Objectives

- Provide overview of hemoglobinopathies: Sickled cell disease and Thalassemia
- Discuss approaches to therapy
- Review recent registry collaboration for treatment of hemoglobinopathies
- Highlight importance of careful data collection for these studies

Hemoglobinopathies

“Quantitative disorder versus Qualitative disorder”

- Two broad categories:
  - Quantitative:
    - Decreased production
    - ex. Thalassemias
  - Qualitative:
    - Production of abnormal chains
    - ex. Sickle Cell Disease

Thalassemia Major: Ineffective erythropoiesis

Thalassemia Major:
Ineffective erythropoiesis

Thalassemia Major:
Ineffective erythropoiesis

Therapy for Thalassemia

- Transfusions
  - Monthly for life
  - Correct anemia
- Hyper-transfuse to suppress erythropoiesis\(^1\)
  - Prevent bone complications
  - Improve growth and development\(^2\)
- Chelation needed to treat iron overload


Iron Accumulation
Iron stores increase
Capacity of transferrin exceeded
Unbound iron accumulates
Toxicity: Cardiac, hepatic, endocrine

Alternative Therapy
- Results of 900 consecutive matched sibling HCTs for thalassemia

Background
- Sickle cell disease (SCD)
  - Multisystem disease process affects more than 80,000 individuals in the United States alone
  - Disproportionally affects African-Americans
  - Prevalence of SCD in US: 1/5,000 live births
  - 2,000 newborns born each year in the United States

Sickle Cell Disease (SCD)
- First disease linked to identified gene defect
- Mutation on chromosome 11
- Single amino acid change: glutamic acid to valine
- Occurs in beta-globin gene of hemoglobin

Genetic Basis of SCD
The change in amino acid sequence causes hemoglobin molecules to crystallize when oxygen levels in the blood are low. As a result, red blood cells sickle and get stuck in small blood vessels.

Image courtesy of: Cardiotoracic and vascular atlas, meduweb.com


Image courtesy of: http://sickle.bwh.harvard.edu/HbS_mutation.gif

Image courtesy of: http://www.bio.miami.edu/~cmallery/150/gene/sf

Image courtesy of: http://www.bios.miami.edu/~cmalley/150/gene/ch
SCD

- Clinical phenotype varies among subtypes of SCD
- Most common form of the disease: HbSS
- Additional variants of SCD: Inheritance of one abnormal beta-globin gene in combination with additional mutations
- Variants include the often less severe types of SCD:
  - HbSβthalassemia, HgSβthalassemia
  - HbSC, HbSD and HbSE disease
- HbSS is most clinically severe phenotype
- Mortality for HbSS is higher

Question 3: Importance of correct diagnosis

SCD Diagnosis

- Hemoglobin electrophoresis
- Isoelectric focusing
- HPLC
- Mass spectrometry
- DNA sequencing

Most Common SCD Forms

<table>
<thead>
<tr>
<th>Genotype</th>
<th>Abbrev</th>
<th>Name</th>
<th>Hgb</th>
<th>MCV</th>
<th>Disease Severity</th>
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<tr>
<td>ββ</td>
<td>SS</td>
<td>Sickle cell anemia</td>
<td>6-9</td>
<td>nl</td>
<td>++++</td>
</tr>
<tr>
<td>ββδ° δβ</td>
<td>Sβδ°</td>
<td>Sickleβδthalassemia</td>
<td>6-9</td>
<td>low</td>
<td>++++</td>
</tr>
<tr>
<td>ββδ° δβ</td>
<td>Sβδ°</td>
<td>Sickleβδthalassemia</td>
<td>10-13</td>
<td>low</td>
<td>+</td>
</tr>
<tr>
<td>δβδ° δβ</td>
<td>SC</td>
<td>Sickle Hgb C disease</td>
<td>9-12</td>
<td>nl</td>
<td>++</td>
</tr>
</tbody>
</table>

SCD Burden

- Complications from vascular occlusion include:
  - Early death from infection
  - Dactylitis
  - Pain crisis
  - Acute chest syndrome
  - Stroke (CVA)

Biology of SCD

- Adhesion of damaged RBCs to the endothelium of the microvasculature is responsible for the phenotype:
  - Vascular occlusion
  - Episodic pain attacks
  - End organ damage from hypoxia

Infection

• At risk from early bacteremia
• Improvements in:
  – Use of antibiotic prophylaxis
  – Pneumococcal vaccines (Prevnar)
  – Monitoring
• Incidence of death from infection is decreasing in United States.

Pain Crisis

• Vaso-occlusive leads to painful crisis
• Deoxygenated and sickled RBC impair oxygen transport to tissues
• Patients suffer from intractable pain during episodes
• Episodes can last hours to days to weeks
• Frequent cause of hospitalization

Acute Chest Syndrome (ACS)

• Involves the infarction of pulmonary tissue
• Associated with both immediate mortality, and long –term mortality
• Can lead to irreversible and often fatal pulmonary hypertension
• Decreased exercise tolerance or chronic hypoxia

CVA

• Cerebral vascular accident (CVA) is a catastrophic complication
• Leading cause of morbidity
• 38% of all pediatric ischemic stroke is related to SCD

CVA in SCD

• Reported incidence of stroke in children with SCD is 0.46 per 100 patient years.
• Estimates for the risk of stroke in patients with HgSS under the age of 20, has been calculated at 11%.

Pathophysiology of Stroke in SCA
Therapy for SCD

• Acute medical management:
  – O2
  – Morphine
  – Fluids
  – Exchange or simple transfusions

• Chronic management:
  – Hydroxyurea
  – Chronic transfusion

Complications of Therapy

• Chronic transfusion:
  – Allo-immunization
  – Iron overload

• Need for better therapy...

Therapeutic Options

• Hydroxyurea: Increase fetal hemoglobin production
  – Large clinical trials demonstrate reduction in:
    • Less ACS
    • Fewer pain crises
  – Trials underway to determine outcomes for children on hydroxyurea

  • Transplantation

Survival in SCD

A Pediatrician’s view...

Survival in SCD

The longer view...
HCT for SCD

HCT = Only curative therapy

History of HCT for SCA

- Allogeneic HCT offers the only chance of cure for patients with thalassemia or SCA
- First HCT for SCA performed for AML
- MSD HCT is standard of care when such donors are available
- Cure rates from MSD approximate 85% for both diseases

Indications for HCT

- Stroke/elevated flow on TCD
- Recurrent VOC
- Recurrent ACS
- Significant end organ damage
- Alloimmunization (-infers chronic tx therapy)

HCT for SCD

- Transplant risk reduction:
  - Ideal donor
  - Reduce toxicity of conditioning
  - Lower mortality
  - No GVHD
  - Infection
  - Graft rejection

MRD for SCD

- Outcomes of 67 patients with SCD w/ HLA-matched sibling donors reported to CIBMTR
- Most common indications:
  - Stroke 38%
  - Vaso-occlusive pain 37%
- Poor performance scores-27%
- Busulfan-Cytoxan conditioning
- Bone marrow

Outcomes of MRD for SCD

- Most had hematopoietic recovery
- No deaths in early post-transplant period
- Rates of:
  - Acute GVHD: 10%
  - Chronic GVHD: 22%
- 9 patients had graft failure with autologous recovery
Survival in SCD after MRD

- 10 consecutive SCA patients: HCT by EBMT
- 90% survival
- 90% SCA disease free survival
- 10% transplant related mortality

Conclusion: HCT from a suitable matched related donor can be primary option for cure

Barriers to HCT in SCD

- Only 25% with related donor
- Only 14% with matched sibling (with high risk disease)
- Lack of matched donor: 85% do NOT have donor
  - Only 40% had HLA typing performed
  - Lack of psychosocial support- 10%
  - Parental refusal- 10%
  - Physician referral to transplant refusal- 4%

HCT Options for SCD

- MSD Transplants (Hope 2010):
  - 25% Seizures
  - 25% aGVHD
  - 12% cGVHD
  - 9% Graft failure
- Alternative Donor
  - Less than 20% have matched donor
  - 50% 5/6 cords- with cell doses of 5 x 10 cells/kg
  - 46% 5/6 cords (Stevens-ASH)

Approximately 50% will have suitable cord unit available

Hematologic Endpoints

- Neutrophil engraftment (ANC)≥500 for three consecutive days
- Sustained donor engraftment defined by chimerism assay (>95%)*
- Primary Graft failure- never achieving ANC≥500 —or— ANC≥500 without donor engraftment (autologous recovery)
- Secondary graft failure- achieved ANC≥500 with subsequent decline to below ANC< 500 or loss of donor engraftment
- Platelets >20K unsupported for 7 days
Other Endpoints

- aGVHD and cGVHD scored by standard criteria
- DFS = Alive with donor chimerism
- Graft failure, second HCT or death were events
- Indications for HCT for SCD
  - Stroke (n=12)
  - ACS (n=4)

Matching and Conditioning

- 7 donor-recipient pairs matched at HLA-A, HLA-B and DRB1
- Other mismatched at HLA loci:
  - 1 (n=18)
  - 2 (n=25)
  - 3 (n=1)

Conditioning

- Myeloablative conditioning in 30/35 with thalassemia and 9/16 with SCD
- Busulfan and cyclophosphamide with or without ATG most common
- 12 patients received reduced intensity (RIC)
- All received calcineurin inhibitor GVHD prophylaxis (CSA most common)
- Median follow up of 2 years

Engraftment Outcomes

- 24/51 patients (15 thalassemia, 9 SCD) achieved hematopoietic recovery
- Median time to engraftment: 22 days
- No patients experienced secondary graft failure
- Multivariate analysis:
  - Engraftment higher in cell doses >5x10^7 (nucleated cells/kg)
  - Cumulative incidence of engraftment:
    - 63% for units > 5x10^7 (nucleated cells/kg)
    - 32% for units < 5x10^7 (nucleated cells/kg)

Graft versus Host Outcomes

- 11/51 patients developed aGVHD
- Cumulative incidence of aGVHD was 22%
- 10 patients developed cGVHD
  - Extensive in 2
  - Limited in 9
- Cumulative incidence of cGVHD was 16%

Outcomes

- Disease free survival (DFS):
  - 50% for SCD
  - 21% for Thalassemia
- DFS higher in CB units >5x10^7/kg
Outcomes

• Effect of TNC on DFS: Independent of disease
• 2 year probability of DFS
  – 45% Good TNC
  – 13% Low TNC

Ruggeri et al. Umbilical cord blood transplantation for children with Thalassemia and sickle cell disease. BBMT. Vol 17; 1375–1382

Conclusions

• Only UCB units containing >5 x 10^7 should be considered for transplantation of hemoglobinopathy
• Alternative donor transplant with UCB may be a feasible solution for severe SCD patients without a matched sibling

Forms

• Define genotype: Hb electrophoresis, sequencing, HPLC
• UCB Study- Table 1:
  – HbSS n=59 (94%)
  – HbSβthalassemia n=1 (1%)
  – Others/missing n=7 (10%)

Overall survival

• SCD – 94%
• Thalassemia – 62%

Forms

• Form Numbers: 2030 pre-HCT, 2130 post-HCT

Forms

• UCB Table 1 - Primary reason for HCT:
  – Stroke n=24 (38%)
  – Acute chest syndrome n=9 (15%)
  – Vaso-occlusive pain n=23 (37%)
  – Recurrent priapism n=1 (2%)
  – Iron overload n=5 (8%)
  – Other/missing** n=8 (12%)
Missing/Others

- Missing n=4 (6%)
- Others:
  - Sister died of SCA
  - Severe disability
  - To achieve remission
  - Recurrent pneumonia

Public Health and HCT for SCD

- 2,000 born in US each year with SCD
- Estimated fewer than 500 patients in US have been transplanted for SCD

Public Health Concerns

- Children accounted for approximately 30,000 hospital admissions for SCD in 2004.
- Estimated cost for SCD admissions for adults and children in single year 500 million dollars.
- Estimated average cost over a lifetime for each patient with SCD is 1 million dollars\(^1\).
- 80% of those charges were paid by government programs. (Medicaid or Medicare).

Forms

- UCB- Table 1:
  - <5 n=9 (14%)
  - 5-10 n=9 (14%)
  - >10 n=43 (67%)
  - 0 n=2 (3%)

Summary: Areas of Concern-Forms

- Units (Both SCD and Thalassemia)
- SCD- Type of SCD (HbSC, Hb-S\(\beta^+\) -Attention)
- SCD- Reason for transplant
- SCD- Status of SCD
- SCD- Transfusions

- Attach reports where necessary

Personal Costs of SCD

- 200,000 ED visits
- 22% had silent stroke by 15 YO
- Neurologically intact patients (adults)
  - 33% had below average IQ

Future of SCD Therapy

- In a chronic disease where symptomatology does not always mirror pathology
  - Do pediatricians need to intervene?

References

- Walters et al. Barriers to bone marrow transplantation for sickle cell anemia. BBMT. 1996 Vol 2: 100-104

Thank you for your attention.

Questions?