Stem Cell Transplantation for non-malignant pediatric conditions

The cost of cure

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Indications in Non-Malignant Disorders

• Immunodeficiency Syndromes
  - Wiskott – Aldrich
  - HLH (Hemophagocytic Lymphohistiocytosis)
    - aka Familial erythro/hemophagocytic lymphohistiocytosis
  - Chronic Granulomatous Disease
Indications in Non-Malignant Disorders

- Storage Diseases
- Osteopetrosis
  aka: malignant infantile osteopetrosis
Indications in Non-Malignant Disorders

• Syndromes of Ineffective Erythropoiesis
  - Thalassemia Major
  - Sickle Cell Disease
Unique considerations in non-malignant diseases

• Rare, heterogeneous group of disorders with variable outcomes
• Diagnosed at young age
• Siblings may have disease or be carriers which affects donor selection/future pregnancies/decisions regarding PGD
• Decision to undergo transplant very complicated in diseases not acutely life-threatening but impacting duration or quality of life
Unique considerations in non-malignant diseases

• If acute SCT toxicities successfully navigated long-term survival is very good unlike in malignant disorders

• Successful SCT does not guarantee reversal of non-hematopoietic abnormalities
Immunodeficiency diseases

• SCT standard approach for infants with significant immunodeficiency syndromes as early death likely without intervention
  – Children are often very ill at diagnosis/increased peri-SCT mortality
  – Role of reduced-intensity conditioning is being elucidated
  – Gene-therapy trials currently available for SCID
WAS

- Rare, X-linked disorder
- Microthrombocytopenia, eczema, recurrent infections
- Cellular and humoral immune dysfunction
- Increased risk of malignancy, mostly lymphomas
- SCT curative for immunodeficiency, thrombocytopenia (Ozsahin, Blood, 2008)
Chronic Granulomatous Disease

- Failure of “oxygen burst” in phagocytes leads to impaired microbial killing
- Patients have recurrent infections
- X-linked or autosomal recessive
- Even with best supportive care only 50% of patients alive at 30 years
- SCT from related or unrelated donor can be curative with remission of colitis and catch-up growth (Soncini, BJH, 2009)
HLH

- Rare inherited disorder
- Defective lymphocyte cytotoxic activity results in uncontrolled proliferation of macrophages and overproduction of inflammatory cytokines
- Children often very ill at presentation and are treated with cytotoxic and immunosuppressive therapy pre-SCT
HLH

• SCT provides only curative option
• Increased peri-SCT mortality
• Reduced intensity regimens being investigated (Baker, BMT 2008) (Jordan, BMT 2008)
Osteopetrosis

- Congenital dysfunction of osteoclasts
- Presents in infancy with extramedullary hematopoiesis, pancytopenia, cranial nerve deficits
- SCT is curative but early transplant is essential and neurological deficits may be permanent (Driessen, BMT 2003)
Storage diseases

• Heterogeneous group of congenital disorders with deficiency in enzyme production that leads to accumulation of substrate in multiple organs
• Marrow from unaffected donor corrects hematopoietic compartment and may provide sufficient enzyme for other organs
Storage diseases

- Age and neurologic status are strongest predictors of outcome
- Successful SCT stops ongoing damage and may reverse existing damage
- Long-term neurologic status of survivors is variable
Storage diseases

- Best outcomes have been reported for Hurlers Disease, Adrenoleukodystrophy and Globoid cell leukodystrophy (Peters, Blood, 2004)
- Use of umbilical cord blood as a stem cell source increases number of potential donors and can shorten time to SCT (Staba, nejm, 2004)
Thalassemia
“of the sea”

• One of the most common genetic disorders and the most common transfusion dependent anemia in the world
• Inherited in an autosomal recessive manner
• Affects almost 70,000 new infants per year
Epidemiology

• Majority of cases occur in “Thalassemia Belt” - Mediterranean area, Africa, middle East, Indian subcontinent, Southeast Asia

• Disease concentrated in tropical areas due to protection against P. falciparum malaria conferred by heterozygous state
Medical management of thalassemia

• Chronic red cell transfusions every 4-6 weeks
  – Goals
    • Correct anemia
    • Suppress erythropoiesis
    • Decrease GI iron absorption
  – Complications
    • Iron overload
    • Infectious exposures
Complications associated with iron overload

- Heart
  - Cardiac hypertrophy and dilatation
    - Magnitude of iron loading in heart determines survival
- Liver
  - Portal fibrosis/cirrhosis
  - Result of hemosiderin deposits in parenchymal and phagocytic cells
- Endocrine glands
  - Pituitary (gonadal failure), pancreas (DM), thyroid, adrenal
Chelation

• Deferoxamine is the “gold standard”
  – Only available by IV or SQ route
  – Usually need to use drug for 8-12 hours 5-6 days a week beginning at age 3-5

• Oral chelators
  – Not as well studied
  – May not be as effective
Outcome with medical management

- Life expectancy
  - Affected enormously by demographic and individual factors
    - Median survival exceeds 50 years in well-chelated patients (Lawson, BrJHeme, 2003) but in UK 50% died before age 35 (Modell, BrMedJ, 1997)
    - At age 25, 99% survival if compliant with therapy but 70% in noncompliant (Piga, AnnNYAcadSci, 1998)
Psychological burden

– Chronic illness that disrupts social relationships, future plans (Atkin, SocSciMed, 2001)

– 60% of children < 18 reported anger/irritability, 50% reported a depressed mood and 21% had a suicide attempt or self-injury (Ghanizadeh, Iran, JPedHO, 2006)
Hemoglobin SS Disease

• Affects 1/400 African-Americans
• Inherited disorder of hemoglobin production leading to polymerization and decreased deformability of the red cell in the deoxygenated state
• Disease of endothelial damage – clinically most prominent in capillaries of lung, cerebral-vascular system, spleen, skeleton, kidneys, eyes, penis
Medical management of Sickle cell disease

• Severity of disease variable with few early predictors available
• Universal prophylaxis has dramatically decreased childhood fatalities
• Severely affected children may be treated with chronic transfusions or hydroxyurea
Medical management of Sickle cell disease

- Life expectancy 40-60 years

- Psychological burden as variable as the disease ranging from minimal symptoms to stroke, pulmonary dysfunction and pain crises causing constant hospitalizations and narcotic dependency
Transplant as a curative modality

- Replacement of affected bone marrow by healthy bone marrow restores normal hematopoiesis and cures disease
- First transplant for thalassemia performed in 1982 and over 1500 transplants have now been done world-wide
- Usually restricted to patients having a matched family donor
- Usually restricted to sickle cell patients with significant disease manifestations
Cure = Normal hemoglobin production

In Sickle cell disease:
• Resolution of VOC
• Stable pulmonary disease
• Possible correction of reticuloendothelial dysfunction (Ferster, Blood 1993)
• Possible correction of osteonecrosis (Bernaudin, BMT 1997)
• Possible improvement in growth
• Stable neurologic function/MRI
• Very good performance status
Cure =
Normal hemoglobin production

In Thalassemia:
- Freedom from transfusions
- Improvement in growth
- Resolution of liver fibrosis
- Very good performance status
The Cost of Cure

- Peri-SCT morbidity and mortality
- Risk of acute and chronic GVHD
- Risk of graft rejection
- Restrictions
- Long-term sequelae
Acute Complications

- Nausea and vomiting
- Mucositis
- Anorexia
- Infections
- 4-6 week hospital stay
- 5-15% risk of mortality during acute transplant period
Graft versus host disease

• Acute GVHD
  – Rash, diarrhea, hepatitis
  – Rarely significant in matched sibling setting in pediatric patients
  – Usually responds to steroid therapy
Graft versus Host Disease

• Chronic GVHD
  – Scarring process that affects skin, liver, GI tract, lung, eyes and mouth
  – Often steroid responsive but requires prolonged immunosuppression
  – Risk factors include patient and donor age, performance status pre-HSCT, multiple transfusions and prior infections
  – Occurs in ~10% of patients receiving matched sibling HSCT
Chronic graft versus host disease
Restrictions or “guidelines for safe living”

• Patients are on immunosuppression for 6-9 months following SCT
• Neutropenia resolved but risk of life-threatening viral or fungal infection remains
• Patients can be inside only in their home/clinic although outdoor activities are allowed
• Requires sophisticated economic and familial infrastructure
Graft rejection

- Autologous reconstitution and return of transfusion dependence
- Largest hurdle in transplant for hemoglobinopathies – hypercellular marrow due to ineffective erythropoiesis, sensitization from transfusions, no prior immunosuppression
- Highest risk in older heavily-transfused patients
Infertility

• The majority of patients undergoing traditional ablative SCT have gonadal failure/infertility

• No definitive studies in this population where radiation is not used/no prior chemotherapy/variable iron overload
Outcomes of matched sibling SCT in thalassemia

• Survival:
  – Class I – 95%
  – Class II – 84%
  – Class III – 79%

• Disease free survival = CURE
  – Class I – 90%
  – Class II – 82%
  – Class III – 57% (Galimberti, BMT, 1997)

• Extensive chronic GVHD in ~ 5%
<table>
<thead>
<tr>
<th>Percentage</th>
<th>Condition</th>
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<tbody>
<tr>
<td>80-85%</td>
<td>Disease Free Survival</td>
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<tr>
<td>5-10%</td>
<td>Transplant-related Mortality</td>
</tr>
<tr>
<td>10%</td>
<td>Graft Rejection</td>
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<tr>
<td>10%</td>
<td>cGVHD</td>
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Causes of death

- Infection
- Acute Chest Syndrome
- Organ Failure
- CVA
- Pulmonary Hypertension (Gladwin, NEJM 2006)
Unrelated donor SCT

• In last decade marked improvement in outcome following URD HSCT
  – High resolution molecular techniques for HLA matching
  – Improved GVHD prophylaxis

• First URD HSCT for thalassemia reported in 1994 (Contu, BMT, 1994)
Nonmyeloablative SCT

• Less intensive conditioning regimen with goal of chimerism post transplant
  – Advantages
    • Less upfront toxicity so attractive for older or high-risk patients
    • Possible preservation of fertility
  – Disadvantages
    • Increased graft rejection – may be overcome with donor stem cell or lymphocyte infusions
    • Increased incidence of chronic GVHD
    • Increased immunosuppression resulting in infectious complications
PBMTC protocols

- Unrelated donor SCT for thalassemia or severe sickle cell disease
- Bone marrow or cord blood as stem cell source
- Reduced-intensity conditioning regimen
Making the decision

• Influenced by
  – Cultural norms
  – Donor availability
  – Availability of well-matched, safe transfusions
  – Availability of chelation therapy
  – Patient compliance with transfusions, chelation
  – Patient and physician judgment re up-front risks, fertility issues, risk of chronic GVHD
  – Availability/accessibility of transplant center
Recommendations

- HLA typing of parents and all siblings for any child diagnosed with thalassemia or sickle cell disease
- Consultation with HSCT physician regarding risks and benefits of HSCT if matched family donor available/ discussion of PGD
- If medical management failing consider referral for consultation and URD search to determine if acceptable donor exists followed by HSCT consultation and SCT on protocol if appropriate
- Ideally both HSCT physician and hematologist are present for all meetings
The goal of HSCT
Acknowledgements

• Physician and nursing staff of DFCI/Children’s Hospital Boston who provide meticulous and compassionate care to our families

• Families whose children have a non-malignant disease potentially cured by SCT who are struggling to determine the best therapy for their child