include pulmonary hypertension and hemangiomas.

Conclusion: Chuvash polycythemia is a rare cause of polycythemia that should be promptly diagnosed and treated based upon clinical symptoms to prevent long term morbidity or mortality.

DIFFUSE MARROW INVOLVEMENT IN METASTATIC OSTEOSARCOMA: AN UNUSUAL PRESENTATION

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Background: Osteosarcoma is the most common primary bone tumor in children. Metastatic disease is seen in 30% of patients with lungs being the most common site of metastasis followed by other boney sites. Bone marrow metastasis affecting hematopoiesis is extremely rare with only a few case reports in the literature.

Objectives: We describe a case of metastatic osteosarcoma with diffuse infiltration of the bone marrow at both contiguous and distant locations. The physiological functions of the bone marrow were compromised and patient showed suppression of the hematopoietic cell lineage.

Design/Method: The discussion includes clinical presentation and diagnostic features noted on initial disease evaluation such as magnetic resonance imaging, computerized tomography scan, bone scintigraphy and serial blood counts. We have provided histologic findings from biopsies of the primary tumor and bone marrow. We also compared and contrasted the symptoms and the course of the disease with those of typical metastatic osteosarcomas.

Results: A 10 year-old Caucasian female presented with intermittent pain in her right leg for 2 weeks. Imaging showed a destructive mass in the right distal femur with local bone marrow and soft tissue involvement. Biopsy revealed a high-grade osteoblastic osteosarcoma. Metastatic evaluation demonstrated sub centimeter nodules in addition to extensive skeletal disease involving the bilateral femurs, bilateral humeri, skull, ribs and pelvis. Complete blood count done prior to biopsy was remarkable for a white blood count 6100/ μ l, hemoglobin 12.3g/dl and Platelets 32000/ μ l. Bone marrow evaluation was performed with samples from bilateral iliac crests demonstrating pleomorphic tumor cells (70% marrow involvement) with osteoid formation along with normal hematopoietic cells. With no available clinical trial, the patient received standard therapy consisting of Methotrexate, Adriamycin and Cisplatin. Her platelet count recovered after the initial course of chemotherapy suggesting that her marrow disease had responded to some extent. Unfortunately her response at other sites was poor resulting in her death from progressive disease after about 5 months of treatment.

Conclusion: Bone marrow involvement impairing hematopoiesis is quite uncommon in metastatic osteosarcoma. Patients with osteosarcoma who present with abnormal complete blood counts should be evaluated for bone marrow metastases; such patients typically have a dismal prognosis.

WHEN CELLULITIS IS ACTUALLY SUBCUTANEOUS PANNICULITIS-LIKE T-CELL LYMPHOMA

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Background: Z.R. is a 2 year old previously healthy male who presented with extensively indurated cellulitis of the right forearm and thigh, with associated right axillary and inguinal lymphadenopathy and fevers after failing oral antibiotics. He was hospitalized and started on appropriate parenteral antibiotics, with no clinical improvement. He developed palpable hepatosplenomegaly, neutropenia and mild anemia.

Objectives: To report a very rare case of Subcutaneous Panniculitis-like T-cell Lymphoma.

Design/Method: A bone marrow biopsy was obtained and significant for hemophagocytosis, but no blast population was observed. Due to concerns for hemophagocytic lymphohistiocytosis, work up was obtained but was non-specific. Ultimately, skin and lymph node biopsy revealed the rare diagnosis of subcutaneous panniculitis-like T-cell lymphoma (SPTCL), a mature T-cell lymphoma of extranodal cutaneous origin.

Results: This process typically presents as single or multiple focal nodules or plaques on the extremities, trunk, or face with associated fever, lymphadenopathy, hepatosplenomegaly, cytopenias, and rarely hemophagocytosis. This is an extremely rare diagnosis for which there is no defined epidemiologic incidence, and no organized treatment approach. Currently, treatment approaches include steroids alone, immunosuppressive agents, multi-agent chemotherapy and even autologous stem cell transplant. The current 5yr median survival is roughly 80%, but this depends greatly upon the phenotype of the T cell receptor (TCR). The $\alpha\beta$ phenotype has a significantly better prognosis than the aggressive $\gamma\delta$ phenotype that is often associated with hemophagocytosis. He was found to have a $\beta\gamma$ TCR, concerning for the more aggressive phenotype. Thus, we have begun treatment with a multi-agent chemotherapy regimen. He has received two cycles of doxorubicin, vincristine, prednisone, and cyclophosphamide per AHOD 0431. He is now receiving methotrexate and cytarabine per AALL1231. MRI of the extremities and CT of the abdomen after 2months of therapy showed near resolution in the size and induration of his plaques. We plan to treat for at least 6 months pending response.

Conclusion: This case stresses the importance of broadening your differential diagnosis when a patient does not respond to appropriate treatment and further, will provide much needed insight as to how to successfully treat pediatric patients with the rare diagnosis of SPTCL and associated hemophagocytosis.

IPHONE AND IPAD: IDENTIFICATION OF UNIQUE TECH-TOOLS ("APPS") FOR THE PEDIATRIC HEMATOLOGY-ONCOLOGY PRACTITIONERS.

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Background: Technology is changing the practice of medicine. Practitioners have accessed e-mail and electronic medical records using desktop and laptop computers. Now, they face the challenge of thousands of healthcare mobile applications (apps) available on smart phones. An app is a self-contained program or piece of software designed to run on handheld devices to perform a specific purpose.

Objectives: To identify a need for pediatric-specific apps for the pediatric hematology-oncology (PHO) community as a tool to improve workflow and enhance trainee and patient education.

Design/Method: Hematology/ Oncology MeSH terms from the 2015 list were searched in the Apple iTunes Store as simple keywords in the English language. A master list of unique apps was created and the apps were divided into four categories (medical teaching, provider tools, resources and consumer) and several subcategories.

Results: A search of the 51 hematology-oncology MeSH terms in the iTunes Store resulted in 689 apps for the iPhone and 476 apps for the iPad. A total of 41 iPhone apps (6%) were considered potentially useful to the PHO field. Categories of medical teaching (42%) and provider tools (31%) yielded the highest number of interesting apps. However, in resources only 12% were found to be pediatric hem/onc-oriented (staging 0%, journals 6.6%, conferences 0% and few useful handbooks). In consumer-related apps (22% potential useful) only four non-english apps (Spanish) apps were found.

Conclusion: Mobile technology and apps are convenient and may lead to superior and faster clinical decision-making, improved accuracy and enhanced productivity for PHOs. However, there is clearly a need for design of pediatric hemato/oncology-specific apps. ASPHO can take the lead in coordinating a response to this fast-moving field by designing and organizing these apps and encourage PHOs for using those new PHO-specific Apps to optimize patient care and education. (Farage, Obstetrics and gynecology, 2014)

NEUTROPENIC ENTEROCOLITIS (TYPHLITIS) VERSUS TUBERCULOUS ENTERITIS, IN AN ADOLESCENT WITH ACUTE MYELOGENOUS LEUKEMIA (AML): CASE REPORT

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Background: Neutropenic enterocolitis occurs commonly in individuals with hematologic malignancies who are neutropenic and develop a breakdown in gut mucosal integrity as a result of cytotoxic chemotherapy. Clinical manifestations include fever and abdominal symptoms (pain, distention, cramping, tenderness, nausea, vomiting, and watery or bloody diarrhea). Diagnosis is confirmed with imaging and treatment is broad spectrum antibiotics. Tuberculous enteritis is rare in the United States (US) with non-specific signs and symptoms, often resulting in diagnostic delays.

Objectives: Report AML complicated by both typhlitis and tuberculous enteritis.

Design/Method: Case report

Results: A 15 year-old Hispanic female with AML received treatment on Children's Oncology Group-protocol (AAML1031-Arm B). Following Induction-I, during neutropenic status, computed tomography (CT) revealed abnormal mucosal enhancement of her ascending colon. CT scans during the remainder of treatment demonstrated necrotic abdominal lymph nodes (LN) and persistent ileocecal inflammation that remained primarily unchanged despite antibiotic therapy and bowel rest. At the end of therapy, she had persistent fevers in the setting of a protracted course with typhlitis. Imaging showed a mildly prominent left supraclavicular LN and partial improvement in the colonic wall thickening with confinement to the cecum and proximal ascending colon. CT also revealed nonspecific pulmonary nodules with no lung parenchymal disease or hilar adenopathy. Excisional biopsy of the left LN showed necrotizing granulomas with rare acid-fast bacilli (AFB). AFB stains, tuberculosis (TB) polymerase chain reaction testing and stool culture were also positive. She was born in the US with family from El Salvador and reported visiting two years prior to her diagnosis. No known TB exposures. Two-weeks after starting anti-tuberculous therapy, she defervesced and neutrophil counts improved. Nine months post completion of therapy she remains in first remission with a hypocellular bone marrow. Bone marrow AFB stains and cultures are negative to date.

Conclusion: Tuberculous enteritis is rarely suspected and even harder to identify in pediatric oncology populations due to the overlap in symptoms from their cancer treatment. Published reports of gastrointestinal TB in children commonly reported abdominal pain, fever and weight loss as presenting symptoms highlighting the deceptive clinical presentation of this disease in the setting of a cancer diagnosis.

DONOR LYMPHOCYTE INFUSIONS FOR MIXED CHIMERISM AFTER HEMATOPOIETIC CELL TRANSPLANTATION IN PEDIATRIC PATIENTS WITH LEUKEMIA

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Background: In leukemia, it has been shown that mixed chimerism (MC) can precede relapse. Strategies to treat patients with MC have varied.

Objectives: Our aim was to study the efficacy and safety of donor lymphocyte infusions (DLI) in patients with leukemia and MC after hematopoietic cell transplantation (HCT).

Design/Method: We evaluated 28 consecutive patients with leukemia who underwent allogeneic HCT at St. Jude Children's Research Hospital between July 2005 and February 2014, and received DLI following HCT for MC. MC was defined as 99% or less donor chimerism from 21 days to 1 year after HCT by variable number of tandem repeats. The dose of DLI was based on donor type, and was gradually escalated as tolerated. A patient was considered a responder if donor chimerism increased and there was no evidence of leukemia.

Results: Diagnoses included acute myelogenous leukemia (13), acute lymphoblastic leukemia (9), chronic myelogenous leukemia (3), biphenotypic leukemia (2), and juvenile myelomonocytic leukemia (1). Donor types were haploidentical (20), matched unrelated donor (4) and matched sibling donor (4). Of the patients that had MC alone, 15 of 16 (94%) responded to DLI. Three of the 15 responders (20%) developed grade II-IV acute graft versus host disease (GVHD) and 2 of 15 (13%) developed limited chronic GVHD. Of the patients with MC who were also MRD positive, 2 of 10 (20%) responded to DLI; one of the responders developed extensive chronic GVHD. Both of these responders had low-level MRD (0.04% and 0.03%) at the time of DLI. Of the nonresponders with MC and MRD positive disease, 3 of 8 (38%) developed GVHD. Neither of the 2 patients with MC and morphologic relapse had a response to DLI, nor developed GVHD. MC predated morphologic relapse by 64 and 65 days in the two patients in which DLI was delayed.

Conclusion: When administered promptly after evidence of MC alone, DLI from any donor type can increase donor chimerism with a low risk of GVHD, and may prevent relapse. We advocate close monitoring of donor chimerism after HCT and early administration of DLI using a dose escalation regimen.

TOTAL NUCLEATED CELL CONCENTRATION DIFFERS BY DONOR ETHNICITY IN ALLOGENEIC HEMATOPOIETIC STEM CELL TRANSPLANTATION

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Background: Donors for patients of African descent requiring a hematopoietic stem cell transplant (HSCT) are limited in national registries. The donor pool is further limited because matched donors are disqualified if the total nucleated cell (TNC) counts of marrow grafts are below required donation thresholds. This is probably more likely in people of African descent who often have lower white blood cell counts than their European counterparts. In addition, for patients with sickle cell disease (SCD), TNC thresholds are higher than in other diseases ($3.5 - 5 \times 10^8$ TNC/kg of recipient's body weight versus 2×10^8 TNC/kg). This threshold was established anecdotally based on the hypothesis that higher TNC dose would decrease the rejection risk. Graft dosing is traditionally done using TNC but CD34 graft content may be a better predictor of transplant outcomes.

Objectives: In a diverse population of HSCT donors, determine whether TNC concentration and CD34 percentage differ by ethnicity. Determine whether TNC or CD34 dose affects post-transplant morbidity and mortality.

Design/Method: Retrospective chart review of allogeneic HSCT donors and recipients from 2000 to 2014. The Mann Whitney U test was used to compare TNC concentration and CD34 percentage between groups and a univariate logistic regression analysis was used to evaluate transplant outcomes.

Results: We included 132 allogeneic HSCT patients and 134 donors. Diagnoses were: SCD (n=35, 26.5%), leukemia/lymphoma/myeloma (n=48, 36.4%), myelodysplastic syndrome (n=7, 5.3%), or other (n=42, 31%). Donors were Caucasian (37.9%), Black (37.1%), Asian (4.5%), Hispanic (9.1%), and other/unknown (12.9%). TNC concentration of bone marrow grafts was lower for Black vs. non-Black donors (n=49 vs 85, median 0.16 vs 0.2 $\times 10^8$ /ml, p=0.01). Median CD34 fraction was higher in Black vs. non-Black donors (1.57 vs 1.22%, p=0.003). Time to engraftment, incidence of acute or chronic GVHD, incidence of rejection, and mortality did not vary significantly based on TNC or CD34 dose.

Conclusion: Our data shows significantly lower TNC concentration but higher CD34 fraction in grafts collected from Black vs non-Black donors with no difference in outcomes. This suggests that the TNC threshold for bone marrow harvest should be lower for Black donors.

LATE EFFECTS AMONG LONG-TERM SURVIVORS OF ALLOGENEIC HEMATOPOIETIC CELL TRANSPLANT (ALLOHCT) FOR NONMALIGNANT DISEASES

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Background: Limited data exists regarding the burden of late morbidity following alloHCT for children with nonmalignant diseases.

Objectives: To assess the incidence and severity of late effects in survivors of alloHCT for nonmalignant conditions.

Design/Method: We conducted a prospective assessment of patients at Columbia University Medical Center who had survived ≥ 2 years disease-free after alloHCT in childhood (age ≤ 21 at transplant). Beginning in March 2015, patients participated in comprehensive clinic visits, which included objective lab and imaging tests to screen for late effects, quality of life evaluation with the Pediatric Quality of Life Inventory (PedsQL), and assessment of educational attainment. Late effects were graded with the Common Terminology Criteria for Adverse Events, version 4.0.

Results: As of January 1, 2016, 34 patients (aged 3.7-29.2 years) enrolled in the study at a mean of 6.0 ± 3.3 years after alloHCT. Diagnoses included hemoglobinopathies (n=18, 53%), bone marrow failure (n=8, 24%), and HLH/immunodeficiencies (n=8, 24%). Among participants, 59% had a matched sibling donor (41% unrelated donor), 68% received bone marrow (21% cord blood, 12% PBSCs), and 44% underwent myeloablative conditioning (38% reduced-toxicity, 15% reduced-intensity). Fifty percent of the participants developed at least one chronic health condition and 12% developed a grade 3 condition. There were no grade 4 conditions. The most frequent late effects were ovarian failure (22% of females), growth impairment (12%), low bone mineral density (12%), thyroid dysfunction (9%), chronic kidney disease (9%), and treatment-related malignancies (6%). In addition, 15% had a history of chronic GVHD, 12% had a history of late acute viral infections requiring hospitalization, 15% had urine microalbuminuria, 9% had hyperferritinemia, and 27% had mild pulmonary function test abnormalities without clinical significance. Mean PedsQL scores were within 1 standard deviation of population norms in all domains, but 24% had overall scores in the impaired range (>1 standard deviation below population norms). Thirty eight percent of participants had delayed educational attainment.

Conclusions: In this heterogeneous cohort of long-term survivors of alloHCT for nonmalignant diseases, mild-to-moderate late effects were common, but severe late effects were infrequent. The ongoing study should be able to identify risk factors for adverse long-term outcomes.

PARENT AND PATIENT PERCEPTIONS OF BEHAVIORAL AND EMOTIONAL FUNCTIONING FOLLOWING HEMATOPOIETIC CELL TRANSPLANTATION FOR INHERITED METABOLIC DISEASE

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Background: Allogeneic hematopoietic cell transplantation (HCT) remains standard therapy for various rare, inherited metabolic diseases (IMD). As survival improves, assessment of long-term outcomes is often hampered by patient attrition and distance from treating centers.

Objectives: We piloted a methodology to remotely study parental and patient perspectives of behavioral and emotional functioning following HCT for IMD.

Design/Method: The University of Minnesota BMT Database was queried for surviving IMD patients and disease characteristics. Parents/patients were invited for study participation. The Research Electronic Data Capture (REDCap) system was used to electronically administer and retrieve the standardized Behavior Assessment System for Children, Second Edition (BASC-2) survey tools in a one-time cross-sectional analysis. The responses for parent/patient pairs were then analyzed by paired samples t-test in the subscale areas of anxiety, depression, atypicality, and attention problems.

Results: We identified 421 patients transplanted for IMD between 1982 and 2015. Of 239 survivors, 96 parents and/or patients (40%) were enrolled. Of those, 8 parent/patient pairs successfully completed the BASC-2 surveys. IMD diagnoses included Hurler syndrome (4 pairs), adrenoleukodystrophy (2 pairs), mannosidosis (1 pair) and Maroteaux-Lamy syndrome (1 pair). The median time from transplant to assessment was 9.8 years (IQR, 4.7 to 15.6, range 2.1 to 19.9). There was not a significant difference in perceptions of anxiety ($p = 0.38$), depression ($p = 0.16$), atypicality ($p = 0.11$) or attention problems ($p = 1.0$) when comparing parent and patient responses. The majority of patients performed at average level in comparison to age and gender based norms from a parent (84% of scores) and patient (88% of scores) perspective in all subscales analyzed.

Conclusion: Effective, remote assessment of behavioral and emotional function via electronic methods is feasible in a large cohort of IMD patients surviving HCT. Importantly, the scores for anxiety, depression, atypicality, and attention disorders did not significantly differ between parent and patient report. This suggests that when patients are unable to provide self-reported functioning, parent perspectives may serve as adequate representation. Continued follow-up of this population is critical to provide appropriate counseling regarding long-term outcomes for patients and families considering HCT as a treatment option for IMD.

LATE EFFECTS FOLLOWING UMBILICAL CORD BLOOD TRANSPLANTATION IN VERY YOUNG CHILDREN AFTER BUSULFAN-BASED, MYELOABLATIVE CONDITIONING

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Background: Infants and young children who undergo hematopoietic stem cell transplantation (HSCT) are at increased risk for late effects due to exposure of developing organs to chemotherapy and radiation therapy typically utilized as part of conditioning regimens. Busulfan (Bu)-based myeloablative conditioning regimens were developed to eliminate radiation exposure in these young children with the hope that late effects would be minimized. As most reports of late effects to date have focused on outcomes in older children and adults, there remains a paucity of data regarding late effects in very young children undergoing HSCT following Bu-based regimens.

Objectives: The aim of this single-center, retrospective study was to describe the late effects observed in a cohort of very young patients who underwent cord blood transplantation (CBT) using Bu-based conditioning regimens.

Design/Method: The medical records of 102 patients who underwent CBT after chemotherapy-based cytoreduction at < 2 years of age from September 1993-August 2008 and who survived > 5 years were reviewed. Overall survival, descriptive statistics, mean height standard deviation scores, and cumulative incidences of key late effects were calculated. Cox regression models explored associations between predictors and late effects.

Results: The median age at transplant was 1 year (range 0.1-2) and median age at follow-up was 13.8 years (range 7.7-23.8). Overall survival at 10 years post-CBT was 93% (range 84.9-96.8). Nearly all patients (98%) experienced at least one significant late effect; two or more late effects were documented in 83.3% of patients and 3 or more in 64.7%. Dental problems were documented in 92.2% of patients. Other commonly observed late effects included short stature (55.9%), cognitive (53.6%), pulmonary (18.6%), and pubertal delay/gonadal failure (14%). Short stature and cognitive deficits were more frequent in patients with inherited metabolic diseases.

Conclusion: Avoiding irradiation in the very young undergoing CBT may decrease, but does not eliminate late effects. These results will inform clinical care and guidelines for long-term follow-up, as well as add to the growing information regarding late effects of HSCT in general. Long-term survivors of CBT in infancy and early childhood require regular follow-up to identify these late effects and ameliorate associated consequences.

COMPARISON OF FUNGAL PROPHYLAXIS WITH ALTERNATIVE DOSING STRATEGIES IN PEDIATRIC PATIENTS UNDERGOING HEMATOPOIETIC STEM CELL TRANSPLANTATION: A RETROSPECTIVE REVIEW

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Background: Pediatric patients undergoing hematopoietic stem cell transplant (HSCT) are at increased risk for invasive fungal disease (IFD). There is no gold standard fungal prophylaxis regimen during HSCT. Cincinnati Children's Hospital Medical Center (CCHMC) utilizes three alternative dosing strategies for antifungal prophylaxis in this population: genotype-directed voriconazole, alternate-day micafungin and once-weekly liposomal-amphotericinB (L-AmB). There is limited data regarding the efficacy of these regimens or comparing superiority.

Objectives: The aim of our study was to assess efficacy of these regimens in preventing IFD in pediatric allogeneic HSCT patients. Secondary aims included: safety comparison and pharmacoeconomic assessment.

Design/Method: A retrospective chart review was conducted for patients ≤ 18 years who received an allogeneic HSCT between January 2010 and July 2015. Proven, probable and possible IFDs were defined using updated 'European Organization for Research and Treatment of Cancer' and the 'Mycoses Study Group' definitions and examined during the first 100 days post-transplant.

Results: Of the 396 allogeneic transplants performed in 374 patients, 244 patients met inclusion criteria. Seventy-eight patients (32%) received L-AmB, 98 (40%) received micafungin and 68 (28%) received voriconazole starting day zero. Proven or probable IFD occurred in 6 patients; three in the micafungin group (*Candida parapsilosis*), 2 in the voriconazole group (*Saccharomyces cerevisiae* and *Candida glabrata*) and 1 in the L-AmB group (*Candida glabrata*) ($p = 0.66$). In eighteen patients, antifungal prophylaxis was changed due to 'possible' IFD, 13 (72%) of these occurred in the micafungin group. Overall, the micafungin group had only 2 adverse events (AEs) out of 103 total AEs, compared to 43 in L-AmB and 58 in voriconazole group ($p < 0.0001$).

Conclusion: Our results show that rates of proven and probable IFD were similar with all three regimens. Although 'possible' infections were increased on alternate day micafungin, overall safety and tolerability were significantly better for the micafungin group when compared to L-AmB and voriconazole groups. Sub analyses are ongoing to further delineate which of these patients had active GVHD and were on increased immune suppression. These data along with the pharmacoeconomic results will add more insight into risk and benefit balance between each of these regimens.

ROLE OF CYCLIN DEPENDENT KINASE 5 IN T-CELLS AND ACUTE GRAFT VERSUS HOST DISEASE

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Background: Cyclin dependent kinase 5 (Cdk5) is a ubiquitously expressed proline directed serine/threonine kinase. Preclinical and clinical data suggest that Cdk5 activity lies at the cross-roads of neuroscience, inflammation and cancer immune surveillance. Our lab has identified a novel role of Cdk5 in T-cells and acute graft-versus-host disease (aGvHD). We hypothesize that Cdk5 inhibition in donor T-cells leads to reduced migration into secondary lymphoid organs (SLOs) and reduced severity of aGvHD in murine models of allogeneic hematopoietic stem cell transplant (allo-HSCT).

Objectives: Investigate the role of Cdk5 in T-cell trafficking in syngeneic and allogeneic HSCT models. The translational goal is to use Cdk5 inhibition as a novel strategy to prevent aGvHD.

Design/Method: Small molecule inhibitor (CIP5) and Roscovitine were used for in vitro and in vivo experiments for pharmacological inhibition of Cdk5, respectively. Donor T-cells from Cdk5 knockout hematopoietic chimeric mice were adoptively transferred into haploidentical mice (B6 into B6D2F1) to study the role of Cdk5 in T-cell functions and aGvHD. Lineage specific T cell Cdk5 knockout (Cdk5Tko) mice will be used for future experiments. Fluorescence activated cell sorting was used to study quantitative differences in migration of Cdk5Tko and Roscovitine treated donor T-cells versus appropriate controls. Cellular interaction patterns of differentially labeled T-cell subsets were used by real time imaging with 2-photon laser scanning microscopy. Results from our baseline syngeneic experiments will be compared with allogeneic model.

Results: 1) Loss of Cdk5 expression in donor T-cells is associated with reduced migration, proliferation and differentiation of donor T-cells. 2) Cdk5 expression is important for development of aGvHD. 3) Loss of Cdk5 in donor T-cells reduces mortality and morbidity due to aGvHD. We will discuss additional results at the conference.

Conclusion: Our preliminary data identifies Cdk5 inhibition in T-cells as a novel approach to prevent aGvHD. Nonspecific Cdk5 inhibitors, such as R-roscovitine, are in early clinical phase trials while specific small molecule inhibitors are under development. Our project will have major translational implications for treatment of numerous diseases where T-cells play a crucial role in inciting inflammation and organ damage.

EFFICACY AND SAFETY OF DEFIBROTIDE IN THE TREATMENT OF HEPATIC VENO-OCCLUSIVE DISEASE/SINUSOIDAL OBSTRUCTION SYNDROME (VOD/SOS) FOLLOWING CHEMOTHERAPY

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Background: VOD/SOS is typically considered an unpredictable, potentially life-threatening hematopoietic stem cell transplantation (HSCT) complication; however, there is a known risk post-chemotherapy without HSCT. Severe hepatic VOD/SOS (with multi-organ dysfunction [MOD]) may be associated with >80% mortality. Defibrotide is approved for severe hepatic VOD/SOS treatment in adult and pediatric patients in the EU. In the US, a new drug application was filed in 2015; there are no approved treatments.

Objectives: Describe updated efficacy and safety results of defibrotide in patients with VOD/SOS post-chemotherapy.

Design/Methods: Defibrotide is available in the US through an ongoing expanded-access protocol for patients with hepatic VOD/SOS (Baltimore/modified Seattle criteria or biopsy) post-HSCT or -chemotherapy, with/without MOD (renal and/or pulmonary dysfunction). Dosing: 25 mg/kg/d, 4 divided doses, recommended for ≥ 21 days.

Results: Of 857 patients developing VOD/SOS with ≥ 1 defibrotide dose through April 18, 2015, 101 (11.8%) received chemotherapy without HSCT; 49 (49%) had MOD. Median age: 7 years (range, 0 months–69.0 years); 81 patients (80%) were ≤ 16 years (59 aged 2–11); 55% were male. Most common primary diseases: acute lymphocytic leukemia (49%), acute myelogenous leukemia (13%). Chemotherapeutic agents received by >30% of patients: vincristine, cyclophosphamide, cytarabine, doxorubicin, methotrexate, and PEG-L-asparaginase. Gemtuzumab and inotuzumab were received by 2 and 0 patients, respectively.

Kaplan-Meier estimated Day+100 survival was 77.0% overall (95% CI, 67.5–84.1%), 71.4% (56.6–82.0%) for patients with MOD, and 82.3% (68.7–90.4%) for patients without MOD. Sixty-two patients (61.4%) reported ≥ 1 adverse event (AE): 22 (21.8%) assessed as at least possibly defibrotide-related, most commonly hypotension (4.0%); nausea (3.0%); and vomiting, epistaxis, hematochezia, gastrointestinal, and pulmonary hemorrhages (2.0% each). Hemorrhagic AEs (any severity) occurring in $\geq 2.0\%$ of patients: pulmonary (6.9%); epistaxis (5.0%); hematochezia, gastric, and gastrointestinal (2.0% each). Serious AEs were reported in 37 patients (36.6%). AEs led to discontinuation in 7 (6.9%) patients. Two (2.0%) deaths were at least possibly defibrotide-related.

Conclusion: Day+100 survival (77.0%) in patients (80% pediatric) developing VOD/SOS post-chemotherapy without HSCT is clinically encouraging. In this study, defibrotide was generally

well-tolerated, with 2 possibly treatment-related fatalities and 6.9% of patients discontinuing due to an AE.

DEFIBROTIDE FOR THE TREATMENT OF HEPATIC VENO-OCCLUSIVE DISEASE/SINUSOIDAL OBSTRUCTION SYNDROME WITH MULTI-ORGAN DYSFUNCTION: RESULTS FROM A PIVOTAL, HISTORICALLY CONTROLLED, PHASE 3 TRIAL

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Background: There is no FDA-approved treatment for hepatic VOD/SOS, a potentially life-threatening complication of conditioning regimens for stem cell transplantation (SCT). Severe cases, defined by multi-organ dysfunction (MOD), may result in >80% mortality.

Objectives: Present updated day+100 survival and complete response (CR) analyses from the pivotal phase 3 trial on defibrotide in VOD/SOS with MOD, including data obtained in response to US health authorities.

Design/Methods: Multicenter, open-label, phase 3 historical control (HC) study. Eligible patients: Baltimore criteria \leq day+21 post-SCT, plus MOD (renal and/or pulmonary dysfunction) \leq day 28 post-SCT. Exclusion criteria: severe liver or gut graft-versus-host disease, clinically significant bleeding, or need for \geq 2 pressors. A blinded medical review committee determined unequivocal VOD/SOS with MOD in HC patients' medical charts. DF dose: 25 mg/kg/d, 2-hour IV infusions q6hx4. Recommended treatment duration: \geq 21 days. Primary endpoint: day+100 survival. Key secondary endpoint: day+100 CR. Survival and CR rate differences, and 95% confidence intervals, were calculated using propensity score-adjusted estimates. Number needed to treat (NNT): absolute risk reduction reciprocal (1/ARR); ARR equals the control minus experimental event rates.

Results: Patients: 102 defibrotide-treated and 32 HCs. Baseline characteristics were similar. Day+100 survival in the defibrotide and HC groups was 38% and 25%, respectively (propensity-stratified difference in survival: 23.0% [95.1% CI, 5.2-40.8], $P = 0.0109$), for an NNT of 5 (1/0.23). Observed day+100 CR rates were 25.5% and 12.5% (propensity-stratified difference in CR: 19.0% [95% CI, 3.5-34.6], $P = 0.0160$), respectively, for an NNT of 6 (1/0.19). In the defibrotide-treated group, 45% had an adverse event (AE), 21% had a serious AE at least possibly related to defibrotide. Patients with \geq 1 AE leading to death were similar between defibrotide and HC patients (64% and 69%), as were hemorrhagic AEs (64%, 75%) and hypotension (39%, 50%).

Conclusion: Defibrotide-treated patients had a 23% improvement in day+100 survival and 19% improvement in day+100 CR rate. Based on these numbers, the expected NNTs to prevent one death or achieve one CR are 5 and 6, respectively. Overall hemorrhage and fatal AE incidences were similar between groups; AEs were consistent with those expected in this critically ill population.

EARLY INITIATION OF DEFIBROTIDE POST-DIAGNOSIS OF HEPATIC VENO-OCCLUSIVE DISEASE/SINUSOIDAL OBSTRUCTION SYNDROME (VOD/SOS) WITH OR WITHOUT MULTI-ORGAN DYSFUNCTION (MOD) POST-HEMATOPOIETIC STEM CELL TRANSPLANTATION (HSCT) IMPROVES SURVIVAL: EXPLORATORY ANA

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Background: VOD/SOS is an unpredictable, potentially life-threatening complication of conditioning for HSCT. Severe VOD/SOS (with MOD) is associated with >80% mortality. Defibrotide is approved for treatment of severe VOD/SOS post-HSCT in the EU. In the US, a new drug application for defibrotide proposed for the treatment of hepatic VOD/SOS with MOD post-HSCT was filed in 2015. In the US, defibrotide has been available through an ongoing, expanded-access study.

Objectives: Investigate the impact of time-to-defibrotide treatment initiation (TI) in patients with VOD/SOS with/without MOD post-HSCT.

Design/Method: In the expanded-access study, patients with VOD/SOS (Baltimore/modified Seattle criteria or biopsy) with/without renal/pulmonary MOD received defibrotide 25 mg/kg/d in 4 divided doses for a recommended ≥ 21 days. Day+100 survival in HSCT patients was examined post hoc based on time from VOD/SOS diagnosis to defibrotide TI. Two analyses were conducted: (1) survival rate by TI for all patients before or after days 1, 2, 3, 4, 7, and 14 (Fisher's exact test); (2) survival rate for those patients with TI on a particular day: 0, 1, 2, 3, 4, 5, 6, 7, 8–14, and ≥ 15 (Cochran-Armitage test for trend across days).

Results: Among HSCT patients enrolled through April 18, 2015, who received ≥ 1 defibrotide dose, TI date was available for 755 patients (426 with MOD). Defibrotide was started on the day of diagnosis in 31.7% of patients; 93.0% of patients started defibrotide on or before day 7 post-diagnosis. In the population-wide analysis of initiation before/after days 1, 2, 3, 4, 7, and 14, earlier defibrotide TI was associated with higher survival rates, and was statistically significant for all cut-points except day 14 (with only 2.8% of pts with TI post-day 14). In the analysis of relationship between Day+100 survival and TI day, there was a statistically significant trend over time for higher Day+100 survival with earlier initiation ($P < .001$).

Conclusion: Data indicate decreased Day+100 survival associated with longer treatment delays, confirmed by the Cochran-Armitage test ($P < .001$). Thus, consider defibrotide initiation as soon as possible after VOD/SOS diagnosis (with/without MOD), as no day post-diagnosis provides a viable cut-point for better outcome.

NOVEL MANAGEMENT OF INVASIVE RHIZOPUS FUNGAL SINUSITIS IN A PEDIATRIC PATIENT WITH SEVERE APLASTIC ANEMIA

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Background: Invasive fungal infection in the setting of profound immune suppression is often lethal. A 2 year-old female with severe aplastic anemia, following 6 months of neutropenia unresponsive to granulocyte-colony stimulating factor presented with *Rhizopus* sinusitis obliterating her nasal septum and invading her cribriform plate despite prophylactic therapy with voriconazole for 5 months and 1 month of micafungin.

Objectives: Demonstrate the effectiveness of a multi-modal approach to *Rhizopus* infection including surgical debridement, systemic and topical anti-fungal medications, granulocyte infusions and allogeneic hematopoietic cell transplantation (alloHCT); the importance of tailoring pharmacotherapy based on fungal susceptibilities and pharmacokinetic monitoring; and the short-term safety of intravenous posaconazole and isavuconazole in a profoundly immunocompromised pediatric patient.

Design/Method: The patient was treated with twice daily intranasal amphotericin B irrigations, periodic surgical sinus debridement with topical amphotericin B washes and tissue sampling. Her initial culture growing *Rhizopus* revealed susceptibility to posaconazole and amphotericin B. Treatment with oral posaconazole and liposomal amphotericin B preceded alloHCT conditioning (cyclophosphamide, fludarabine, anti-thymocyte globulin) and radiation by one month. Posaconazole was held during cyclophosphamide administration and restarted as intravenous therapy. During her conditioning regimen and until neutrophil engraftment, the patient received 7 donor granulocyte infusions. After 7 weeks of therapy, the patient's *Rhizopus* demonstrated resistance to posaconazole and increased amphotericin B MIC. As such, posaconazole was discontinued and amphotericin B dose increased. After isavuconazole was confirmed susceptible, treatment was initiated to achieve a minimum goal trough level of 4 ug/ml. Studies thus far have found no correlation between trough levels and efficacy/safety and no report to date of use in a pediatric patient. The patient engrafted neutrophils on day +14 following alloHCT.

Results: Endoscopic sinus and radiologic evaluations show resolution of infection. No side effects of isavuconazole and posaconazole have been observed. Surgical debridement and topical therapies were discontinued. Now 8 weeks post-alloHCT, the patient remains on liposomal amphotericin B and isavuconazole.

Conclusion: A multi-modal approach including surgical debridement, evolving topical and systemic anti-fungal therapy adjusted based on serial susceptibility testing and pharmacokinetic monitoring, adoptive immunotherapy by granulocytes and alloHCT successfully rescued a severely immunocompromised patient from an invasive *Rhizopus* infection.

FAMILIAL HAPLOIDENTICAL (FHI) ALLOGENEIC STEM CELL TRANSPLANTATION UTILIZING CD34 ENRICHMENT AND T CELL ADDBACK IN CHILDREN, ADOLESCENTS & ADULTS WITH HIGH-RISK SICKLE CELL DISEASE. RAPID ENGRAFTMENT, ROBUST IMMUNE RECONSTITUTION, LOW INCIDENCE OF GVHD, A

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Background: HLA MSD AlloSCT remains the only curative therapy in patients with SCD. However, less than 15% of eligible SCD patients have an unaffected MSD. FHI AlloSCT as an alternative allogeneic donor source has been limited by graft failure (GF), delayed immune reconstitution and/or severe GVHD. To overcome these barriers we previously investigated an approach of CD34 enrichment with T cell addback (2.0×10^5 CD3/kg) in pediatric recipients utilizing MUDs and demonstrated 100% engraftment and $\leq 15\%$ incidence of grade II-IV AGVHD.

Design/Method: SCD patients 2-21yrs of age with one or more high risk features (Talano/Cairo et al. EJM 2015) received a FHI AlloSCT from a parental donor, following CD34 enrichment (CliniMACS®) (target 10×10^6 CD34/kg final product) and T cell addback (2×10^5 CD3/kg final product) and tacrolimus AGVHD prophylaxis. WBC donor and CD71+ (RBC) chimerism was performed by STR. Immune reconstitution studies were performed locally and at central core laboratories.

Results: Fifteen patients have been enrolled. Median engraftment of myeloid cells and platelets was 10 and 16 days, respectively. Probability of aGVHD and cGVHD: 8.33% (CI95: 0-70.5) and 25% (CI95: 0.4-70.8). Donor chimerism in the peripheral blood was $\geq 95\%$, day 30-730. Donor chimerism in the erythroid lineage was $\geq 95\%$ by day 60. NK cells (CD56+/CD3-) reconstitution following FHI AlloSCT with CD34 enrichment/T cells add back was rapid and peaked at d+30 ($35.52 \pm 8.57\%$, 2710 cells/ul). NK cells expressed high level of activating receptors NKp46, NKG2D and KIR2DS and inhibitory receptors NKG2A, CD94 and KIR2DL2/3 at d+30. Median CD3, CD4, CD8 and CD19 at day 270 were CD3: 584 ± 73.62 cells/ul, CD4: 277 ± 52.5 cells/ul, CD8: 228 ± 66.83 cell/ul and CD19: 537 ± 135.2 cells/ul. There have been no graft failures. The one-yr probability of OS 85.1% (CI95: 52.3-96.1).

Conclusion: These preliminary results demonstrate the safety, feasibility and efficacy of FHI AlloSCT utilizing CD34 enrichment and T cell addback from parental SCD trait donors. All patients engrafted with a very low incidence of grade II-IV AGVHD, high sustained donor chimerism and robust immune reconstitution with an absence of SCD symptoms or organ

complications in this high-risk SCD population. This research was supported by FDA grant 5R01FD004090 (IND14359).

OUTCOMES FOLLOWING UMBILICAL CORD BLOOD TRANSPLANTATION FOR INHERITED METABOLIC DISORDERS: DOES UCB/RECIPIENT HLA ALLELEIC DISPARITY MATTER FOR ENGRAFTED SURVIVAL?

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Background: Umbilical cord blood transplant (UCBT) has demonstrated efficacy for numerous inherited metabolic disorders (IMD). In several IMD, post-transplant donor chimerism may correlate with treatment effectiveness.

Objectives: We sought to evaluate the impact of UCB/recipient HLA allelic disparity (compared to that of conventional matching algorithm) on engrafted survival (> 90% donor myeloid chimerism) and other outcomes following UCBT for IMD.

Design/Methods: 106 consecutive first, single UCBT for IMD at the University of Minnesota from 2003 to 2015 were evaluable for UCB/recipient HLA allelic matching (HLA-A, -B, -C, and -DRB1). Disease-, patient- and transplant-related characteristics, as well as major outcomes, were assessed.

Results: The median age at UCBT was 1 year; 87 patients (82%) received myeloablative conditioning. Primary diagnoses were Hurler syndrome (41%), cALD (35%), MLD/GLD (9%), and other (16%). The median TNC was $8 \times 10^7/\text{kg}$. The 5 year estimated overall survival for the entire cohort was 70% (95% CI, 59 - 79%). The median time to neutrophil and platelet recovery was 20.5 and 60 days, respectively. Rates of severe acute and chronic GvHD were low (each 6%). Of 46 conventional matched UCBT, 20 (43%) were mis-matched at ≥ 1 allele. Of 49 conventional 5/6 UCBT, 34 (69%) were mis-matched at ≥ 2 alleles and 19 (39%) were disparate at ≥ 3 alleles. Engrafted survival at 1 year was observed in 67%, 63% and 36% of conventional 6/6, 5/6 and 4/6 UCB recipients, respectively ($p = 0.15$). Using allelic criteria, one-year engrafted survival was observed in 73% of (6-8)/8 recipients and 42% of (2-5)/8 recipients ($p < 0.01$). Overall graft failure rate for conventional 5/6 UCBT was 27%. Analysis of the same patients using allelic criteria revealed the graft failure rate was 17% for (6-8)/8 recipients and 42% for (2-5)/8 recipients ($p < 0.05$).

Conclusion: In a large, single-center cohort of patients undergoing UCBT for IMD, HLA allelic matching considerations may better predict fully engrafted survival post-transplant. Multivariable analysis to confirm these findings is ongoing. Evaluation of the significance of particular allele mismatches, including other class II MCH loci, continues as well.

LATE EFFECTS IN PEDIATRIC HIGH RISK NEUROBLASTOMA SURVIVORS AFTER INTENSIVE INDUCTION CHEMOTHERAPY FOLLOWED BY MYELOABLATIVE CONSOLIDATION CHEMOTHERAPY AND INTENDED TRIPLE AUTOLOGOUS STEM CELL RESCUE

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Background: Outcomes for high-risk neuroblastoma (HR-NBL) remain sub-optimal. Modern treatment protocols utilizing intense induction followed by myeloablative consolidation chemotherapy with autologous stem cell rescue (ASCR) have improved survival rates, but long-term sequelae emerge over time.

Objectives: To evaluate the late effects of high dose chemotherapy induction followed by myeloablative consolidation chemotherapy with triple ASCR in pediatric HR-NBL, in the following organ systems: endocrine, renal, and cardiac. Second malignant neoplasms in this cohort have been reported.

Design/Method: We retrospectively reviewed data from 63 patients who were treated on or following the Chicago Pilot 2 protocol; 58 patients who received contemporary standard intensive NBL chemotherapy followed by triple ASCR between 1991 and 2011 were evaluable. Triple ASCR conditioning chemotherapy included: two cycles of carboplatin/etoposide and one cyclophosphamide/thiotepa. All received focal radiation to the primary site of disease; none received total body irradiation. Data included: age at diagnosis, gender, chemo-radiotherapy prior to and post ASCR, height, weight, blood pressure, BUN/Cr, ejection and shortening fractions, fT4/TSH, and gonadal status.

Results: Twenty-three patients (40%) are alive; 19 with complete data. Focal radiation sites included: whole abdomen, left flank, right flank, mediastinum, chest, pelvis, focal brain and spine. Short stature, defined as either failure to reach mid-parental height 3 (16%) or growth <5th% 12 (63%), occurred in 15 (79%). Seven patients have hypothyroidism (37%), including 2 with surgical hypothyroidism due to papillary carcinoma. Gonadal failure occurred in 6 (32%; 5 females, 1 male); there were no cardiac morbidities. All had normal renal function as calculated by CKD-EPI Creatinine Equation (2009). The median time of follow-up from initial diagnosis is 15.56 years.

Conclusion: Significant hormonal (growth, thyroid, gonadal) late effects are noted after intense induction followed by myeloablative consolidation chemotherapy with triple ASCR. In our patient cohort there were minimal renal and cardiac long term effects. Survivors treated for HR-NBL require life-long follow-up to ensure appropriate surveillance for and treatment of such sequelae.

LATE EFFECTS OF THE SKIN IN CHILDREN AFTER HEMATOPOIETIC STEM CELL TRANSPLANTATION

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Background: There is data to suggest that childhood cancer survivors are at risk for melanoma and nonmelanoma skin cancer. However, late effects of the skin after pediatric hematopoietic stem cell transplantation (HSCT) have not been well described

Objectives: The primary objective of this study was to characterize nevi and associated risk factors in pediatric HSCT recipients. We also examined the incidence of cancerous and precancerous skin lesions in this cohort.

Design/Method: This study was a single-center cross-sectional cohort study of pediatric HSCT recipients and controls matched by age, gender, and Fitzpatrick skin type. All study participants underwent a full skin, hair, and nail examination by a pediatric dermatologist. Medical records were reviewed to obtain demographic and clinical data.

Results: 85 HSCT patients and 85 matched controls were enrolled over a 1.5 year period.

Median age at study visit was 13.6 years in HSCT patients with median time after HSCT of 3.6 years. HSCT patients had significantly more nevi than control patients (median [range]: 44 [0-150] vs. 11 [0-94], $p < 0.0001$). HSCT patients had significantly more nevi > 5 mm in diameter and atypical nevi than controls.

Factors associated with increased nevi count in HSCT patients included malignant indication for HSCT, pretransplant chemotherapy, exposure to total body irradiation (TBI), myeloablative conditioning, fair skin, and history of sunburn. Factors associated with atypical nevi included malignant indication, exposure to TBI, myeloablative conditioning, and chronic graft versus host disease (cGvHD).

16.5% (14/85) of HSCT patients had a history of other cancerous or precancerous skin lesions, including solar lentigo, SCC, actinic keratosis, prokeratosis, and BCC. In sum, 41.2% (35/85) of our HSCT cohort developed one or more cancerous or precancerous skin lesion or lesion that is associated with increased melanoma risk.

Conclusion: We found an increased number of benign nevi, atypical nevi, and other cancerous and precancerous skin lesions in our cohort of 85 pediatric HSCT recipients. We identified malignant disease, total body irradiation, and chronic GvHD as significant risk factors for these findings. Larger prospective studies and long term follow up of this cohort are needed to confirm and expand on our findings.

OPTIMIZING A NOVEL NON-ABLATIVE CONDITIONING TRANSPLANT REGIMEN IN A MURINE MODEL OF SICKLE CELL DISEASE

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Background: Hematopoietic stem cell transplantation (HSCT) for patients with sickle cell disease (SCD) is curative, though significant toxicity from myeloablative conditioning has limited its utility. We have previously developed knockin mice producing normal (AA) or sickle (SS) human hemoglobin recapitulating severe anemia, hyposthanuria and limited lifespan found in SCD patients. Reduced intensity preparative regimens decrease transplant toxicity and are preferable in non-malignant disorders. Newer agents under development include Treosulfan, an alkylator, and anti-c-kit antibodies (ACK2), which create bone marrow (BM) niches by blocking c-kit function.

Objectives: To optimize non-myeloablative conditioning in a murine model of SCD that allows for sufficient donor RBC chimerism and disease amelioration.

Design/Method: Mice received varying conditioning regimens (+/- rescue with control AA marrow), including irradiation (2-8 Gy, TBI), Treosulfan (2-5g/kg; IP), or ACK2 (100-500ug; IP). The hematologic effects of respective treatments were determined by assessment of marrow cellularity, peripheral CBCs, and erythroid donor chimerism (by Iso-electric focusing). Urine concentrating ability, a surrogate of renal tubular function, was also assessed.

Results: Erythroid hyperplasia was noted in the BM of SCD mice. ACK2 and Treosulfan, independently and in a dose-dependent manner, decreased BM cellularity and induced cytopenia in control and SCD mice. Overall, SCD mice were able to tolerate ~50% dosing of Treosulfan (and TBI), relative to controls. While all Treosulfan-treated SCD mice (3g/kg) had evidence of donor erythroid engraftment 2 weeks post-transplant, only 25% had sustained donor erythroid chimerism. Normalization of reticulocytes and urine osmolality was found in SCD mice with sustained donor erythroid chimerism, while non-engrafted mice remained hyposthanuric. These animals are being followed long-term for fertility and survival.

Conclusion: SCD mice closely mimic human disease in phenotype and ablative conditioning intolerance. Treosulfan alone was unable to sustain erythroid chimerism in the majority of SCD-transplanted animals, suggesting that current dosing is non-myeloablative. Nonetheless, animals with at least 50% donor erythroid chimerism had normalization of urine osmolality and CBCs. This is consistent with the clinical experience with SCD transplants where incomplete donor erythroid engraftment is sufficient to ameliorate the disease phenotype. Current studies are now assessing the combinatorial effect of ACK2 and Treosulfan.

SEVERE TRANSPLANT-ASSOCIATED THROMBOTIC MICROANGIOPATHY (TA-TMA) IN PATIENTS WITH HEMOGLOBINOPATHIES: A CASE SERIES

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Background: Transplant-associated thrombotic microangiopathy (TA-TMA) occurs in around 30% of hematopoietic cell transplant (HCT) recipients. However, TA-TMA in pediatric patients receiving HCT for hemoglobinopathies has largely been undescribed. Herein, we report three patients with hemoglobinopathies whom developed sequelae from severe progressive TA-TMA despite treatment with eculizumab.

Patient 1: 2 year old male with sickle cell disease (SCD) presented with TA-TMA related massive pericardial effusion, tamponade and uncontrolled hypertension 70 days post myeloablative matched related umbilical cord blood transplant. Despite discontinuation of tacrolimus, the effusion worsened and he required polypharmacy anti-hypertensive therapy. After treatment with eculizumab, his effusion resolved, hypertension improved, and TMA labs normalized. He is now 20 months post-transplant and continues to have chronic kidney disease (estimated GFR 45 ml/min/1.73m²). Patient 2: 25 year old male with SCD developed posterior reversible encephalopathy syndrome (PRES) with seizures 18 days following reduced-intensity matched sibling bone marrow transplant. Despite discontinuation of tacrolimus, one month later he presented with refractory status epilepticus requiring six anti-epileptics and hypertension. Imaging confirmed recurrence of PRES with left temporal hemorrhage. Laboratory testing was consistent with TA-TMA. Post treatment with eculizumab, his seizures abated and TMA labs normalized. He is currently 15 months post-transplant and has residual neurocognitive defects. Patient 3: 7 year old Asian female with beta-thalassemia major received a myeloablative matched unrelated bone marrow transplant. Six months post-transplant she presented with TMA related intractable hypertension, acute kidney injury requiring dialysis, and seizures. Renal biopsy and MRI brain showed changes consistent with TMA. She had minimal response to discontinuation of tacrolimus and therapeutic plasma exchange. Following eculizumab therapy, her hematological parameters normalized and she was taken off dialysis. However, she developed severe chronic kidney disease (estimated GFR 35ml/min/1.73m²) and hypertension. She died sixteen months post-transplant due to respiratory failure caused by RSV.

Conclusion: In patients with hemoglobinopathies, ongoing endothelial dysfunction may place them at greater risk for TA-TMA. The latter can have long-term devastating clinical consequences. Further investigation is needed in order to determine if pre-emptive eculizumab may be warranted for treatment of TA-TMA in this seemingly high-risk population.

T-CELL-DEPLETED REDUCED-INTENSITY MISMATCHED RELATED AND UNRELATED DONOR STEM CELL TRANSPLANTATION FOR PEDIATRIC SICKLE CELL DISEASE

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Background: Most patients that could be cured of sickle cell disease (SCD) with stem cell transplantation do not have a matched sibling donor and many do not have a matched unrelated donor. Successful use of alternative donors including mismatched family members could provide a donor for almost all patients with SCD.

Objectives: The use of a reduced-intensity conditioning regimen and a CD34+ selected, T-cell-depleted peripheral blood stem cell (PBSC) graft will allow engraftment with a low incidence of graft-versus-host disease (GVHD).

Design/Method: Between 2009-2015, ten pediatric SCD patients underwent CD34+selected, T-cell-depleted transplantation from alternative donors. Indications for transplantation included vaso-occlusive pain crisis (n=6), concurrent Kostmann's (n=1), stroke (n=2) and conditional transcranial Doppler, developmental delay with nocturnal hypoxia (n=1). Patients received a median of 26 pRBC transfusions (range 4-31) within three years prior to transplantation. Conditioning regimen consisted of melphalan 140mg/m², thiotepa 5mg/kg x 2, fludarabine 40mg/m² x 5, and rabbit-ATG 2.5mg/kg x 4 without post-transplant immunosuppression. Six patients received rituximab during conditioning. Seven patients received a planned donor lymphocyte infusion (DLI) between days 33 and 42 with methotrexate IV for GVHD prophylaxis on a companion study. Two patients received therapeutic DLI infusions post-transplant.

Results: Median age at transplantation was 14.7 years (range 5-23). Eight patients had mismatched-related and two had matched unrelated donors. Median PBSC dose was 18x10⁶ CD34+/kg (range 9-25) and all patients received <1x10⁴ CD3+/kg. All patients engrafted with an ANC>500 at median 14.5 days (range 10-17). Nine out of ten patients (90%) are alive with median follow-up of 33 months (range 4-60). Three patients had EBV-related post-transplant lymphoproliferative disorder (PTLD), and one died as a consequence of treatment for PTLD. No other serious viral disease was observed. No acute grade II-IV GVHD developed after transplant and before DLI and only one case occurred after DLI. No patient had chronic GVHD.

Conclusion: A reduced-intensity conditioning regimen followed by a T-cell-depleted alternative donor transplantation provided reliable engraftment and a low incidence of GVHD. This approach may increase the availability of transplantation for pediatric patients with SCD who do not have a matched sibling donor.

THE IMPACT OF GRAFT/RECIPIENT ABO COMPATIBILITY ON OUTCOMES AFTER UMBILICAL CORD BLOOD TRANSPLANT FOR NON-MALIGNANT DISEASE

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Background: Existing literature shows mixed conclusions regarding the impact of ABO incompatibility on outcomes following hematopoietic cell transplantation. As the future for umbilical cord blood (UCB) expansion technologies is bright, we assessed whether this typically-overlooked graft characteristic impacted various outcomes following UCB transplantation (UCBT) for non-malignant disorders (NMD).

Objectives: To determine the impact of ABO match status on outcomes of interest in patients undergoing first UCBT for NMD.

Design/Method: A prospectively maintained institutional BMT program database was queried for all patients undergoing first UCBT for NMD and their demographic, disease and transplant-related characteristics. UCB and recipient ABO compatibility was considered (1) matched, (2) major mismatched (recipient isoagglutinins against UCB antigen), (3) minor mismatched (UCB isoagglutinins against recipient antigen), or (4) bi-directional mismatched. In double UCBT, compatibility status of the dominant unit was considered. The impact of ABO incompatibility was assessed on the following: overall survival, graft failure, aGvHD (grade II-IV and III-IV), cGvHD, times to neutrophil and platelet recovery, post-transplant pRBC transfusion requirements, and donor hematopoietic chimerism.

Results: Through December 2014, 270 patients have undergone first UCBT for various NMD. Sixty-one percent had an underlying storage disorder; 26% had marrow failure; 13% had another indication. Among all four ABO compatibility groups, no significant difference was seen in age, gender, NMD diagnosis category, conditioning intensity, HLA-matching, cell dose, number of UCB units, transplant era, performance score, GvHD prophylaxis, or CMV serostatus. ABO compatibility status did not appear to impact any outcomes assessed, though a trend toward increased grade III - IV aGvHD was seen in recipients of major mismatched units. In multivariable and initial subgroup analyses, ABO compatibility did not significantly impact study end-points, including post-transplant pRBC transfusion burden.

Conclusion: ABO compatibility status did not appear to impact selected post-transplant outcomes following UCBT for our large NMD cohort.

ENHANCED IN-VITRO AND IN-VIVO TARGETING OF RITUXIMAB SENSITIVE AND RESISTANT BURKITT LYMPHOMA (BL) BY ANTI-CD20 CHIMERIC ANTIGEN RECEPTOR (CAR) MODIFIED EXPANDED NATURAL KILLER CELLS IN COMBINATION WITH A HISTONE DEACETYLASE INHIBITOR, ROMIDEPSIN

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Background: For BL patients who relapse, the prognosis is dismal due to chemo-immunotherapy resistance. Our group has successfully modified expanded peripheral blood Natural killer cells (exPBNK) with an anti-CD20 CAR to target CD20+ BL cells in vitro and in NSG mice. Romidepsin is a histone deacetylase (HDAC) inhibitor that increases the expression of NKG2D ligands in BL.

Objectives: We investigated the effect of romidepsin alone and in combination with anti-CD20 CAR modified exPBNK cells against CD20+ BL cells in vitro and in humanized BL NSG mice.

Design/Method: Anti-CD20 CAR modified exPBNK cells were produced as we have described. Daudi, Raji, Raji-2R and Raji-4RH cells were treated with 10ng/ml romidepsin, generously provided by Celgene. Raji-Luc engrafted mice were injected with romidepsin (2.2mg/kg) or PBS followed by anti-CD20 CAR exPBNK cell or mock exPBNK cell injections 24hrs later. Tumor regression and/or progression were monitored weekly.

Results: HDAC 1, 3, 6 levels were significantly increased in BL cells compared to white blood cells. Total H3K9 acetylation was enhanced in Raji, Raji-2R, and Raji-4RH following romidepsin. More importantly, romidepsin significantly inhibited BL cell proliferation ($p<0.001$), induced apoptosis only in rituximab sensitive BL cells and cell cycle arrest in resistant BL cells ($p<0.001$). Romidepsin significantly inhibited in vivo Daudi, Raji and Raji-2R cells growth in xenografted NSG mice with reduced tumor burden ($p<0.05$) and bioluminescence ($p<0.05$).

In vitro cytotoxicity of anti-CD20 CAR exPBNK cells was significantly enhanced against romidepsin treated BL cells compared to the untreated at E:T=3:1 ($P<0.001$; $n=4$), or compared to the mock exPBNK ($P<0.05$; $n=4$).

In humanized Raji xenograft NSG mice, survival time in romidepsin+CAR exPBNK treated mice was significantly extended compared to the untreated mice (median 28 days, $P<0.001$), the CAR exPBNK treated mice (median 42.5 days, $P<0.05$), the romidepsin treated mice (median 30 days, $P<0.001$). Additionally, we observed the enhanced MICA/B expression in Daudi xenograft mice after romidepsin treatment.

Conclusion: These results suggest the therapeutic potential of the combination of anti-CD20 CAR modified exPBNK cells and romidepsin against chemo-immunotherapy resistant BL. We are continuing investigating whether the enhanced MICA/B expression in mice is associated with the extended survival.

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A PILOT STUDY OF UNRELATED CORD BLOOD (UCB) TRANSPLANTATION FOLLOWED BY UNMATCHED HUMAN PLACENTAL DERIVED STEM CELLS (HPDSC) IN CHILDREN AND YOUNG ADULTS WITH MALIGNANT AND NON-MALIGNANT DISEASES

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Background: Rapid availability, allowance for greater HLA mismatch and low rates of GVHD make UCB an attractive stem cell source . However, low cell dose leads to delayed engraftment and increased transplant related mortality . Celgene Cellular Therapeutics (CCT) has developed a proprietary process for the collection of HPDSC's which have a higher concentration of CD34+ cells and lower HLA Class I and II expression than UCB. HPDSC's have been shown to enhance rate and probability of engraftment and potentially suppress inflammation when combined with UCB transplant in NOD-SCID mice .

Objectives: To determine the safety and feasibility of UCB transplantation followed by HPDSC's using myeloablative (MA) or reduced intensity (RI) conditioning for malignant and non-malignant diseases.

Design/Method: A multicenter consortium (CCT-HPDSC-UCBT-PI-001) enrolled patients with eligible malignant or nonmalignant conditions. Patients had a single or double cord blood unit with at least 4/6 HLA match and cumulative TNC $>5.0 \times 10^7/\text{kg}$. After MA or RI conditioning, single or double UCB infusion was followed by the infusion of HPDSC's. Donor chimerism was performed as previously described

Results: 18 patients have been enrolled to date, with 12 receiving single and 6 receiving double UCB transplant. 11 patients were transplanted for high-risk malignancy and 7 for non-malignant conditions. 74% of patients are alive at 34-1005 days post-transplant. With the exception of 1 patient with early relapse, all patients had neutrophil engraftment at a median of 23 days (range 13-53). HPDSC's did not persist beyond day 60 in any patient, although mixed chimerism persisted to at least day 100 in all double UCBT. Probability of Grade II-IV aGVHD was only 17% and cGVHD was 0%. Immune reconstitution was rapid, with day 270 absolute CD4 counts $>200\text{cells}/\text{ul}$ and IgG levels $>500\text{mg}/\text{dl}$ in 63% and 88% of surviving patients, respectively.

Conclusions: UCB transplant followed by HPDSC infusion in children and young adults with malignant and non-malignant diseases appears to be safe and well-tolerated with a lower than expected incidence.

INCIDENCE AND ETIOLOGIES OF EARLY READMISSION FOLLOWING UMBILICAL CORD BLOOD AND HAPLOIDENTICAL TRANSPLANT IN PEDIATRIC AND YOUNG ADULT PATIENTS

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Background: Allogeneic Hematopoietic stem cell transplant (HSCT) relies on the availability of suitable donor, with only 30% of the patients having matched sibling donor. Alternative donor HSCT such as umbilical cord blood (UCBT) or haploidentical donors (haplo-transplant) continue to increase as a viable donor source.

Objectives: Evaluate leading causes of readmissions following UCBT and haplo-transplant in pediatric and young adult patients.

Design/Method: We conducted a retrospective review of patient's age ≤ 26 years who were readmitted within 6 months following either UCBT or haplo-transplant between 2007 - 2014. Information on patient's characteristics, including diagnosis, conditioning regimens, GVHD-prophylaxis, transplant-related complications, and reasons for readmission were analyzed

Results: Seventy-three patients with median age 20 (Range 3-26) received either UCBT (n=51) or haplo-transplant (n=22). Forty-one patients required re-admission to the hospital; 31 received UCBT and 10 underwent haplo-transplant (p=0.34). These 41 patients had 71 re-admissions events. Among the readmitted group, all patient received mainly myeloablative regimen and the majority had a hematological malignancies. Five patients were not in complete remission. Three patients had non-malignant conditions (UCBT=1, haplo=2). All patients received similar aGVHD prophylaxis, however haplo-transplant also received additional post-transplant cyclophosphamide. There were no significant differences in univariate analysis at index admission among documented infection, aGVHD, ICU-admission, engraftment syndrome and VOD. Fourteen patients from the UCBT and 8 patients from the haplo-transplant had only one admission (p=0.24). Nineteen patients had ≥ 2 admissions within 6 months; 17 of them from the UCBT group (p=0.075). Documented infection was the leading cause of admission in both groups (UCBT= 25, haplo=4). Acute GVHD complications were the cause for 15 admissions (UCBT=11, haplo=4). Relapse was the etiology of admission in 10 patients (UCBT=8, haplo=2). In both groups, the first readmission and the number of subsequent readmissions did not have an influence on outcome.

Conclusion: There was a trend towards more readmissions in the UCBT group. However, significant differences were not reached in number of readmissions caused by each source in this cohort. The leading cause of admissions was documented infections in both groups. Larger and multi-institutional collaborative studies are warranted.

MYCOPHENOLATE MOFETIL (MMF) ADMINISTERED EVERY EIGHT HOURS WITH TACROLIMUS IS EFFICACIOUS IN ACUTE GRAFT VERSUS HOST DISEASE (aGVHD) PROPHYLAXIS IN CHILDHOOD, ADOLESCENT AND YOUNG ADULT (CAYA) ALLOGENEIC HEMATOPOIETIC PROGENITOR TRANSPLANT (ALLOHPT) RECIPIENTS

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Background: Acute GVHD remains a major challenge in AlloHPT. We previously demonstrated safety of tacrolimus/MMF 900 mg/m² Q6H combination. Pharmacokinetic studies suggested MMF Q8H dosing to be optimal.¹ The ideal dosing of MMF in the pediatric AlloHPT recipients remains to be defined.

Objectives: To investigate efficacy of tacrolimus plus MMF administered Q8H for aGVHD prophylaxis in CAYA recipients of AlloHPT.

Design/Method: CAYA recipients of AlloHPT were recruited over a 52 months period from 2011-2015. AGVHD prophylaxis consisted of tacrolimus 0.03-0.04 mg/kg/day IV continuous infusion or 0.12-0.16 mg/kg/day PO divided q8-12h (target concentration 10-20 ng/mL) and MMF 900 mg/m² (max 1.5 g/dose) or 15 mg/kg (for patients \geq 18 years of age or weight \geq 70 kg; max 1.5 g/dose) IV/PO Q8H starting on Day +1. MMF was discontinued on Day +30 or +60 in absence of aGVHD.

Results: Thirty-five CAYA recipients (Sex: 26M:9F; Median age: 12.54 years [0.11-23.45 years]) with either malignant (71%) or nonmalignant (29%) conditions were analyzed. Donor sources included 6/6 matched sibling donor (MSD) peripheral blood stem cells (PBSC) (1), 10/10 matched unrelated donor (MUD) PBSC (3), 5/6 unrelated cord blood (CB) (8), 6/6 MSD CB (1), 6/6 matched sibling CB plus bone marrow (BM) (1), 10/10 MUD BM (4), 6/6 matched sibling BM (13), and 9/10 MUD BM (4). Conditioning regimens included both myeloablative (n=18, 51%) and non-myeloablative (n=17, 49%) regimens. Median time to myeloid and platelet engraftment was 15 and 30 days, respectively. Probability of grade II-IV and grade III-IV acute GVHD was 22.8% (CI95: 5.2-47.9) and 5.7% (CI95: 0-48.9), respectively. Probability of extensive and limited chronic GVHD was 22.6% (CI95: 3.4-52.2) and 12.2% (CI95: 0.3-45.7), respectively. Probability of 1-year OS was 82% (CI95: 64.1-99.8). MAC was predictive of a significantly higher risk of aGVHD in the univariate analysis (p = 0.01, HR = 6.6, CI95:0.91-48).

Conclusion: This study demonstrated a very low incidence of aGVHD and cGVHD in a diverse cohort of CAYA AlloHPT recipients following tacrolimus and MMF Q8H prophylaxis compared to our prior study utilizing Q6H dosing of MMF1.

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NONMYELOABLATIVE HAPLOIDENTICAL BMT WITH POST-TRANSPLANT
CYCLOPHOSPHAMIDE FOR PEDIATRIC AND YOUNG ADULT PATIENTS WITH HIGH-
RISK HEMATOLOGIC MALIGNANCIES

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Background: Lower intensity conditioning regimens for haploidentical bone marrow transplantation (BMT) are safe and efficacious for adult patients with hematologic malignancies. **Objectives:** We report the first data for pediatric/young adult patients with high-risk hematologic malignancies (n=40) treated with nonmyeloablative haploidentical BMT with post-transplantation cyclophosphamide (PT/Cy).

Design/Method: The majority of patients (n=36) received a preparative regimen of IV fludarabine (30 mg/m²/day) days -6 to -2, IV low-dose cyclophosphamide (14.5 mg/kg/day) days -6 and -5, and total body irradiation (200 cGy) day -1. Two patients received the above along with alemtuzumab, and two patients received IV busulfan (0.8mg/kg IV every 12 hours) days -6 to -3 instead of Cy. All patients received haploidentical, T-cell replete bone marrow (n=37) or peripheral blood stem cells (n=3) on Day 0. Post-transplant immunosuppression consisted of IV cyclophosphamide (50 mg/kg/day) days +3 and +4, mycophenolate mofetil through day +35, and tacrolimus through days +60 to +180.

Results: Median age was 20 years (range 1-25) and diagnoses included AML (n=9), ALL (n=9), mixed-lineage leukemia (n=1), MDS (n=5), CML (n=1), Hodgkin lymphoma (n=14), and NHL (n=1). Seventeen patients (43%) had undergone prior myeloablative BMT. Donor engraftment occurred in 29/32 (91%) of patients evaluable at Day 60. Median time to neutrophils >500/ μ L was 16 days (range 13-22) and platelets >20,000/ μ L without transfusion was 18 days (range 12-62). Cumulative incidences of acute GVHD grades II-IV and grades III-IV at day 100 were 33% and 13%, respectively. Cumulative incidence of chronic GVHD was 23%, including 7% moderate-severe chronic GVHD. Transplant related mortality (TRM) at 1 year was 13%; causes included infection (n=3) and diffuse alveolar hemorrhage (n=1). Cumulative incidence of relapse at 2 years was 52%. With a median follow-up of 20 months (range 3-148), actuarial overall survival is 58% and event-free survival is 43% at 2 years.

Conclusion: We demonstrate excellent rates of engraftment, GVHD, and TRM in pediatric/young adult patients treated with this regimen, comparable to published adult data. This approach is safe and feasible for young patients with high risk hematologic malignancies, including those with co-morbidities that preclude eligibility for myeloablation. Clinical trials are warranted to directly assess the benefit of preparative regimen intensity.

LONG-TERM FUNCTIONAL OUTCOMES FOLLOWING HEMATOPOIETIC STEM CELL TRANSPLANTATION FOR INFANTILE KRABBE DISEASE

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Background: Hematopoietic stem cell transplantation (HSCT) can halt the progression of Krabbe disease (KD) via engraftment of donor-derived, enzyme-producing cells in the bone marrow, brain, and other organs. While HSCT prior to the development of symptoms is associated with improved survival, there remains a paucity of information regarding the long-term function and quality of life for surviving patients.

Objectives: The aim of this study is to report long-term functional outcomes following HSCT in a series of presymptomatic infants with infantile KD, in order to inform guidelines for early intervention with HSCT and long-term follow-up care following HSCT for infantile KD.

Design/Method: The records of 19 patients followed by the Duke Pediatric Blood and Marrow Transplant Program after HSCT for KD at < 2 months of age were reviewed for information regarding long-term functional outcomes. Overall survival and descriptive statistics were calculated. Functional outcomes were compared between those transplanted at <30 days (n = 12) and >30 days of life (n = 7).

Results: All patients were diagnosed due to family history (n = 16) or via newborn screening (NBS, n = 3). Median age at transplant was 27 days (range 19-61). Five and 10 year overall survival (OS) post-HSCT were 84.2% (95% CI: 58.7-94.6%) and 78.6% (95% CI: 52.5-91.4%). Median time from transplant was 11.3 years (range 0.01–18.2). One death due to disease progression occurred 15 years post-HSCT. Sixteen patients survived > 5 years post-HSCT. Nine patients (56%) were able to communicate normally. Eleven patients (69%) attended school at the appropriate grade level. Twelve patients (75%) were able to feed themselves independently. Ten patients (63%) remained ambulatory. Poorer outcomes occurred more frequently in those who were transplanted at >30 days than those transplanted at <30 days in the domains of communication (P=0.01), feeding (P=0.01), and mobility (P=0.004).

Conclusion: Improved functional outcomes were observed in patients with presymptomatic infantile KD for whom HSCT was performed in the first month of life. Defining this critical period for early intervention emphasizes the need for accelerated pre-HSCT evaluation and decision-making, and will influence public policy regarding NBS.

LOW INCIDENCE OF LONG-TERM, PERSISTENT GRAFT VERSUS HOST DISEASE AFTER PEDIATRIC UNRELATED CORD BLOOD TRANSPLANT WITH MINIMAL GRAFT VERSUS HOST DISEASE SEQUELAE

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Background: Unrelated cord blood transplant (UCBT) offers a readily available stem cell source for individuals lacking a suitable related donor. Acute and chronic graft versus host disease (GVHD) are important contributors to transplant-related morbidity and mortality. Current literature supports a lower incidence of GVHD with UCBT when compared to other alternative donor sources and has shown that GVHD following UCBT has no impact on overall survival.

Objectives: We aimed to define the course and long-term outcomes of GVHD following UCBT.

Design/Method: Eighty-one patients were enrolled on an IRB-approved, UCBT trial between January 1996 and July 2007. Thirteen patients were excluded from analysis due to death prior to engraftment (7), graft rejection (4), or re-transplantation (2). GVHD activity, use of immunosuppressive therapy, and overall survival were collected at 1, 2 and 3 years post-UCBT. Performance scores were determined at 3 years post-UCBT and pulmonary function tests (PFTs) were analyzed at two to eight years post-UCBT.

Results: The median age at transplant of the 68 evaluable patients was 7.2 years (range 0.3-24.4). Forty patients (59%) developed GVHD with 36 (53%) having Grade I-IV acute GVHD and 4 having de novo chronic GVHD occurring after day 100. Seventeen patients (25%) with acute GVHD had active GVHD extending past day 100. In patients with prior GVHD, presence of active GVHD was 29% (8/28), 13% (3/24) and 0% (0/22) at 1, 2 and 3 years post-transplant with 68% (19/28), 33% (8/24) and 9% (2/22) of patients remaining on immunosuppressive therapy, respectively. Survival of those diagnosed with GVHD was 70% (28/40) at 1 year, 60% (24/40) at 2 years and 55% (22/40) at 3 years post-UCBT. Twenty patients with prior GVHD had interpretable post-transplant PFTs with 15 (75%) demonstrating normal or stable lung function. Performance scores in 21 patients at 3 years post-transplant showed 17 (81%) with scores of 90 or 100 and 4 (19%) with scores of 70 or 80.

Conclusion: GVHD following UCBT is not associated with increased mortality, resolves in nearly all patients by 3 years post-transplant, and has limited impact on long-term pulmonary function and overall quality of life.

ANTI-HLA ANTIBODIES ARE NOT ASSOCIATED WITH POOR OUTCOME IN HEMATOPOIETIC STEM CELL TRANSPLANT RECIPIENTS

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Background: Increased numbers of human leukocyte antigen (HLA)-mismatched allogeneic hematopoietic stem cell transplants (HSCTs) are now being performed. Anti-HLA antibodies in the recipient are routinely tested prior to stem cell transplant, and may be donor-specific or non-donor specific. There are few data regarding general anti-HLA antibodies and their role in stem cell transplant outcomes.

Objectives: To determine the incidence and risk factors for the development of anti-HLA antibodies in stem cell transplant recipients and association with outcomes.

Design/Method: We reviewed all allogeneic transplant patients at our institution from 2009-2013. Data collected included anti-HLA antibody presence, strength, and specificity. Transplant recipients were screened for panel reactive antibodies for class I and class II HLA and mean fluorescence intensity (MFI) was calculated. Additional data collected included demographic information, prior transfusions, pregnancies, transplant type, conditioning regimen used, overall survival (OS), event-free survival (EFS), and transplant-related mortality (TRM).

Results: Our cohort included 157 patients with mean age at transplant 51 years (range 3-72 years). Patients were 52.2% male, 55.4% received myeloablative conditioning, 70.1% of patients had an unrelated donor, and 81.5% of patients had an HLA-matched donor. Forty-five recipient patients (28.7%) had detectable anti-HLA antibodies prior to transplant, including 37 (23.6%) patients to class I, 24 (15.3%) to class II, and 16 (10.2%) to both. Only one patient (0.6%) in our cohort had a donor-specific anti-HLA antibody. Significant risk factors for the development of anti-HLA antibodies included any prior pregnancy (odds ratio (OR)=8.0) and >20 blood transfusions (OR=9.4). OS for the entire cohort was 50.0% at 4.26 years follow-up. OS, EFS, and TRM were similar in recipients both with and without anti-HLA antibodies. Outcomes remained similar when broken up by anti-HLA antibody type and titer. Graft failure rate was identical among those with and without detectable anti-HLA antibodies. The one patient with donor-specific anti-HLA antibody died due to TRM.

Conclusion: Anti-HLA antibodies are detectable in a significant portion of stem cell transplant recipients. Prior pregnancy and >20 prior transfusions are both significant risk factors for the development of anti-HLA antibodies. The presence of general anti-HLA antibodies in the recipient does not correlate with patient outcomes after stem cell transplantation.

HIGH RISK OF MALE INFERTILITY AFTER HEMATOPOIETIC STEM CELL TRANSPLANTATION IN CHILDREN AND YOUNG ADULTS DESPITE REDUCED INTENSITY CONDITIONING

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Background: Reduced intensity conditioning (RIC) is increasingly used for hematopoietic stem cell transplantation (HSCT) with the goal of maintaining therapeutic efficacy while limiting toxicity. Current understanding of late endocrine effects using RIC HSCT is extremely limited. While the risk of infertility after myeloablative HSCT is known to be high (>80%), there is currently no data regarding infertility risk with RIC HSCT.

Objectives: Longitudinally evaluate gonadal function and fertility potential in young men after RIC HSCT.

Design/Method: Children and young adults, ≥ 1 year after a single RIC HSCT regimen were followed in a prospective cohort study to evaluate late endocrine effects and fertility potential. Subjects were evaluated for pubertal development, hormonal status, and some subjects had a semen analysis performed.

Results: Preliminary results were obtained from 14 subjects. Most subjects received Fludarabine and Melphalan +/- Campath, without total body irradiation. Five of 14 subjects (36%) had received prior chemotherapy for malignancy. The median age at time of HSCT was 13.6 years (range 3.4-24.3). The average age at time of evaluation was 20.3 years (range 15.6-25.2), with a median time from HSCT of 5.6 years (range 1.9-10.0). Eleven subjects were pubertal. Of the 9 pubertal subjects with available laboratory testing, only one (11%) had abnormally elevated gonadotropins (LH and FSH). Similarly, only one (11%) had an abnormally low testosterone level. The remainder had normal testing for Tanner stage. Four of 9 (44%) had abnormally low inhibin B levels, suggestive of reduced fertility and Sertoli cell dysfunction. Semen analysis was abnormal in all 8 subjects tested: 7 had azoospermia and 1 had oligoteratospermia.

Conclusion: Results suggest that RIC HSCT may be associated with a high risk of infertility. However, gonadotropin and testosterone levels appear to be normal in most young male after RIC HSCT, therefore, normal pubertal development does not ensure normal fertility potential. Our data suggests that inhibin B levels could be a useful screening test; however semen analysis remains the gold standard to test fertility potential. Risk of infertility should be included in counseling about RIC HSCT, and fertility preservation should be discussed and offered prior to HSCT.

EXPLORATORY STUDY INVESTIGATING THE ROLE OF SIRTUIN 3 IN AMELIORATING RADIATION INDUCED LATE BONE MARROW INJURY

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Background: Radiation therapy induces chronic oxidative stress in hematopoietic stem cells (HSC) leading to impairment of HSC self renewal ability, induction of senescence and increase in oxidative DNA damage. This results in premature exhaustion of HSC reserves with subsequent development of late bone marrow injury. Sirtuin 3 (SIRT-3) is a mitochondrial protein deacetylase which reduces cellular reactive oxygen species (ROS) level by activating mitochondrial antioxidant enzymes like superoxide dismutase and isocitrate dehydrogenase. Though mitochondria is the seat of cellular respiration and the main source of cellular ROS, it has yet to be proven whether mitigating mitochondrial ROS can play an essential role in HSC maintenance under stress conditions like radiation.

Objectives: To determine whether radiation induced chronic oxidative stress can be ameliorated by Sirtuin 3 overexpression.

Design/Method: Sirtuin 3 overexpressing transgenic (T3TG) and cre mice strains were used. Each strain of mice was divided into 2 groups. One group was exposed to 6.5 Gy X-ray total body radiation, while the other group was not radiated. All mice were sacrificed 4 weeks later and the HSC population (Lin-ckit+Sca-1+CD150+) was isolated. ROS levels were detected after incubating HSCs with 2',7' dichlorohydrofluorescein diacetate (H2DCFDA) for 30 min. Data was collected with LSRII flow cytometer and then analyzed using FlowJo (TreeStar).

Results: On comparing the HSC population between the irradiated and unirradiated cre mice, we noted a 1.6 fold increase in ROS level after radiation. Similarly in the SIRT3 overexpressed mice the HSC population exhibited a 1.5 fold increase in ROS level after radiation. HSCs in both mice strains demonstrated persistent oxidative stress a month after radiation; however the ROS levels of T3TG mice were not significantly lower than in the cre mice.

Conclusion: Our study was limited by its small sample size and failure to optimize radiation dose according to the body surface area of the mice. Though we were unable to demonstrate the protective effect of Sirtuin 3 overexpression in significantly decreasing radiation induced chronic oxidative stress, yet our results did show this interesting trend and we aim to explore it further in future experiments after correcting for the aforementioned factors.

UVEITIS PRESENTING AFTER ALLOGENEIC HSCT, AN UNDERRECOGNIZED COMPLICATION OF CIDOFOVIR THERAPY

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Background: Cidofovir is the only treatment for disseminated adenovirus infection, a life-threatening complication of hematopoietic stem cell transplantation (HSCT). Patients at our institution are monitored for the toxicities of cidofovir often cited in the literature including renal insufficiency and marrow suppression.

Objectives: We present a 5 year old female with history of M7 Acute Myelogenous Leukemia in second complete remission who is status post 5/6 umbilical cord HSCT complicated by acute graft versus host disease (skin and lower GI tract, GVHD) and developed protracted disseminated adenovirus (nasopharynx, gastrointestinal tract, blood) 7 months after HSCT. Due to persistent positive infection and continued concern for GVHD flare of the GI tract, the patient continued on weekly cidofovir for 8 months total, at which time she presented with 2 week history of injected and irritated eyes without other symptoms of infection or GVHD. Patient was referred to ophthalmology.

Design/Method: Differential diagnosis included infectious etiologies which were ruled out by chart review and ongoing surveillance as part of standard BMT care (adenovirus pcr, CMV pcr).

Results: Diagnosis was chronic bilateral uveitis though complete exam was hindered from poor dilation as a result of iris synechia. Vitreous was clear and ultrasound of eyes within normal limits. She was treated with cessation of cidofovir and steroid drops, which was feasible at the time due to recent negative blood adenovirus PCRs and absence of diarrhea despite positive stool test.

Conclusion: Review of the ophthalmology literature shows that after 8 doses of cidofovir (2 months), patients are at a significant risk for developing uveitis that could result in vision loss, an underappreciated fact in HSCT literature and practice. In discussion with ophthalmology experts, the recommendation was made to involve ophthalmology for any patient requiring chronic cidofovir therapy for greater than 8 doses and any HSCT patient who presents with injected and irritated eyes.

CARDIAC DYSFUNCTION 100 DAYS AFTER STEM CELL TRANSPLANT IS ASSOCIATED WITH EARLY ELEVATION IN CARDIAC BIOMARKERS AND CYCLOPHOSPHAMIDE PREPARATIVE CHEMOTHERAPY IN PEDIATRIC AND YOUNG ADULT PATIENTS

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Background: Cardiac dysfunction is an increasingly recognized complication for long-term survivors of pediatric Stem Cell Transplant (SCT). We have recently reported a 9% incidence of left ventricular systolic dysfunction (LVSD) by 100 days post-SCT.

Objectives: We hypothesized that chemotherapy preparative regimen was the source of cardiac injury and subsequent LVSD seen in the first 100 days after SCT in pediatric patients.

Design/Method: We retrospectively assayed cardiac biomarkers cardiac troponin-I (cTn-I) and N-terminal prohormone of brain natriuretic peptide (NT-proBNP) from stored specimens in 12 patients with new LVSD and 13 controls, at six time points peri-transplant. LVSD was defined as ejection fraction less than 55% or shortening fraction less than two standard deviations below the age adjusted mean, newly occurring during the first 100 days post-SCT.

Results: Among 145 samples tested for cTn-I, elevation ≥ 0.03 ng/mL occurred in 49 samples (33.8%), and 15 of 25 patients (60%) had at least one sample with elevated cTn-I. Among 143 samples tested for NT-proBNP, elevation ≥ 450 pg/mL occurred in 80 samples (55.9%), and 21 of 25 patients (84.0%) had at least one sample with elevated NT-proBNP. Among patients with LVSD by day 100, on day 7, 50% had cTn-I ≥ 0.03 , whereas only 8% of controls had elevated cTn-I ($p=0.03$). In our cohort, cyclophosphamide preparative chemotherapy (CPC) was associated with new LVSD (8/12 with LVSD v. 2/13 control; $p=0.02$). No association was seen with previous anthracycline use, cell source, bacteremia, total body irradiation, thrombotic microangiopathy, or acute graft versus host disease.

Conclusion: Cardiac injury occurs frequently in patients undergoing SCT as evidenced by elevated cTn-I in up to 34% of patients. In those who develop LVSD in the first 100 days post-SCT, an association with CPC and day 7 cTn-I is evident. We are now prospectively monitoring patients receiving CPC with cTn-I measurements during and after infusion.

CAUSES AND IMPACT OF HOSPITAL READMISSIONS IN THE FIRST 180 DAYS AFTER HEMATOPOIETIC STEM CELL TRANSPLANTATION IN CHILDREN, ADOLESCENTS, AND YOUNG ADULTS

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Background: Hematopoietic stem cell transplantation (HSCT) provides potential curative treatment for various conditions. However, there is a high rate of patients require readmission to the hospital after transplantation.

Design/Method: A retrospective analysis of patients 26 years or younger treated with HSCT at The University of Texas MD Anderson Cancer Center was conducted.

Results: A chart review of 435 children, adolescent, and young adult patients who underwent HSCT from 2008 to 2015 revealed that 171 patients (39%) had at least 1 hospital readmission. The median age at transplant was 21 years (range, 2-26 years). The primary diagnoses were as follows: hematological malignancy (n=122), solid tumor (n=35), and non-malignant conditions (n= 14); 86.5% received allogeneic HSCT, and 13.5% received autologous HSCT. A total of 312 readmission events were reported: documented infection (n=99), graft versus host disease complications (n=60), fever without source (n=52), gastrointestinal related symptoms (n=34), relapse (n=33), other (n=34). The median follow-up time after transplant was 31 months (95% confidence interval [CI], 28.1–35.4). Among patients who underwent allogeneic HSCT, those who were readmitted to the hospital at least once within 180 days after HSCT had lower overall survival (OS; P = 0.005) and disease-free survival (DFS; P = 0.034). Higher readmission rates were associated with lower rates of OS (P = 0.001) and DFS (P <0.001) in allogeneic recipients. In a multivariate analysis, male sex (hazard ratio [HR], 3.25; 95% CI: 1.50-7.03; P = 0.003), documented infection at index admission or subsequent readmissions (HR, 1.92; 95% CI, 0.89-4.13; P = 0.09), and prior treatment with 2 or more chemotherapy regimens (HR, 4.94; 95% CI, 1.18-20.63; P = 0.03), were associated with lower rates of OS; and age 18 years or younger was associated with lower rates of DFS (HR, 2.51; 95% CI, 1.08-5.82; P = 0.03) in the allogeneic group.

Conclusion: Early hospital readmission (within 180 days) affected survival outcomes in patients who underwent allogeneic HSCT but not those who underwent autologous HSCT. Frequent monitoring of patients with transplant-related morbidities and improving education for health care providers might help to prevent early hospital readmission.

FECAL CALPROTECTIN, A USEFUL TOOL TO PREDICT STEROID RESPONSIVENESS OF GASTROINTESTINAL ACUTE GRAFT VERSUS HOST DISEASE

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Background: Calprotectin, a protein found in neutrophils, can be quantified in fecal samples during gastrointestinal inflammation. It's a diagnostic screening test for inflammatory bowel disease (IBD), differentiating IBD (>100µg/g) from non-IBD enteritis. Few studies have evaluated fecal calprotectin as a marker of gastrointestinal (GI) acute graft versus host disease (aGVHD) after hematopoietic cell transplant (HCT).

Objectives: This study sought to determine if fecal calprotectin levels would predict development of gastrointestinal aGVHD prior to the onset of symptoms and predict steroid responsiveness of aGVHD.

Design/Method: Stool samples were obtained before conditioning, at D+14 and D+ 28 post-HCT. In patients diagnosed with aGVHD, an additional sample was obtained at the onset of symptoms and after 1 week of treatment. Serum albumin was obtained at all time points. ELISA for calprotectin was performed on each stool sample. aGVHD was graded per standard criteria. Median values were determined and compared using a 2-sample t-test.

Results: Sixty patients were enrolled. Data is currently available for 52 patients. aGVHD occurred in 25 patients post-HCT - 14 with skin only and 9 with GI aGVHD. Fecal calprotectin levels were not significantly different at preconditioning, D+14, and D+28 post-HCT in those that developed aGVHD, those with any GI aGVHD, or with severe (> grade 2) aGVHD. Pre-conditioning and D+14 albumin levels were not significantly different in those with and without aGVHD. At D+28 post-HCT, those with GI aGVHD had a median albumin of 3.0 and those with >Grade 2 aGVHD had a median albumin 2.7 compared with a median of 3.65 in those with non-GI aGVHD and those with less severe aGVHD (<grade 2) (p= 0.04 and p=0.01, respectively). Higher fecal calprotectin at onset of aGVHD was predictive of steroid refractoriness (116 versus 31 ug/g, p=0.046).

Conclusion: Although fecal calprotectin was unable to predict occurrence of aGVHD or differentiate between GI and non-GI aGVHD, it was able to predict steroid refractory GI aGVHD at the onset of symptoms. Low albumin was a better predictor of GI and >grade 2 aGVHD. These markers may help identify patients with more aggressive disease and guide management of aGVHD.

OUTCOMES AFTER DONOR LYMPHOCYTE INFUSION FOR INSUFFICIENT DONOR CHIMERISM FOLLOWING HEMATOPOIETIC STEM CELL TRANSPLANTATION FOR NON-MALIGNANT DISORDERS

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Background: Donor lymphocyte infusion (DLI) is one strategy to potentially stabilize or reverse waning donor chimerism. Little is reported of the utility of donor DLI following hematopoietic stem cell transplantation (HCT) for non-malignant disorders (NMD).

Objectives: We describe outcomes of DLI for insufficient donor chimerism after HCT in a large pediatric NMD cohort.

Design/Methods: We queried the Institutional BMT Database for patients with NMD receiving DLI for insufficient post-HCT donor chimerism. Human leukocyte antigen (HLA) typing, graft selection and original conditioning were per institutional guidelines. The use, timing and dosing of DLI was at the discretion of the treating physician. Donor chimerism values on the myeloid fraction of peripheral blood at pre-DLI and most-recent time-points were reviewed. Patients were considered best responders if donor chimerism improved (pre-DLI to most-recent) and most recent chimerism was $\geq 80\%$.

Results: Twenty-four patients (46% female) were identified who underwent 56 total DLIs and a median 2 DLI cycles per patient (IQR, 2 - 3; maximum, 5). The median cumulative CD3+ dose per-patient was $11.5 \times 10^6/\text{kg}$. The median zenith chimerism post-HCT (but pre-DLI) was 84% (IQR, 39 - 99%), observed at a median 28 days post-HCT. The median chimerism just prior to first DLI was 40%. The median time to first DLI was 90 days. Five patients (21%) were best DLI responders. At a mean 3.6 years post-HCT, they retained mean chimerism of 94% (mean increase from pre-DLI of 37%). Best response to DLI did not depend on HCT total nucleated cell dose, donor relatedness, serotherapy agent of HCT regimen, pre-DLI chimerism, or total DLI CD3+ dose. Best responders tended to have undergone myeloablative conditioning, be HLA-matched to the donor and receive first DLI later post-HCT (median 102 days, versus 83 days). Of the 19 non-best responders (79%), median chimerism at last follow-up was 10% (IQR, 2 - 25%). Post DLI, two patients developed aGvHD and two patients developed cGvHD.

Conclusion: In a large NMD cohort undergoing DLI after HCT, sustained high donor chimerism response was observed in 21% of patients and stable NMD at most recent follow-up was observed in 58% of patients.

TIMELY RESOLUTION OF BRAIN MRI GADOLINIUM ENHANCEMENT IN ADVANCED CEREBRAL ADRENOLEUKODYSTROPHY: AN IMAGING SURROGATE FOR LONG-TERM NEUROLOGIC RESPONSE FOLLOWING ALLOGENEIC HEMATOPOIETIC STEM CELL TRANSPLANTION

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Background: Neurologic functional outcomes are unpredictable and varied following allogeneic hematopoietic stem cell transplantation (HSCT) for advanced, childhood-onset cerebral adrenoleukodystrophy (cALD). Resolution of contrast enhancing MRI lesions is considered extinguishment of active cALD pathophysiology. For this patient population, we have observed variable time-to-resolution of brain MRI contrast enhancement following HSCT.

Objectives: We retrospectively analyzed patients transplanted for advanced cALD for the significance of contrast resolution by post-transplant Day +60.

Design/Method: Patients undergoing HSCT for contrast-enhancing, advanced cALD (Loes radiographic severity score ≥ 10) were assessed by MRI with gadolinium contrast after HSCT. Correlations between Day +60 enhancement status (resolved versus not-resolved) were made with patient-, disease-, transplant- and outcome characteristics.

Results: Of 30 evaluable patients, 13 (43%) demonstrated resolution by Day +60. Patients with rapid resolution of enhancement (resolvers) showed less clinical neurologic progression in the long-term (neurologic function scale score mean change of 6.6 versus 12.9, non-resolvers; $p < 0.05$). Day +60 resolution status did not correlate with 2-year survival (94% versus 92%, non-resolvers; $p = 0.78$) or long-term change in Loes score (2.0 versus 2.7, non-resolvers; $p = 0.40$). Patients demonstrating resolution by Day +60 on average experienced faster neutrophil recovery (day 16 versus 20, non-resolvers; $p = 0.03$) and greater donor myeloid chimerism (86% versus 70%, non-resolvers; $p = 0.02$). In the pre-transplant setting, Loes score and neurologic disability rating, but not patient age or allograft type, correlated with Day +60 MRI enhancement status. A trend toward greater likelihood of Day +60 resolution of contrast enhancement following myeloablative conditioning was observed.

Conclusion: Resolution of gadolinium enhancement on brain MRI by Day +60 following HSCT for advanced cALD predicts more favorable clinical neurologic outcome. Faster post-transplant neutrophil recovery and greater donor chimerism correlate significantly with extinguishment by Day +60. This radiographic marker may be a useful, immediate surrogate for longer-term clinical outcomes when assessing both established and novel therapies for enhancing cALD.

ADVANCED CHILDHOOD CEREBRAL ADRENOLEUKODYSTROPHY: RAPID PRE-TRANSPLANT RADIOGRAPHIC PROGRESSION PREDICTS POOR CLINICAL OUTCOMES

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Background: Clinical outcomes following HSCT for boys with advanced cerebral adrenoleukodystrophy (cALD) are variable. While an MRI severity score (Loes score) ≥ 10 is a risk factor for unfavorable long-term neurologic function, not all such boys go on to have severe disease progression after transplant. Additional prognostic factors are sought.

Objectives: We assessed the impact of pre-transplant disease "velocity" (rate of change of Loes score over time) on post-transplant outcomes in boys with advanced cALD (pre-HSCT Loes score ≥ 10).

Design/Method: 98 consecutive patients with cALD underwent MRI for evaluation for HSCT at the University of Minnesota from February 2000 to March 2015. In most instances, >1 previous scans were available for review, thus allowing for determination of pre-transplant rate of change of radiographic Loes score (dLoes/dt). HSCT was performed in 90 patients, 74 of whom had sufficient imaging to meet inclusion criteria. Clinical disease progression was evaluated with the ALD neurologic function scale (NFS). Correlations were assessed between dLoes/dt and post-HSCT changes in Loes and NFS scores (Δ Loes and Δ NFS, difference between most recent and pre-HSCT values).

Results: Of the 74 patients included, two groups were defined: "standard-risk" patients with pre-HSCT Loes scores < 10 (n=35), and "higher-risk" patients with pre-HSCT Loes scores ≥ 10 (n=39). Standard-risk patients had a median Δ NFS of 0 (IQR 0 – 0) after HSCT, with no correlation with pre-HSCT dLoes/dt. Higher-risk patients had highly variable Δ NFS scores following transplant. For these patients with slow pre-transplant MRI progression (dLoes/dt < 1.00 Loes/100 days, n=15), the median Δ NFS was 5 (IQR 1.5-7) at a median follow-up of 19 months (IQR 12-39). In contrast, higher-risk patients with rapid pre-transplant MRI progression (dLoes/dt ≥ 2.00 Loes/100 days, n=11) had a median Δ NFS of 20 (IQR 15-22; $p < 0.001$) at a median follow-up of 15 months (IQR 13-22). In contrast, the change in MRI severity score following transplant did not depend upon the pre-transplant dLoes/dt (median Δ Loes = 4; IQR 2-6 at median 15 months follow-up).

Conclusion: When evaluable for boys undergoing HSCT for advanced cALD, pre-HSCT dLoes/dt may be a useful predictor of long-term clinical outcomes.

SECOND ALLOGENEIC HEMATOPOIETIC CELL TRANSPLANT FOR GRAFT FAILURE IN NON-MALIGNANT PATIENTS: HIGH RATE OF ENGRAFTMENT WITH LOW-DOSE BUSULFAN, FLUDARABINE, LOW-DOSE TOTAL BODY IRRADIATION CONDITIONING

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Background: Allogeneic hematopoietic cell transplant (HCT) offers a curative therapy for several non-malignant conditions. However, rates of graft failure in non-malignant populations exceed those of patients with malignant indications for HCT. Salvage conditioning regimens and outcomes for second allogeneic HCT for graft failure vary immensely in the literature.

Objectives: We sought to evaluate the feasibility and outcomes of a reduced intensity busulfan-based conditioning regimen for patients with non-malignant diseases requiring a second allogeneic HCT for graft failure.

Design/Method: We report 19 consecutive patients with non-malignant diseases who underwent a second allogeneic HCT for graft failure at the University of Minnesota Children's Hospital from January 2000 to July 2014 using a single reduced intensity regimen. Median time to second HCT was 85 days (IQR 67-119 days). For their second HCT, patients received intravenous busulfan 1.6 mg/kg/day divided Q6H (2.0 mg/kg/day if <4 years of age) on day-8 and day-7 (total 3.2 mg/kg or 4 mg/kg, respectively), intravenous fludarabine 40 mg/m²/day on days -6 to day -2 (total 200 mg/m²), and a single fraction of 200 cGy total body irradiation on day-1. Cyclosporine and mycophenylate mofetil began on day-3 for GvHD prophylaxis. Graft sources included umbilical cord blood in 68%, unrelated bone marrow in 21% and unrelated peripheral blood stem cells in 11% of the patients.

Results: Seventy-nine percent of patients (15 of 19) achieved stable donor hematopoiesis, with a 3 year overall survival of 74% (95% CI, 47-88%). Transplant related mortality was 26%, including death attributable to sepsis, pneumonitis and multi-organ failure. The cumulative incidence of neutrophil recovery by 42 days after second HCT was 74% (95% CI, 53-90%), with a neutropenic graft failure rate of 21%. A third allogeneic HCT was performed in 2 of the 4 individuals with failed donor engraftment. Infectious complications following second HCT included viral reactivation (35%) and invasive fungal infections (26%). The incidence of grade II-IV acute graft-versus-host disease was 33% with 6% grade III-IV.

Conclusion: In summary, we demonstrate the excellent overall survival and acceptable toxicity of a novel, reduced intensity low-dose busulfan-based conditioning regimen for second HCT to salvage initial HCT graft failure in patients with non-malignant conditions.

SUCCESSFUL CLINICAL OUTCOME IN THE PRESENCE OF SIGNIFICANTLY REDUCED DONOR CHIMERISM AFTER UNRELATED ALLOGENIC BONE MARROW TRANSPLANT IN CHEDIAK- HIGASHI SYNDROME

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Background: Chediak-Higashi syndrome (CHS) is a rare autosomal recessive disease due to mutation in the lysosomal trafficking regulator gene *LYST*, characterized by oculocutaneous albinism, immunodeficiency, platelet aggregation disorder, and microscopic findings of large granules in hematopoietic and other cells. Patients with CHS experience a life-threatening hemophagocytic lymphohistiocytosis (HLH)-like disorder termed accelerated phase (AP).

Allogenic hematopoietic stem cell transplantation is the sole curative therapy to prevent AP.

Objectives: Describe the clinical course of a CHS patient who underwent HLA-matched unrelated donor bone marrow transplant (MUD BMT) with successful outcome despite very low donor T cell chimerism.

Design/Method: Case report.

Results: Patient underwent a myeloablative 10/10 MUD-BMT at the age of sixteen months. Preparative regimen included IV busulfan (4.4 mg/kg/day x 4 days with targeted pharmacokinetics) and cyclophosphamide (50 mg/kg/day x 4 days). He received an unmanipulated bone marrow (BM) graft of 5.21×10^8 TNC/kg. GVHD prophylaxis consisted of cyclosporine and methotrexate. Initial course was complicated by engraftment syndrome and coronavirus requiring intubation and steroids. He had engraftment of neutrophils on day +21 and platelets on day +33. BM donor chimerism was 98% at day +30 but fell to 88% at day +60. Subsequent peripheral blood (PB) monitoring showed T-cell sorted chimerism stable at 89-92%. BM donor chimerism at day +90 was only 43%. Despite an early cyclosporine taper, PB T-cell sorted chimerism continued falling to 41% on day +224 when he began donor lymphocyte infusions (DLI). He received a total of 7 DLIs with CD3 doses ranging from 1×10^6 /kg to 1×10^8 /kg. At the completion of DLI, PB T-cell sorted chimerism was 20%, and whole blood chimerism was 12%. These levels have remained stable for one year. He has had occasional fluctuating mild neutropenia and several viral infections without evidence of AP.

Conclusion: Despite recurrence of his underlying disease, the patient is currently alive and well with no episodes of AP during viral infections for 2 years post-BMT. Similar to HLH, very low levels of T-cell donor chimerism may be sufficient for prevention of AP.

HEMORRHAGIC CYSTITIS FOLLOWING ALLOGENEIC HEMATOPOIETIC STEM CELL TRANSPLANTATION FOR HURLER SYNDROME: A CURIOUSLY INFREQUENT COMPLICATION

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Background: Allogeneic hematopoietic stem cell transplantation (HSCT) remains standard treatment for Hurler syndrome and other inherited metabolic disorders (IMD). Though transplant-related complications are common in patients with Hurler syndrome, we have observed infrequent hemorrhagic cystitis (HC) in this patient population. Furthermore, medical reports suggest a therapeutic effect on severe HC from intra-vesicular administered glycosaminoglycans (GAG). Interestingly, GAG accumulate in high levels in untreated Hurler patients due to impaired catabolism.

Objectives: We aimed to determine the incidence of hemorrhagic cystitis following HSCT for Hurler syndrome and compare it to that following HSCT for other IMD.

Design/Method: We identified all patients with IMD transplanted at our center between 1995 and 2013 following a myeloablative regimen containing cyclophosphamide and/or TBI. Allograft sources varied. The incidence of HC was determined for patients with Hurler syndrome and compared to that in patients with other IMD.

Results: 190 patients were included for analysis: 27% with Hurler syndrome; 44%, cerebral adrenoleukodystrophy (cALD); 17%, globoid cell leukodystrophy (GLD) or metachromatic leukodystrophy (MLD); 12%, other IMD. The observed frequency of HC in each disease was as follows: Hurler syndrome, 2%; cALD, 37%; GLD/MLD, 27%; other IMD, 14% ($p < 0.001$). There were no significant differences between patients with Hurler syndrome and those with non-Hurler IMD with respect to the following characteristics: allograft source, the use of serotherapy, or exposure to TBI. As the median age at transplant between Hurler (1.4 years) and non-Hurler IMD (8.1 years) was significantly different, an age-matched non-Hurler IMD sub-cohort was identified from the larger group ($n = 30$ patients, median age at HSCT of 1.6 years; $p = 0.02$, difference in median age at HSCT compared to patients with Hurler syndrome). This age-matched non-Hurler IMD sub-cohort continued to demonstrate a higher incidence of HC compared to patients with Hurler syndrome (14% versus 2%; $p = 0.04$, difference in observed frequencies).

Conclusion: Hurler patients appear less susceptible to HC following HSCT compared to patients with other IMD diagnoses. A protective benefit from excess urinary GAG in Hurler syndrome is a plausible reason.

EVALUATION OF VORICONAZOLE DOSING PROTOCOL IN PEDIATRIC BONE MARROW TRANSPLANT PATIENTS

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Background: Increased risk factors for invasive mold infections led to a change in primary fungal prophylaxis from fluconazole to voriconazole for allogeneic stem cell transplant patients at our institution. Due to wide inter-patient variability from polymorphisms and variable bioavailability within the pediatric population, therapeutic drug monitoring of voriconazole is essential to assess safety and efficacy. Previously all patients received a standard dose of 4mg/kg every 12 hours. Currently voriconazole is dosed 12mg/kg every 12 hours for patients <2 years and 8mg/kg every 12 hours for patients <2 years in addition to dual anti-fungal therapy with caspofungin until the trough is therapeutic (\geq mcg/mL). Results of a study evaluating alterations in voriconazole dosing practice to determine the effect on attaining therapeutic troughs and incidence of breakthrough fungal infections are reported.

Objectives: The primary objective was time to first therapeutic voriconazole trough, and secondary objectives included corresponding dose at therapeutic trough, concomitant dosing factors, incidence of breakthrough fungal infections, and adherence to protocol changes.

Design/Method: A retrospective single-center chart review of pediatric patients admitted to the BMT service, receiving voriconazole for primary antifungal prophylaxis between July 1, 2011 and August 31, 2014 was performed. Patients were divided based on dosing: weight based versus age-and-weight based.

Results: Fifty-seven patients were included for analysis. Baseline characteristics were not significantly different between groups. Age-and-weight adjusted dosing increased the probability of reaching a therapeutic trough level by more than six-fold (29 days vs. 16 days; $p = 0.05$). Higher dosage (HR 0.86 [0.77 - 0.96]), drug-drug interactions (HR 0.74 [0.43-1.37]) and the oral formulation of voriconazole (HR 0.38 [0.20- 0.72]) were associated with a lower probability of achieving a therapeutic level. The incidence of fungal infections was not statistically significant between groups. Overall, protocol adherence also decreased after the institution change.

Conclusion: Age-and-weight based dosing is superior to weight based dosing in achieving therapeutic voriconazole trough levels. Due to limitations of the study, we are unable to conclude a definitive association between dose and time to therapeutic trough. Larger, prospective studies should be performed to determine optimal dosing in pediatrics, specifically in children \leq 2 years of age.

A PHASE 1 PERSPECTIVE: MULTIVIRUS-SPECIFIC T CELLS FROM BOTH CORD BLOOD AND BONE MARROW TRANSPLANT DONORS

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Background: Deficiencies in conventional antiviral therapeutics after stem cell(SCT) and cord blood transplantation(CBT) have increased interest in an immunotherapeutic approach to viral disorders.

Objectives: We have developed 2 strategies to grow multivirus-specific donor-derived T-cells(mCTL) targeting Cytomegalovirus(CMV), Epstein-Barr Virus(EBV), and adenovirus, one from peripheral blood(PB) of adult CMV-seropositive donors and another from naive cord blood(CB) to treat or prevent viral infections post-transplant.

Design/Method: Using an adenoviral-vector expressing CMVpp65 or overlapping viral peptides for CMV(pp65 and IE-1), EBV(EBNA1 and LMP2), and Adenovirus(Hexon and Penton) presented to T-cells by dendritic cells, monocytes, or EBV-LCL, we generated a single culture of mCTL. PB-mCTL (Mean SFC:adeno:666, EBV:129, CMV:535) had more spot forming cells (SFC/100,000 cells) (Mean, adeno:666, EBV:129, CMV:535) than CB-mCTL (adeno:117, EBV:95, CMV:67) by IFN-gamma ELISPOT assay but both contained cells specific for at least 1 virus. mCTL derived from both CB and PB contained a mixture of CD4+ and CD8+ T-cells with an effector and central memory phenotype. Based on deep T-cell receptor sequencing, CB-mCTL were more polyclonal than PB-derived mCTL.

Results: Thirteen patients were infused with PB-mCTL and 12 patients with CB-mCTL. Patients received mCTL infusions from 35-384 days post-transplant at a range of 5×10^6 - 2×10^7 cells/m² with no toxicity or GvHD >grade II. We observed up to a 160-fold increase in virus-specific T-cells by 4 weeks post-CTL as measured by IFN-g ELISPOT. In 25 patients enrolled on these two studies, 16 patients experienced CMV, EBV, or adenovirus viral infections/reactivations before or immediately after mCTL infusion. Nine patients remained infection/reactivation-free. Eight of the patients had a complete response post-mCTL and 5 had a partial response, most coinciding with an increase in virus-specific T-cells. Three patients did not respond to therapy. The overall the response rate in both groups was 81%--even in patients with drug-resistant viral disease. This study demonstrates that mCTL derived from the PB of seropositive donors as well as the CB of virus naive donors expand in vivo and are active against multiple viruses.

Conclusion: By restoring immunity to multiple viruses simultaneously, prophylaxis with pharmacotherapy is eliminated, thus, improving the efficiency and cost-effectiveness of protecting recipients from these potentially-lethal viruses.

IL-15/4-1BBL ACTIVATED AND EXPANDED NATURAL KILLER CELLS IN PAEDIATRIC PATIENTS WITH REFRACTORY ACUTE LEUKAEMIA

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Background: Current therapies fail in most children with refractory or relapse leukaemia. Novel therapies are needed. Leukaemia cells are susceptible to be killed by activated Natural Killer (NK) cells.

Objectives: Generate ex-vivo highly activated/expanded NK cells by stimulation with the human leukocyte antigen-deficient cell line K562, genetically modified to Express 41BB-ligand and membrane-bound interleukin-15, developed at SJCRH (Memphis, TN).

Method: We tested the safety and feasibility of haploidentical activated and expanded NK cell therapy in this heavily pre-treated paediatric population in two phase I/II trials (EudraCT: 2012-005146-38 and EudraCT: 2012-000054-63).

Design/Method: Twenty one children with a median age of 12 years who had refractory (11 of them after allogeneic stem cell transplantation) acute leukaemia (6 B cell lymphoblastic leukaemia, 8 T cell lymphoblastic leukaemia and 7 acute myeloid leukaemia) were treated with rescue chemotherapy followed by the infusion of fresh activated and expanded NK cells obtained from haploidentical donor peripheral blood followed by three times a Hjek subcutaneous administration of low dose of IL-2. Rescue chemotherapy consisted in Cy-Flu (4 patients), clofarabinebased (7 patients), FLAG-IDA (3 patients) or nelarabine-based (7 patients).

Results: To date, we have infused 52 NK cell products containing a median of 11.74×10^6 /kg. All infusions were well tolerated. Thirteen patients have completed treatment and this is ongoing in 3; in 5 additional patients treatment could not be completed because of leukaemia progression (n = 2) or chemotherapy-related toxicities (n = 3). Among the 13 patients who completed the treatment, 6 achieved negative minimal residual disease, 5 had cytological remission and 2 had disease progression. All patients that achieved negative minimal residual disease received an allogeneic stem cell transplantation. Four of them are and leukemia-free with a median of 200 days post-transplant.

Conclusion: Infusion of fresh activated and expanded NK cell therapy was feasible and safe in a heavily pre-treated paediatric population, and should be further investigated in patients with high-risk leukaemia.

PROGNOSTIC FACTORS AND OUTCOMES FOR PEDIATRIC PATIENTS RECEIVING AN HAPLOIDENTICAL RELATIVE ALLOGENEIC TRANSPLANT USING CD3/CD19-DEPLETED GRAFTS

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Background: Haploidentical hematopoietic stem cell transplantation using T-cell depleted grafts is a valid option for pediatric patients with hematological malignancies in need of an allogeneic transplantation and lacking an HLA-identical donor. The use of CD3/CD19 depletion as a graft manipulation method helps retain large numbers of important immune cells in the graft as well as “unaltered” CD34+ cells.

Objectives: The aim of this prospective study was to analyze the outcomes and risk factors for survival of pediatric patients who received an allogeneic transplant from a mismatched and/or full haploidentical relative donor using a CD3/CD19-depleted graft.

Design/Method: Patients were enrolled in the study from January 2005 to December 2013. We included pediatric patients diagnosed with high-risk hematological malignancies in need of an allogeneic transplantation and in good clinical condition who lacked either a matched related donor (MRD) or a matched unrelated donor (MUD).

Results: Seventy-five transplantations were performed in seventy patients. Thirty-eight patients had ALL, 32 AML, 3 advanced MDS and 2 JMMCL; 19 were in 1st CR, 30 in 2nd CR, 12 in > 2nd CR and 14 were considered in refractory disease at time of transplantation. Four patients developed graft failure. Among engrafted patients, the median time to neutrophil and platelet recovery was 13 (range; 8-20) and 10 days (range 8-70), respectively. In 64 (85%) cases, ≥ 1 infections were diagnosed after transplant. The probability of NRM by day +100 after transplantation was $10 \pm 4\%$. With a median follow-up of 22 months, the probability of relapse was $32 \pm 6\%$ and $52 \pm 6\%$ for DFS.

Conclusion: Haploidentical transplantation using CD3/CD19 depletion is associated with encouraging results especially in patients in early phase of disease. KIR B haplotype donors confer a rapid NK cells expansion early after transplantation, resulting in lower probability of relapse and suggesting a GvL effect apart from GvH reactions. Donor infusion of high amounts of CD34+ cells is recommended in order to improve T-cell reconstitution.

SAFETY, TOLERABILITY AND RAPID IMMUNOLOGIC RECONSTITUTION IN CD45RA DEPLETED HAPLOIDENTICAL HEMATOPOIETIC STEM CELL TRANSPLANTATION

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Background: Allogeneic hematopoietic cell transplantation (HCT) is the only potential curative option for some hematologic childhood cancers, but many children do not have a HLA-matched donor.

Objectives: Haploidentical stem cell transplantation (haplo-HCT) has become an interesting strategy to avoid this problem, but the required T-cell depletion produce a profound and long-lasting immunosuppression, as well as graft failure and rejection. As naïve T-cells (identified by CD45RA expression) are believed to cause graft versus host disease (GvHD), while memory T-cell (CD45RA-) provide immediate anti-infection, anti-leukemia and anti-rejection effects, allogeneic HCT using CD45RA depletion arises as a novel approach to haplo-HCT.

Design/Method: Six children, 5 of them with high-risk malignancies and 1 with a immunodeficiency

were transplanted following nonmyeloablative conditioning regimen. Each patient received two cell products, one created by CD34 selection and the other through CD45RA depletion from the CD34- fraction by CliniMACS device.

Results: Graft consisted in a mean of 7×10^6 /kg CD34+ cells/kg ($4,5-9,89 \times 10^6$ /kg), 3×10^5 /kg CD3+ cells/kg ($6,9 \times 10^3-1 \times 10^6$ /kg), 1×10^6 /kg CD45RA+ cells ($1 \times 10^4-4,98 \times 10^6$ /kg) and 7×10^8 /kg CD45RO+ cells ($3,8 \times 10^8-1,9 \times 10^9$ /kg). CD45RA depletion resulted in a mean of 3 log ($2,2-4,29$ log). All six patients engrafted with a mean of 11 days (10-12) and rapidly achieved 100% donor chimerism. No graft failure was observed. Only one patient developed GVHD>II that was sensible to steroids. T-cells led immune recovery. They achieved values higher than 700 cells/mL and 1000 cells/mL at day 30 and 60 respectively. Most of T cells were both CD8+CD45RA- and CD4+CD45RA- T cells (median of $395 \times 10^6/\text{mm}^3$ and $243 \times 10^6/\text{mm}^3$, respectively), while the number of CD8+45RA+ and CD4+45RA+ cells remained low (median of $0,7 \times 10^6$ and $0,07 \times 10^6$ respectively), recapitulating the CD45RA depleted graft composition. A total of 4 patients presented CMV reactivation, but none progressed to disease. With a mean of 100 days of follow up two patients relapsed, both had minimal residual disease positive at haplo-TPH and two patient died, one debt to leukemia progression and one because cardiogenic shock.

Conclusion: CD45RA depleted haplo-HCT is well tolerated with a rapid engraftment, minimal risk of GvHD and an accelerated immunologic reconstitution.

LONG-TERM IMMUNE RECONSTITUTION POST-HEMATOPOIETIC STEM CELL TRANSPLANTATION IN IL2RG/JAK3 SCID, NEWCASTLE EXPERIENCE

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Background: Hematopoietic stem cell transplantation (HSCT) is proven to be curative for severe combined immunodeficiency (SCID).

Objectives: We discuss the outcome of donor chimerism and thymic output for IL2RG/JAK3 SCID post-transplantation at our centre.

Design/Method: A cross-sectional study of IL2RG/JAK3 SCID patients who underwent HSCT from 1987-2012. The conditioning regimens used were reduced intensity conditioning (RIC) (Fludarabine/Melphalan), low toxicity myelo-ablative conditioning (Treosulphan/Fludarabine or Treosulphan/Cyclophosphamide) and myelo-ablative conditioning (MAC) (Busulphan/Cyclophosphamide). CD4+ naïve cells (CD3+CD4+45RA+) measurement was used as an indicator of the thymic output post-transplantation.

Results: Thirty-one of 43 patients with IL2RG/JAK3 SCID survived. The 10-year survival was 71.9%. Median age at last follow up was 10 years old (range 2 – 25). Full donor T cell chimerism (>95% donor cells) was observed for all patients irrespective of donor and conditioning regimen received. However, B cell and myeloid donor chimerism at last follow up was best following low toxicity or myelo-ablative conditioning regimen with matched related (MRD) or matched unrelated donor (MURD) compared to unconditioned and matched sibling donor (MSD) recipients. Most haplo-identical donor recipients have poor myeloid chimerism (<5% donor cells), despite receiving MAC conditioning. Sixteen patients are off IVIG (10 B and myeloid chimerism >50% donor, 6 B and myeloid chimerism <50% donor). Thirteen patients with B and myeloid chimerism <50% donor continue IVIG. The mean CD3+ count at last follow up is highest for those who received MSD and unconditioned transplants. Recipients of low toxicity conditioning have higher CD3+ counts compared to RIC and MAC conditioning, across all types of donor. MSD with unconditioned transplants have the best thymic output at last follow up, followed by MRD and MURD with low toxicity myelo-ablative conditioning.

Conclusion: T cell donor chimerism is not influenced by conditioning or donor types. However, conditioning with MRD or MURD demonstrated better myeloid cell chimerism compared to unconditioned MSD or haplo-identical donor recipients with MAC. Sustained CD3+ output is seen after 20 years post-HSCT for of IL2RG/JAK3 SCID and even though unconditioned MSD recipients have poor myeloid chimerism; they have highest thymic output at last follow up.

POST-TRANSPLANT HEALTH-RELATED QUALITY OF LIFE FOR DIFFERENT SEVERE COMBINED IMMUNODEFICIENCY GENOTYPES

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Background: Many studies have demonstrated evolution of immune-reconstitution, but there are scarce data considering long-term quality of life (QoL), with one study suggesting poor function compared to healthy controls (1).

Objectives: We objectively assessed QoL of SCID survivors at our centre according to their genetic diagnosis.

Design/Method: All SCID patients more than 2 years post-transplant attending the post-transplant clinic follow up were invited to answer the Pediatric Quality of Life Inventory (PedsQL), Generic Score Scale v4.0 questionnaires as part of the routine psychology assessment. The PedsQL questionnaires consist of parent and patient reports, both have 6 domains (physical, emotional, social, school, psychosocial and total).

Results: Fifty-nine of 88 (67%) patients responded; comprising 45/73 (62%) patients aged >5 years and 49/77 (64%) families. Fourteen children aged <5 years old were excluded from the child questionnaires. Twenty-eight patients were not contactable and three refused. The median interval post-HSCT was 11 years (range, 2-27). The proportions of responder according to SCID genotypes were IL2RG/JAK3 SCID (20 of 31, 65%), IL-7Ra Deficiency (10/14, 71%), Adenosine Deaminase (ADA) (12/16, 75%), Artemis (5/7, 71%). QoL for patients with IL2RG/JAK3, IL-7Ra Deficiency and Artemis SCID were not significantly different to published UK norm (Patient Report) in all domains, in contrast to a previous study(1). However, ADA SCID survivors had significantly lower QoL, across all except the emotional components.

Parents of IL2RG/JAK3 SCID reported significantly lower QoL in 3 domains compared to UK normal, whilst parents of ADA SCID reported significantly lower QoL across all except the emotional domain. The QoL scores were not significantly different between IL-7Ra and Artemis deficient SCID (all domains). Parents and children of RAG1/2 SCID reported significantly lower QoL in school domain. Parents of IL2RG/JAK3 SCID with on-going intravenous immunoglobulin therapy reported lower QoL compared to those without the therapy.

Conclusion: In contrast to previously (1), a number of SCID genotypes were associated with normal QoL. Particular risk factors include ADA SCID and need for ongoing medication. Larger qualitative studies are needed to clarify QoL differences in SCID survivors.

References:

1. Titman P et al, Blood, 2008.

VITAMIN D DEFICIENCY AFFECTS OUTCOME IN PEDIATRIC HEMATOPOIETIC STEM CELL TRANSPLANTATION

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Background: Reports indicate that pediatric patients undergoing hematopoietic stem cell transplantation (HSCT) are frequently afflicted by vitamin D deficiency. Whether vitamin D deficiency affects HSCT outcomes in pediatric patients is yet to be proven.

Objectives: To report the prevalence of Vitamin D deficiency in pediatric patients that underwent HSCT and to determine its short term impact on survival.

Design/Method: We reviewed serum 25-hydroxyvitamin D levels performed prospectively before starting HSCT (baseline) and at 100 days after transplantation in children that presented for HSCT from January 2011 to December 2014. We also abstracted demographic, laboratory, co-morbidity and treatment data.

Results: Seventy-two children (39 males and 33 females), with a median age of 9 (range 0.25-22 years) were assessed. At the pre-HSCT stage, the median serum 25-hydroxyvitamin D level 25.5ng/ml (range: 19-34ng/ml) with only 2 patients on supplemental therapy. Forty-five of 72 patients (62.5%) had a suboptimal vitamin D level (< 30 ng/mL) before HSCT and about half had severe vitamin D deficiency (<20 ng/mL). Prevalence did not change after hematopoietic stem cell transplantation (p-value = 0.7) with 63% of the patients having suboptimal (< 30ng/mL) vitamin D levels and 45% having severe vitamin D deficiency (<20ng/mL) at 100 days after transplantation despite supplemental therapy in 74% of subjects. There were no statistically significant associations between low Vitamin D levels prior to HSCT and the development of acute or chronic GVHD, infectious rates or immune recovery. However, severe vitamin D deficiency (<20 ng/mL) at pre-HSCT was associated with decreased overall survival after transplantation (P = .007, 1-year rate of overall survival: 65% versus 92.6%).

Conclusion: Majority of pediatric patients that come to transplant have vitamin D deficient. Vitamin D may play a role in outcomes of pediatric HSCT. Further studies investigating its impact are needed.

THE INBORN ERRORS WORKING PARTY (EBMT) STUDY OF LONG-TERM OUTCOMES OF HAEMATOPOIETIC STEM CELL TRANSPLANTATION IN PATIENTS WITH SEVERE COMBINED IMMUNODEFICIENCIES

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Background: SCIDs are T-, +/-B- and NK-cell maturation/function disorders presenting with life-threatening infections in infancy. HSCT is curative but there are few data on long-term immune function, physical status and quality of life (QoL) outcomes.

Objectives: To gather these missing data.

Design/Method: 183 European SCID patients (using PIDTC definitions¹, and including reticular dysgenesis) transplanted > 20 years ago were identified from SCETIDE registry.

Results: Median age at diagnosis of 0,2 months (range 0-12), at transplant 6,1 months (range 0,4-13,7). 53 had CgC, 17- ADA, 16- JAK3, 14- Artemis, 8- RAG 1/2, 8- AK2, 6- IL7Ra, 2 - other known, 59 - unknown defects. 68 received conditioning (52 with pre-transplant infections), 115- unconditioned HSCTs. 126 had haploidentical, 42- MRD, 9- mMRD, 6- URD. Median last FU was 23,28 years (10,4-42,7). OS was 0,58 (95% CI 0,5-0,66). EFS (deaths, re-transplant considered as events) was 0,46 (95% CI 0,34-0,57). No significant difference in OS (p=0,26) and EFS (p=0,04) in conditioned and unconditioned transplants. 40 patients required second (11 after unconditioned, 29 after conditioned) and 7 third transplants. 69 died <5 years post-transplant (57 had pre-transplant infections), 4 died late after first but early after second and third HSCTs. TRM was 0,32 (95% CI 0,26-0,4) (no difference in conditioned and unconditioned transplants) 49 patients (26,7%) had aGVHD grade 2-4. 26 (14,2%) had cGVHD. 60 were alive with >20 years follow up:- 11 had impaired immune function (8 after conditioned, 3 after unconditioned transplants) with low lymphocyte levels or TRECs or required IVIG/antimicrobial prophylaxis. 19 had persistent warts (CgC/JAK3 12 as previously reported², but also 2 ADA, 1 RAG2, 1 Artemis, 1 IL7Ra, 1 T-B+NK- and T-B- phenotypes). 1 developed malignancy (meningeoma). 4 had autoimmunity (SLE, hemolytic anemia, vitiligo, autoimmune hepatitis). 7 had QoL considered as below normal, 17 patients had university/college education (10 - unknown).

Conclusions: There is no significant difference in OS, EFS and TRM after conditioned and unconditioned HSCTs. Despite missing follow-up data, preliminary analysis demonstrates requirement of further estimate of risk factors for impaired immune function, physical status and QoL in SCID patient's long-term post-HSCT.

References:

1. J Allergy Clin Immunol 2014;133:1092
2. Lancet 2004;363:2051