**Stem Cell Transplantation**

**Mike Pulsipher**

1. A 14-year-old girl with high-risk relapsed acute myelogenous leukemia is a member of a large family and has five HLA-matched siblings. The patient is blood group O+ and is cytomegalovirus (CMV) seronegative.

Which sibling would be the best donor?

A. 16-year-old sister, CMV negative, blood group O+

B. 12-year-old brother, CMV positive, blood group A+

C. 2-year-old brother, CMV negative, blood group O+

D. 14-year-old identical twin sister, CMV negative, blood group O+

E. 22-year-old pregnant sister, CMV negative, blood group A+

**Explanation**

The correct answer is A. When considering optimal stem cell donors, after HLA matching there are a host of other factors to consider. In general, younger donors are preferred. The thought is that a younger patient has had less antigenic exposure, and therefore his or her immune cells will be less immunogenic. Because there is evidence that receiving stem cells from a female donor who has had children increases the risk of graft-versus-host disease (GVHD) in the recipient, donors with a history of multiple pregnancies are generally avoided. Donation from a pregnant donor is inappropriate because it may put the donor or the donor’s child at unnecessary risk. Blood type is not a major factor, but when all factors are equal, having similar blood groups is preferable. A syngeneic donor (identical twin) in acute myelogenous leukemia leads to outcomes similar to an autologous bone marrow transplant and would never be used when matched nonsyngeneic siblings are available. Finally, with regard to CMV infection, patients at highest risk are themselves CMV seropositive or patients who are CMV seronegative and receive stem cells from a donor who is CMV seropositive. Using these criteria, the best donors are answers A and C. However, donor C is only 2 years old, and therefore it would be difficult to harvest enough bone marrow stem cells to avoid graft failure. Therefore, answer A, the 16-year-old sister who is CMV negative, is the best choice.

2. An 8-year-old boy with acute myelogenous leukemia (AML) 6 months after transplant comes to the clinic complaining of an erythematous maculopapular rash on his arms and legs; dry, irritated eyes; and a persistent cough. His mother has noticed that he gets winded much more quickly than he used to and has difficulty climbing the stairs.

Which of the following tests is most essential for choosing optimal therapy?

A. Blood polymerase chain reaction (PCR) for cytomegalovirus

B. Skin biopsy

C. Pulmonary function tests and high-resolution CT

D. Galactomannan and beta-D-glucan tests for fungus

E. Upper GI endoscopy

**Explanation**

The correct answer is C. Chronic graft-versus-host disease (GVHD) typically develops between 3 and 6 months after a hematopoietic stem cell transplant. Rash and dry eyes suggest chronic GVHD, but a biopsy is only confirmatory, and the patient could be treated clinically without the biopsy. The cough, shortness of breath, and exertional dyspnea are very concerning for chronic GVHD of the lungs, specifically bronchiolitis obliterans. It is important to make the diagnosis quickly, because it requires systemic therapy, whereas the eyes and skin could possibly be treated with local therapy alone. Pulmonary function tests and a high-resolution CT can significantly aid in the diagnosis of pulmonary GVHD. Diagnostic investigation and prompt treatment are urgent. Further pulmonary workup after the CT to rule out infection may be necessary if the patient has symptoms or findings consistent with infection.

3. A 12-year-old child with acute myelogenous leukemia develops conjugated hyperbilirubinemia (6.8 mg/dL) and fluid retention on day 9 after a sibling donor transplant.

Which test would be appropriate to identify the cause of the hyperbilirubinemia?

A. CT scan of the abdomen

B. Abdominal ultrasound with Doppler measurements of portal blood flow

C. Hepatobiliary iminodiacetic acid scan of the gallbladder

D. Upper GI endoscopy

E. Immediate liver biopsy

**Explanation**

The correct answer is B. Veno-occlusive disease (sinusoidal obstructive syndrome) typically occurs within the first 30 days after stem cell transplantation. Clinical signs include conjugated hyperbilirubinemia, weight gain, right upper quadrant abdominal pain, platelet consumption, and renal dysfunction. Reversal of flow in the portal vein is a common finding and is best observed on an abdominal ultrasound with Doppler. Liver biopsy is hazardous because of coagulopathy and is seldom used.

4. A 2-year-old child presents with high fevers, pancytopenia, and organomegaly. Bone marrow aspirate and biopsy are remarkable for stromal macrophages containing numerous red blood cells in the cytoplasm. Laboratory studies identify the patient to have a bi-allelic mutation in the perforin gene.

What is the most appropriate plan of action?

A. Treat with immunosuppression.

B. Treat the child with chemotherapy then watch closely for relapse; consider hematopoietic stem cell transplantation if the child relapses.

C. Perform hematopoietic stem cell transplantation as soon as possible with the best available donor.

D. Perform hematopoietic stem cell transplantation with the best available donor after disease is controlled with appropriate therapy.

E. Treat the child with hematopoietic growth factors and transfusion support.

**Explanation**

The correct answer is D. The child has familial hemophagocytic lymphohistiocytosis (HLH). Children with HLH have worse outcomes if they undergo transplantation while they have poorly controlled disease because of the highly proinflammatory environment associated with HLH. The child has a clear genetic basis for the disease and therefore will need hematopoietic stem cell transplantation to restore normal NK cell function. Disease status can be monitored by improvement of fever, hepatosplenomegaly, and pancytopenia. Patients with HLH also have markedly elevated serum ferritin and IL-2R levels and often have abnormal liver enzymes. These laboratory studies can be used to monitor disease status.

5. A 6-year-old child with a history of acute myelogenous leukemia comes to your clinic for routine follow-up 60 days after a matched unrelated stem cell transplant. The child is being treated with tacrolimus for graft-versus-host disease (GVHD) prophylaxis. The child is hypertensive and has proteinuria. The child is on a high dosage of steroids for treatment of GVHD, and she has had a good response but has a mildly elevated unconjugated bilirubin, her creatinine is up, and her platelets have fallen.

Which test is most likely to yield a diagnosis?

A. Kidney biopsy

B. Skin biopsy

C. LDH, haptoglobin, and examination of smear for schistocytes

D. Renal ultrasound

E. CT examination of the abdomen

**Explanation**

The correct answer is C. Transplant-associated thrombotic microangiopathy (TA-TMA) is a significant complication of hematopoietic stem cell transplantation (HSCT). TA-TMA belongs to the family of thrombotic microangiopathies including hemolytic uremic syndrome and thrombotic thrombocytopenic purpura. TA-TMA occurs when endothelial damage resulting from HSCT causes microangiopathic hemolytic anemia and platelet consumption, resulting in thrombosis and fibrin deposition in the microcirculation. The kidney is most commonly affected. Patients present with anemia, thrombocytopenia, schistocytes on blood smear, elevated LDH, and decreased haptoglobin. Calcineurin inhibitors, sirolimus, total body irradiation, high-dose busulfan, and infections may be potential risk factors for the development of TA-TMA.

6. A 3-year-old child with a history of acute lymphoblastic leukemia (ALL) presents with high fevers and low blood pressure 9 days after an unrelated donor hematopoietic stem cell transplant (HSCT). The child has significant mucositis, gastrointestinal distension, and abdominal pain.

Which is the most likely infection that is causing the fever?

A. Adenovirus

B. Cytomegalovirus (CMV)

C. Pneumocystis

D. Aspergillus

E. Gram-negative bacteria

**Explanation**

The correct answer is E. Early in the transplant process (before a patient engrafts), the patient’s greatest immune system defects are neutropenia, mucositis, and the presence of a central line. The high-incidence infections during this period are predominantly bacterial and some fungal infections. Of the viral pathogens, only herpes simplex virus (HSV) is typically seen during this period. Because most HSCT centers use some sort of antiviral prophylaxis (eg, acyclovir) during this period, it is very rare to see active HSV infections at this time. Therefore, the best answer is gram-negative bacteria. Infection with gram-negative bacteria is common after transplant, particularly at times when the mucosal barrier of the gut is disrupted and the patient is severely neutropenic. Interestingly, after a patient has neutrophil engraftment, which also coincides with resolution of mucositis, the incidence of bacterial infections decreases dramatically and the incidence of viral infections (adenovirus, CMV, varicella zoster virus) and aspergillus infections increases. This is no doubt a result of continued lymphopenia and use of lymphocyte-specific immunosuppression such as calcineurin inhibitors and the development of graft-versus-host disease in some patients, which requires further immunosuppressive therapy.

7. A 12-year-old girl is doing well 21 days after a hematopoietic stem cell transplant (HSCT). She is on tacrolimus and mycophenolate for graft-versus-host disease prophylaxis. Over 2 days she develops high blood pressure that is refractory to medication. On the third day she has a 2-minute tonic-clonic seizure.

What is the most useful investigation at this time?

A. MRI of the head

B. CT of the head

C. Lumbar puncture

D. Renal ultrasound

E. EEG

**Explanation**

The correct answer is A. Posterior reversible encephalopathy syndrome (PRES) is a syndrome characterized by headache, confusion, seizures, and visual loss and is most often caused by malignant hypertension. For patients with HSCT, intractable hypertension and the associated PRES have been linked to the use of calcineurin inhibitors (tacrolimus or cyclosporine). The diagnosis of PRES typically is made with MRI imaging of the brain, which reveals a characteristic pattern of enhancement, commonly in the posterior circulation. The findings of PRES may be seen on CT but are better visualized with MRI.

8. You are treating a 12-year-old boy with relapsed acute myeloid leukemia with a haploidentical T-cell-depleted allogeneic hematopoietic stem cell transplant (HSCT) from his father. At day +55 you note painless cervical adenopathy.

What should your workup and treatment plan include?

A. Blood culture, a throat swab, and antibiotics covering oral flora

B. Serum Epstein-Barr virus (EBV) titers, a PET scan, and therapy with rituximab if EBV titers are elevated

C. A biopsy of the mass followed by withdrawal of immune suppression to stimulate a graft-versus-leukemia effect

D. Serum CMV titers followed by ganciclovir therapy if elevated

E. Serum galactomannan and beta glucan testing followed by broad-spectrum antifungal therapy

**Explanation**

The correct answer is B. Although the scenario of throat infection causing cervical adenopathy is possible, no throat pain or painful adenopathy is noted. Given the risk of posttransplant lymphoproliferative disease (PTLD) in a patient receiving haploidentical HSCT, EBV-lymphoproliferative disorder (EBV-LPD) should be considered; therefore, assessment for EBV titers is vital. Further staging for posttransplant EBV-LPD includes a PET scan. Treatment in the setting of posttransplant rising EBV titers can be initiated before any visible disease is noted and would be initiated if positive in this case. A biopsy is sometimes performed if there is a question about relapsed disease or if more definitive confirmation of LPD is needed. Therapy for EBV-LPD involves the use of rituximab and decreased immune suppression if possible. More intense therapy with cyclophosphamide or other agents is sometimes necessary, and cytotoxic T-lymphocytes against EBV are also useful therapy when available. It is unlikely that fungal or CMV infections would present with cervical adenopathy.

9. A 4-year-old boy with Wiskott-Aldrich syndrome who is day +60 after cord blood transplantation presents with a hemoglobin of 6. Donor blood type was O+, recipient was A–. He has been transfusion independent for several weeks, WBC and platelets are normal, and LDH is 1,550. The patient has 100% donor chimerism.

Which of the following is the best combination of potential causes and treatments?

A. Posttransplant autoimmune hemolytic anemia. The patient should be assessed for anti-RBC antibodies and signs of hemolysis. Treatment considerations include steroids and rituximab.

B. Pure red cell aplasia due to switching blood types. Isohemagglutinin titers should be assessed, and the patient should be treated with steroids.

C. Autoimmunity from his Wiskott-Aldrich syndrome. Patient should be treated with steroids, and splenectomy should be considered if symptoms persist.

D. Drug-induced hemolysis from cyclosporine. The patient should be weaned from cyclosporine and started on other immune-suppressive agents.

E. Late rejection. Chimerism should be assessed and immune suppression should be tapered to stimulate T-cell function and assist in salvaging the graft.

**Explanation**

The correct answer is A. Autoimmune hemolytic anemia occurs after transplant and more often occurs after cord and possibly after immune deficiency transplant. Steroids and rituximab are well-established therapies for this. Answer B is not correct because a switch from type A to O should not cause hemolysis due to persistent anti-A titers. Answer C is not correct because the autoimmunity is really in the context of the transplant, and splenectomy is not an appropriate therapy at this stage of the disease. Answer D is not correct because cyclosporine has not been shown to be associated with hemolysis. Hemolysis can be caused by a number of other drugs, which should be considered. Finally, for answer E, with the other counts intact and a high LDH, this is unlikely to be graft failure.

10. All of the following conditions in a patient should prompt consideration of cancelation of transplantation or use of a minimal or reduced-intensity regimen *except* which of the following?

A. Direct bilirubin of 3.0

B. Karnofsky/Lansky score of 50%

C. Corrected DLCO of 52%

D. GFR of 70%

E. Cardiac ejection fraction of 45%

**Explanation**

The correct answer is D. For answer A, the risk of veno-occlusive disease/sinusoidal obstruction syndrome is markedly increased when bilirubin is elevated above 2, and total body irradiation/busulfan approaches need to be modified. For answer B, a Karnofsky score less than 80% should prompt consideration and less than 60 definitely result in modification of myeloablative approaches. For answer C, FEV1, FVC, and DLCO corrected less than 60 markedly increase risk of complications with myeloablative approaches. For answer D, most transplant centers allow patients with GFR above 60 to undergo full-intensity approaches. For answer E, cardiac ejection fraction less than 50% is associated with significant risk.

11. An 11-year-old with B-cell acute lymphoblastic leukemia (B-ALL) who is 8 months from a total body irradiation–based matched unrelated donor transplant and off immune suppression has an elevated WBC of 20,000/μL along with circulating peripheral blasts.

What treatment options offer the best chance of long-term remission?

A. Reinduction with an intensive relapse regimen followed by second bone marrow transplant from a different donor if minimal residual disease (MRD)-negative remission can be obtained

B. Treatment with blinatumomab

C. Treatment with chemotherapy followed by donor lymphocyte infusions

D. Collection of T cells from the patient followed by bridging chemotherapy and infusion of tisagenlecleucel after lymphodepleting chemotherapy once the patient goes into remission

E. Treatment with inotuzumab

**Explanation**

The correct answer is D. Relapse of B-ALL after transplant is challenging to treat, and traditional intensive reinduction regimens lead to remission only 40% to 50% of the time. Second hematopoietic stem cell transplant (HSCT) is not likely to be successful unless patients achieve an MRD-negative remission, but with chemotherapy alone they are not likely to be able to get to HSCT. In addition, relapse after second HSCT is very high. Treatment with blinatumomab when patients are in a full relapse results in remission only 40% of the time and may not be sustained long term for patients who relapse after transplant. Similarly, treatment with inotuzumab results in remission in up to 60% of patients, but remissions are not sustained without a second HSCT. Tisagenlecleucel, a 4-1BB based chimeric antigen receptor T-cell product, puts 80% to 90% of patients into remission, with sustained remissions at 1 year noted in half of the patients without further therapy. Tisagenlecleucel is approved by the Food and Drug Administration for the treatment of multiply relapsed or refractory CD19+ B-ALL in patients up to age 25.

12. A 16-year-old who underwent hematopoietic stem cell transplant with a matched sibling donor for chronic myelogenous leukemia (CML) resistant to dasatinib and nilotinib is noted to have detectable BCR-ABL 5 months after transplant. The patient is on 100 mg twice daily of cyclosporine and has no graft-versus-host disease (GVHD).

What is the best treatment option?

A. Keep the immune suppression stable and start a second-generation tyrosine kinase inhibitor (TKI).

B. Wean immune suppression quickly, and if no GVHD, give escalating doses of donor lymphocyte infusions until the BCR-ABL disappears.

C. Wean off immune suppression and give chemotherapy followed by donor lymphocyte infusion (DLI).

D. Continue immune suppression and start a third-generation TKI.

E. Treat with interferon to enhance graft-versus-leukemia effect.

**Explanation**

The answer is B. CML is very sensitive to immune therapy manipulation and DLI. Because this was a matched sibling transplant, the first step should be to wean immune suppression. Starting a second-generation TKI is not likely to help because the patient has been noted to be resistant to two second-generation TKIs. A third-generation TKI could help, but weaning immune suppression should be done first, and side effects can be problematic. For a young patient with a sibling donor, DLI is an effective therapy in CML, and if given in sequential escalating doses, it generally is safe and effective.

13. What is the best infusion product for a 10-year-old Hispanic girl undergoing hematopoietic stem cell transplant for relapsed T-cell acute lymphoblastic leukemia (T-ALL) in second complete remission?

A. Two cord blood units, the first unit a 5/6 match with a total nucleated cell (TNC) count of 5 × 107/kg recipient weight (CD34+ count 0.2 × 106/kg) and the second unit a 4/6 match with a TNC of 2.5 × 107/kg (CD34+ count 0.23 × 106/kg)

B. A haploidentical family T-cell–depleted donor with a CD34+ count of 2 × 106/kg and a CD3+ count of 1 × 106/kg

C. A single cord unit 5/6 match with a count of 4 × 107/kg (CD34+ count 0.2 × 106/kg)

D. A 7/8 allele (8/10 including HLA DQB1, 9/12 including HLA DQB1 and DPB1) unrelated donor with a bone marrow cell dose of 4 × 106 CD 34+ cells/kg and 2 × 107 CD3+/kg

E. A partially mismatched sibling donor with a C/DRB1 crossover (5/6 or 6/8 match) with a CD34+ dose of 6 × 106 CD34+ cells/kg and a CD3+ dose of 4 × 107/kg

**Explanation**

The correct answer is C. Answer A has an excellent cell dose with the combination of 2 cord units, although one of the single units had a cell count greater than 4 × 107/kg and would be adequate, with no advantage to giving the second unit. Answer B shows a haplo T-cell–depleted donor who should have a much higher CD34+ count (doses closer to 10 × 106 CD34+ cells/kg are preferred, and the T-cell dose is too high [maximum 1 × 105/kg]). Answer C is a single cord unit with an appropriate dose and thus is the correct answer. Answer D is an unrelated donor, and although they are a 7/8 match, they have DQ and DP mismatches. When 7/8 donors have additional mismatches at DP or DQ, the risk of transplant-related mortality and graft-versus-host disease is increased. Finally, answer E is a crossover sibling donor with a C and DR mismatch. This donor would be appropriate only if treated like a haplo donor. Sibling donors with a single HLA crossover (A or DRB1) can be considered for use in bone marrow transplant and have outcomes similar to fully matched unrelated donors.

14. You are collecting autologous peripheral blood stem cells from a teenaged patient with a relapsed brain tumor. You are treating the patient with daily G-CSF at 10 µg/kg and testing the peripheral blood CD34+ count daily as the patient recovers from salvage chemotherapy. The absolute neutrophil count is now 5,000/µL and CD34+ count is 5/µL.

How should you proceed?

A. Proceed with collection because counts have recovered.

B. Double G-CSF, add GM-CSF, and wait for a rise in CD34+ count before beginning collection.

C. Continue the G-CSF dosage as is, add plerixafor in the evening, and collect the next morning.

D. Do not attempt to collect. Stop the G-CSF and after a period of time do a collection with plerixafor alone.

E. Allow the patient to recover from chemotherapy and then do a mobilization with G-CSF without chemotherapy.

**Explanation**

The correct answer is C. Answer A is not appropriate; with precollection numbers less than 20 CD34+ cells/μL it is unlikely that sufficient cell numbers will be collected with the procedure. Doubling the G-CSF and adding GM-CSF (answer B) may improve CD34+ numbers, but adding plerixafor in the evening (answer C) will markedly improve collection numbers, probably making it so that the next day there will be sufficient numbers for collection. Answer D is not a good idea, because collecting with plerixafor alone does not yield CD34+ numbers as high as G-CSF/plerixafor combinations, and G-CSF alone mobilization can work, but when someone fails to mobilize with chemotherapy, using G-CSF alone is less effective than a combination of G-CSF and plerixafor.

15. Your patient presents with a diffuse rash on the trunk and extremities, including palms and soles on day +16 after cord blood transplant. Liver function tests are normal; weight is stable; oxygen saturation is normal; the patient is not eating; and stool output includes 2 small, loose stools per day.

How should you proceed?

A. Treat with 2 mg/kg prednisolone and wean after 3 days for engraftment syndrome.

B. Obtain a skin biopsy, because this is probably a drug rash or viral exanthem.

C. Treat with topical steroids alone.

D. Treat with both IV and topical steroids and follow closely for response, increasing therapy if the rash worsens or does not resolve within a week.

E. Push the patient’s trough level of cyclosporine to the high end of the therapeutic range for graft-versus-host disease (GVHD).

**Explanation**

The correct answer is D. Engraftment syndrome can mimic acute GVHD and happens more often with cord blood transplant. It generally happens early after transplant (days 8 to 14 after infusion) and usually is accompanied by fever, hypoxia, and weight gain. Given that this patient does not have those characteristics and has involvement of palms and soles, this is probably acute skin GVHD. Because it covers the trunk and extremities, it involves more than 50% of the skin area and therefore is skin stage 3. Stage 3 skin GVHD is often difficult to treat by topical therapy or increasing calcineurin inhibitors alone. Systemic therapy with prednisolone is probably necessary, so this therapy should be started along with topical therapy to help with pruritus and speed response. A skin biopsy to rule out a drug rash or viral exanthem is not often helpful but may be performed. Judgment about possible viral or drug reactions should be made in the context of the addition of new medications or other signs and symptoms. In this case, the patient is at a classic time for acute GVHD, so treatment with or without a skin biopsy is appropriate.