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Immune-based Therapies for Refractory Pediatric Leukemia
Lia Gore, MD
Shannon Maude, MD PhD
Moderated by: Leslie Kersun, MD MSCE MSEd

Disclosures for Dr. Gore
• Consultant or Advisory role in the past 2 years: Amgen, Celgene, Eisai, Genentech/Roche, GlaxoSmithKline, Jazz, MedImmune, Merck, Meryu, Millennium/Takeda, Novartis, US Food and Drug Administration, US National Cancer Institute
• PI or Sub-Investigator on active clinical trials sponsored by: Agios, Amgen, Astellas, AstraZeneca, Bayer, Boehringer-Ingelheim, Bristol Myers-Squibb, Children’s Oncology Group, Cleave Biosciences, Dana Farber Cancer Institute, Decehpera, Epizyme, Genentech-Roche, GlaxoSmithkline, Immunomedics, Karyopharma, KinexPharma, Kito, Merck, Millennium/Takeda, NANT, Novartis, OncoMed, Onconova, Onyx, Peloton, Pfizer, POETIC, Progen, Raxahn, Sanofi-Aventis, SunPharma, Syndax, US NCI
• Employment: State of Colorado
• Endowed Chairs: Children’s Hospital Colorado
• Spouse Employment and Stock Ownership: Ariad

Objectives / Learning Questions
1. Describe some possible uses and advantages of immunotherapy approaches for childhood ALL and how these approaches differ from conventional chemotherapy regimens.
2. Describe some unique classes of toxicities observed in patients treated with agents targeting the immune response.
(Some) Current Dilemmas in Pediatric Cancer Treatment

• Cure rates are 85-90+% for some types, but <10% for others
  o Minimal progress in the most refractory diseases
• Current therapies are at the limits of dose escalation and intensity
• Most new agents are very “young” and underdeveloped
  o When to introduce new agents to children?
  o In which patient population(s)?

Introduction

• Acute lymphoblastic leukemia (ALL) is the most common cancer in children and cure is risk-factor-dependent
• Although CR rates are high with first-line therapy, they are significantly lower in children with relapsed disease
• Short duration of first remission is a predictor of poor prognosis

Introduction (Cont.)

• HSCT confers a survival benefit, regardless of number of previous lines of treatment, but not all patients have a donor or can get to SCT
• Transplantation, while effective, is not without risks and toxicities
• Novel treatments are needed that may increase the number of children with relapsed/refractory ALL who achieve CR
Chemotherapy Agents Used in Childhood ALL: Year of US FDA Approval

- 6-Mercaptopurine 1953
- Methotrexate 1953
- Prednisone 1955
- Dexamethasone 1958
- Cyclophosphamide 1959
- Vincristine 1964
- Cytosine Arabinoside 1969
- L’Asparaginase 1978
- Daunorubicin 1979
- Clofarabine 2004
- Blinatumomab 2014

Rationale for the use of Immunotherapy in Pediatric ALL

- 10-15% of children with ALL die, mostly due to relapse/refractory disease
- Effector memory T-cells have the potential to kill autologous tumor cells when being directed accordingly
- Durability and control of the immune response directly correlates with disease-free state in many conditions:
  - Infections – cancer - autoimmune disease - organ transplant

"New approaches are needed"……
- Improve outcome for those who don’t do well
- Reduce the burden of therapy for those who do

Blinatumomab as a Lead Example

- CD19 is highly expressed on B cells throughout development in >90% of B-cell–lineage cancers and virtually all childhood precursor B acute lymphoblastic leukemia.
- Blinatumomab is a BiTE® antibody construct that redirects T cells to CD19-expressing B cells.
- In phase 2 studies, single-agent blinatumomab has shown antileukemic activity in adults and children with relapsed/refractory ALL.
Case Study

- 3 year old with developmental delay diagnosed with ALL
  - Treated on COG AALL0331
  - Relapsed < 1 year off therapy
  - Refractory to two re-induction attempts (COG AALL07P4 and clo/cy/etop)
- Now 6 years old, remains non-verbal
- Options?
  - Enrolled on COG AALL1121 (blinatumomab)

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Case Study

- Started treatment at 5 mcg/m2/day
- At ~ hour 18, developed fever to 38.7, flushing
- At hour 20, developed gr 1-2 hypotension
- Labs show grade 2 ALT, AST, elevated PT, PTT, decreased fibrinogen
- At hour 24, patient more somnolent, less interactive, but more combative when awake
Case Study – What to do?

• Do nothing?
• Stop infusion?
• Start steroids?
• Culture? Tap? Start antibiotics?
• Give volume?
  ○ What kind?
• Image liver?
• Image brain?

Case Study – What to do?

• Do nothing? No
• Stop infusion? No
• Start steroids? Yes: Dex 4 mg IV q 6 hours x 24 h
• Culture? Tap? Start antibiotics? Yes, No, Yes: Broad spectrum (Cefpime)
• Give volume? Yes
  ○ What kind? Vitamin K, albumin and platelets
• Image liver? Maybe – we didn’t
• Image brain? Maybe – we didn’t

Case Study – Tox Management

• Grade 2 neurotox:
  ○ Steroids can be very helpful
    • Use for as short a time as possible -- no need to taper if less than 5-7 day course
  ○ May need to stop infusion, start anti-sz prophylaxis if not responding to steroids quickly
  ○ May restart @ 5 mcg/m2/day dose without escalation if < grade 4 if resolves w/in 14 days

Case Study – Tox Management (Cont.)

• Grade 2 and higher CRS:
  ○ Steroids ok once the tox develops
  ○ Consider tocilizumab
• Grade 3 DIC/TTP/HUS:
  ○ Supportive care with vitamin K, blood product/factor support, albumin per institutional preference
  ○ May restart and dose escalate
Efficacy of Children Treated with Blina for all Patients Treated at 5/15 Dose

<table>
<thead>
<tr>
<th>Patients* (N=79)</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>All patients with CR within the first two cycles, n (%)</td>
<td>27 (35)</td>
</tr>
<tr>
<td>M1 marrow, full recovery of peripheral blood counts</td>
<td>12 (17)</td>
</tr>
<tr>
<td>M1 marrow, incomplete recovery of peripheral blood counts</td>
<td>10 (14)</td>
</tr>
<tr>
<td>M1 marrow, neither full nor incomplete recovery of peripheral blood counts</td>
<td>5 (7)</td>
</tr>
<tr>
<td>Hematologic or a cellular marrow</td>
<td>2 (3)</td>
</tr>
<tr>
<td>Partial remission</td>
<td>4 (6)</td>
</tr>
<tr>
<td>Nonresponders, n (%)</td>
<td>10 (14)</td>
</tr>
<tr>
<td>Progressive disease</td>
<td>2 (3)</td>
</tr>
<tr>
<td>No response</td>
<td>21 (30)</td>
</tr>
<tr>
<td>No response data available, n (%)</td>
<td>6 (9)</td>
</tr>
<tr>
<td>MRD response in patients who achieved remission within the first two cycles of treatment, n (%)</td>
<td></td>
</tr>
<tr>
<td>MRD response (MRD &lt; 10^-5)</td>
<td>13/27 (48)</td>
</tr>
<tr>
<td>Complete MRD response</td>
<td>13/27 (48)</td>
</tr>
<tr>
<td>No MRD response</td>
<td>12/27 (44)</td>
</tr>
<tr>
<td>No MRD data available</td>
<td>2/27 (7)</td>
</tr>
</tbody>
</table>

*All subjects treated at 5-15 μg/m²/day in Phase 1 and 2.

Efficacy and Ability to Proceed to Stem Cell Transplant for 10 Subjects < 2 Years Old

<table>
<thead>
<tr>
<th>Patients* (n=10)</th>
</tr>
</thead>
<tbody>
<tr>
<td>All patients with CR within the first two cycles, n (%)</td>
</tr>
<tr>
<td>M1 marrow, full recovery of peripheral blood counts</td>
</tr>
<tr>
<td>M1 marrow, incomplete recovery of peripheral blood counts</td>
</tr>
<tr>
<td>M1 marrow, neither full nor incomplete recovery of peripheral blood counts</td>
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<tr>
<td>Nonresponders, n (%)</td>
</tr>
<tr>
<td>Progressive disease</td>
</tr>
<tr>
<td>No response</td>
</tr>
<tr>
<td>MRD response (MRD &lt; 10^-5) in patients who achieved remission within the first two cycles, n (%)</td>
</tr>
<tr>
<td>Received HSCT</td>
</tr>
</tbody>
</table>

Adverse Events Grade ≥ 3 Regardless of Relationship to Treatment Occurring in ≥ 10% of Pediatric Subjects

<table>
<thead>
<tr>
<th>Patients (N = 79)*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any adverse events grade ≥3, n (%)</td>
</tr>
<tr>
<td>Anemia</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
</tr>
<tr>
<td>Febria neutropenia</td>
</tr>
<tr>
<td>Hypokalemia</td>
</tr>
<tr>
<td>Neutropenia</td>
</tr>
<tr>
<td>Alkaline aminotransferase increased</td>
</tr>
<tr>
<td>Platelet count decreased</td>
</tr>
<tr>
<td>Pyrexia</td>
</tr>
<tr>
<td>Neutrophil count decreased</td>
</tr>
<tr>
<td>Aspartate aminotransferase increased</td>
</tr>
<tr>
<td>Leucopenia</td>
</tr>
<tr>
<td>White blood cell count decreased</td>
</tr>
</tbody>
</table>

*All patients treated at 5-15 μg/m²/day in Phase 1 and 2.

Toxicities of Special Interest with Blinatumomab – Phase I/II results

**Cytokine Release Syndrome (CRS) in 8 pediatric patients (11%)**
- Grade ≥ 3: 4 (6%) patients
  - 3 grade 3; 1 grade 4

**Neurologic Events**
- Grade ≥ 3: 4 patients (6%)
  - Somnolence (n = 2), neuralgia (n = 1), and confusional state (n = 1)
- Neurologic events leading to temporary treatment interruption:
  - 2 patients with grade 2 seizure

*Per CTCAE v4.0*
Blinatumomab Induces Transient Cytokine Elevation

Cytokine Concentrations (Mean ± SD) Under Blinatumomab Continuous IV Infusion (Cycle 1, Week 1)

<table>
<thead>
<tr>
<th>Cytokine</th>
<th>Baseline</th>
<th>2 Hours</th>
<th>4 Hours</th>
<th>24 Hours</th>
<th>48 Hours</th>
</tr>
</thead>
<tbody>
<tr>
<td>IL-2</td>
<td>107</td>
<td>43.4 ± 13.3</td>
<td>111 ± 4.8</td>
<td>38.3 ± 12.8</td>
<td>10.8 ± 1.8</td>
</tr>
<tr>
<td>IL-6</td>
<td>16.5 ± 25.7</td>
<td>59.1 ± 180</td>
<td>949 ± 200</td>
<td>4530 ± 15500</td>
<td>1510 ± 250</td>
</tr>
<tr>
<td>IL-10</td>
<td>16.7 ± 21.6</td>
<td>152 ± 228</td>
<td>603 ± 976</td>
<td>754 ± 1390</td>
<td>260 ± 570</td>
</tr>
<tr>
<td>IFN-α</td>
<td>10</td>
<td>3.8 ± 78.3</td>
<td>191 ± 547</td>
<td>352 ± 581</td>
<td>115 ± 414</td>
</tr>
<tr>
<td>TNF-α</td>
<td>10</td>
<td>93.7 ± 229</td>
<td>40.2 ± 63.3</td>
<td>16.7 ± 5.11</td>
<td>10</td>
</tr>
</tbody>
</table>

*Values below the Limit of Detection (<LOD: 20 pg/mL) were set at 1% LOD (10 pg/mL) before analysis.

Summary of Blinatumomab and Other Newer Era Treatments Today

- Immune-based therapies have anti-leukemic activity in very heavily pretreated pediatric subjects with relapsed/refractory ALL, including the ability to induce MRD negative remissions

- Adverse events associated with immunotherapies can include life-threatening cytokine release and neurologic toxicities
  - Generally reversible and can be managed with meticulous/intensive supportive care measures

Case Study – Do NOT Stop Infusion for:

- Cytopenias
  - Usually nadir within first week, and recover after that, IF anti-leukemic response occurs

- Chemical lab abnormalities without clinical relationship or findings
  - Especially transaminase elevation in the absence of clinical symptoms, hyperbilirubinemia or other problems suggestive of typhlitis, VOD

Summary of Blinatumomab and Other Newer Era Treatments Today (Cont.)

- Role of blinatumomab and other novel therapies have the potential to provide a bridge to HSCT for some children with highly refractory ALL with minimal toxicities
Acknowledgements

• The CHCO and Amgen Teams
• The participating Investigators and Clinical teams
• The patients and families who entrust their care to us

Acknowledgements

• COG AALL1121 Investigators, participants, and sponsors
  • Jim Whitlock and Steve Hunger
• Children’s Hospital Colorado Experimental Therapeutics Team and Center for Cancer and Blood Disorders
  o Meg Macy, MD
  o Kelly Maloney, MD
  o Carreye Cool, MD
  o Katie Dorris, MD
  o Debra Schissel, RN
  o Cheri Adams, RN
  o Angie Peltz, PA-C
  o Seda Carlton
  o Gentry Greene
  o Pam Bowry, CCRA, MBA

• University of Colorado Cancer Center and Developmental Therapeutics and Heme Malignancies Teams
  o Gail Eckhardt, MD
  o Craig Jordan, PhD
  o 78 NPs, RNs, MDs, CRAs and research nurses
• Funding:
  o Alex’s Lemonade Stand
  o The Clark and Ergen Family Chairs in Pediatric Cancer Therapeutics
  o The Morgan Adams Foundation
  o NCI/NIH

Disclosures for Dr. Maude

• Advisory role in clinical trial development for Novartis
  • CTL019 licensed by Novartis
  • Sponsor holds patent for technology

Chimeric Antigen Receptor (CAR)
CAR T cell Engineering

• Lentiviral vector introduces gene encoding CAR into T cell

• CAR links extracellular antibody to intracellular T cell signaling domains

• T cells expanded ex vivo

• Reinfused → come in contact with antigen

• Persistent CART19 (CTL019) cells may allow long-term disease control
CTL019 Proliferation and Efficacy

CTL019 experience in ALL
Pediatric ALL phase 1/2a study

Study population (N = 48):
• Multiply relapsed (≥ 2nd relapse) or refractory
• Majority refractory to chemotherapy
• 2/3 relapsed post allo BMT

Response rate:
• 45/48 (94%) in complete remission at 1 month

Patient Selection

Think about CAR T cell therapy in
• 2nd or greater relapse
• Relapse post SCT
• Refractory ALL

Think twice in
• Conditions likely to preclude infusion
  o Pre-existing organ dysfunction
  o Uncontrolled infection
  o Rapidly progressive disease

Timing of Leukapheresis

Known eligible:
- Relapsed/refractory
  - Relapsed after allo SCT
  - Not eligible for allo SCT
  - Refractory to multiple therapies
- Reserve for patients in need
- Intensive therapy may limit T cell expansion
- May be difficult to stabilize patient

Potentially eligible:
- High-risk disease
- Primary induction failure
- Early BM relapse
- High-risk cytogenetics
- Better T cell growth
- Unnecessary procedure
(Not your typical) Enrollment process

Enrollment
- Screening
- Leukapheresis

Manufacture

• Stabilization

• Infusion

CTL019

Patient Stabilization

Between screening and infusion

• Goals:
  - Prevent rapid progression
  - Avoid organ toxicity and infectious complications
  - NOT to induce remission or reduce disease burden

• Options:
  - Maintenance or low intensity chemotherapy
  - Hydroxyurea

CTL019 Infusion

- Premedication:
  - Tylenol and Benadryl

- Infusion:
  - Cell product thawed per Stem Cell Lab SOPs
  - Outpatient infusion center
  - Infused over 2 minutes by trained staff
  - Vital signs monitored every 15 minutes for 1 hour
  - Acute infusional toxicities rare

Cytokine Release Syndrome

CRS is related to T cell expansion and is likely necessary for efficacy

• Symptoms typically occur 1-14 days after CTL019 cell infusion in ALL
  - Fever
  - Myalgias
  - Nausea/Vomiting
  - Respiratory insufficiency
  - Renal insufficiency
  - Coagulopathy

• Severity scales with disease burden
### Case #1

**9 year old female with multiply relapsed ALL**

**ALL History**
- MUD PSCT for induction failure
- Relapsed post SCT
- Responded to reinduction

<table>
<thead>
<tr>
<th>Timing</th>
<th>Key events</th>
</tr>
</thead>
<tbody>
<tr>
<td>Month -2</td>
<td>T cells collected (one week after completing reinduction chemotherapy)</td>
</tr>
<tr>
<td>Week -1</td>
<td>Received lymphodepleting chemotherapy (fludarabine/cyclophosphamide)</td>
</tr>
<tr>
<td>Day -1</td>
<td>Disease evaluation showed 5% blasts in bone marrow, no peripheral blasts</td>
</tr>
</tbody>
</table>

### Case #2

**22 year old male with 1st relapse of ALL**

**ALL History**
- 1st relapse in maintenance therapy
- Refractory to reinduction chemotherapy and clofarabine/cytarabine

<table>
<thead>
<tr>
<th>Timing</th>
<th>Key notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Month -2</td>
<td>T cells collected after failed reinduction</td>
</tr>
<tr>
<td>Month -1</td>
<td>Started hydroxyurea</td>
</tr>
<tr>
<td>Week -1</td>
<td>Received lymphodepleting chemotherapy (fludarabine/cyclophosphamide)</td>
</tr>
<tr>
<td>Day -1</td>
<td>Disease evaluation showed 97% blasts in BM, no peripheral blasts</td>
</tr>
</tbody>
</table>
Case #2 - Coagulopathy

Toxicity

- Cytokine Release Syndrome (CRS)
  o Correlates with T cell proliferation and efficacy
  o Severity related to disease burden
  o Reversed with novel approach – cytokine blockade

- Cytopenias
  o Likely related to inflammatory process and bone marrow reserve

- Neurotoxicity
  o Seen in several CD19 immunotherapy trials: NCI, CHOP/UPenn, MSKCC, Seattle, Blinatumomab
  o In our experience - generally untreated, fully resolves

- Chronic B cell aplasia requiring Ig replacement

Severe CRS management

- Supportive Care
  o Vasopressors
  o O2, CPAP, ventilation
  o Blood products (FFP, cryo)

- Lympholytics
  o Steroids tried with some effect but potential to reduce efficacy

- Cytokine-directed therapy
  o IL-6 noted to be very elevated
  o Anti-IL-6 therapy highly effective with no apparent effect on efficacy

Disease Burden Correlates with CRS Severity

- Risk of severe CRS higher with >50% blasts
- Minimal risk with <5% blasts

Grupp et al. NEJM 2103
Long-term outcomes

Pediatric ALL phase 1/2a study (N = 48):
- 45/48 (94%) in complete remission at 1 month
- 13 patients in remission ≥1 year, 10 without further therapy
- Median follow-up 8 months, range 1-36 months
- 15 relapses, 5 CD19(+) and 10 CD19(-)
- 5 patients proceeded to SCT

CTL019 Persistence


Disease-free and Overall Survival

Long-term Management

- B cell aplasia:
  - Monthly IVIG
  - Or subcutaneous immunoglobulin
- Follow-up:
  - 1st year
  - Close follow-up for CTL019 persistence and relapse
  - Long-term
  - 15-year follow-up for gene therapy
Comparing CD19 CARs for Leukemia

CAR design important for persistence and sustained efficacy

<table>
<thead>
<tr>
<th>Vector</th>
<th>Retention*</th>
<th>Retention*</th>
<th>Lenvima*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Retroviral</td>
<td>90%</td>
<td>80%</td>
<td>90%</td>
</tr>
<tr>
<td>Lentiviral</td>
<td>30 Days</td>
<td>30 Days</td>
<td>&gt;3 years</td>
</tr>
</tbody>
</table>


What is the potential for cellular immunotherapy?

- Induce deep remission in relapsed patients refractory to chemotherapy
- With adequate persistence, can we achieve long-term remissions?

Expanding access
- FDA Breakthrough Designation for CTL019, 1st indication is pediatric ALL
- CTL019 multisite trial open at >10 sites in US, Canada, and Australia
- Moving into upfront therapy for VHR subsets at high risk of relapse

THANK YOU!

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ASPHO’s Compensation Survey Preview Webinar
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