Objectives

• Provide overview of sickle cell anemia:
  – Sickle cell disease and complications
• Review current standard approaches to therapy for SCD
• Discuss approaches to SCD therapy including matched sibling donor and alternative donor
• Review data on alternative donor transplantation
• Discuss future approaches to alternative donor transplantation

Background

• Sickle cell disease (SCD)
  – Multisystem disease process affects more than 100,000 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 to be linked to identified gene defect
• Mutation on chromosome 11
• Occurs in beta-globin gene of hemoglobin

Genetic Basis of SCD

Disclosures

• No financial disclosures
• Discussion of off-label use of the CliniMACS® device
  – (IND 14045)
**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

**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:
  - HbS/βthalassemia
  - Less severe types of SCD: HbSβ^0^thalassemia, HbSC, HbSD and HbSE disease
- HbSS is most clinically severe phenotype
- Mortality for HbSS, HbSβ^0^thalassemia is higher

**Most Common SCD Forms**

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<th>Genotype</th>
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**SCD Burden**

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

**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-occlusion leads to painful crisis
- Deoxygenated and sickled RBC impair oxygen transport to tissues
- Patients suffer from intractable pain
- Episodes can last hours to days to weeks
- Frequent cause of hospitalization
Acute Chest Syndrome (ACS)

- Infarction of pulmonary tissue
- Associated with both immediate mortality, and long-term mortality
- Can lead to irreversible and often fatal pulmonary hypertension

CVA

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

Pathophysiology of Stroke in SCD

CVA in SCD

- Stroke risk is 0.46 per 100 pt years
- Estimates for HbSS under age 20, is calculated at 11%

What We Know

- Strokes in SCD are relatively common
  – About 10%
- Strokes in SCD are preventable
- National Guidelines recommend screening

Transcranial Doppler (TCD)

- TCD measures the blood flow velocity in the Circle of Willis
- Velocity of greater than 200cm/sec predicts stroke

Screening for Stroke in SCA


Stroke during STOP trial

- Observation vs. chronic transfusion HbS <30%
- Prematurely stopped due to marked benefit in treatment group

Prevention

- Universally accepted approaches include:
  - Penicillin prophylaxis to prevent invasive bacterial infection
  - Educating parents to detect splenomegaly
  - Routine vaccinations, including Prevnar
  - Regular use of TCD to detect patients with increased risk of stroke

Crisis Prevention

![Chart showing survival of patients by crises/year.]

End Organ Damage

- Most oscillate between long periods of being asymptomatic and severe vaso-occlusive crisis manifesting as ACS or pain crisis
- Infants as young as 12 months will demonstrate end organ damage

Prevention Leads to Improvement

![Chart showing improved survival.]

Quinn CT, et al. Improved survival of children and adolescents with sickle cell disease. Blood. 2010
Baseline GFR in SCA

MRI in Infants
- MRI examinations of infants with SCA
- >10% had silent infarcts
- Silent infarcts occur in small but significant number of infants as early as one year

Acute Silent Cerebral Events
- Produce no motor or sensory deficits
- Associated with neurocognitive impairment

Acute Silent Cerebral Events
- Baseline
- 10 months later...

Hemolysis
- Chronic ongoing hemolysis
- Associated with decreased survival

Pulmonary Hypertension
- Resulting from intravascular hemolysis
- Associated with elevated cardiac output
- Independently correlates with survival
Cardiac Arrhythmias

- Associated with increased TRV
- Independently associated with increased mortality


Summary of SCD and Complications

- Clinically severe and evident events
- Accumulation of end organ disease leads to increased mortality in adults with SCD


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Therapy for SCD

- Acute medical management:
  - O2
  - Morphine
  - Fluids
  - Exchange or simple transfusions
- Chronic management:
  - Hydroxyurea
  - Chronic transfusion

Hydroxyurea

- Increase fetal hemoglobin production
- Cost effective


BABY HUG Trial

- Large multi-center randomized trial for infants 9 to 17 months
- Randomized between hydroxyurea and placebo x 24 months
- Endpoints: Renal and splenic function
  - Assessed by spleen uptake 99mTc-sulphur colloid and quantitative GFR

Eckrich - Medical school notes on SCD management, 03/30/2018
**Results of BABY HUG Trial**

- HU demonstrates reduction:
  - Fewer pain crises
  - Less ACS
  - Fewer hospitalizations
- Improved urine concentrating ability and less renal hypertrophy

**SWiTCCH Trial**

- No strokes in transfusion group
- 7 strokes in HU group
- Study closed

**TWiTCCH Trial Recommendations**

- Transition patients to HU after a period of chronic transfusion if they meet the following:
  - Completion of 2 years with stable HbS levels
  - Normalization of TCD
  - No evidence of vasculopathy on MRI
  - Demonstrate HU compliance
  - Demonstrate WBC response to HU

**Complications of RBC Therapy**

- RBC allo-immunization
  - Results in modern era improving:
    - 14% of chronically transfused develop new antibody
    - Most common against C, E, Kell
  - Extended RBC matching is standard of care
  - Iron overload

**Iron Accumulation**

Iron stores increase

Capacity of transferrin exceeded

Unbound iron accumulates

Toxicity: hepatic, endocrine, cardiac

IRON OVERLOAD

**Iron Overload**

Iron Overload

• Deposition of iron in tissue
  - Liver failure
  - Endocrine toxicity
  - Cardiac toxicity

• Cardiac tissue may be relatively spared

Kaushik N, Eckrich, MJ et al. Chronically transfused pediatric sickle cell patients are protected from cardiac iron overload. Pediatric Hematology Oncology. 2012.

Causes of Death in SCD

Pediatric
Adult

Survival Improving

• Chronic transfusion:
  – Allo-immunization
  – Iron overload

• Need for better therapy...

Survival in SCD

The Pediatrician’s view...

Survival in SCD

The longer view...

SCD Therapy

• In a chronic disease where symptomatology does not always mirror pathology:
  “Do pediatricians need to consider offering intervention with curative therapy?”
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HCT for SCD

HCT = Only readily available curative therapy

Goal of Transplant

- Create a “Chimera”
- Donor derived hematopoietic system
- Donor derived immune system
- Tolerant to recipient HLA antigens

Inheritance of HLA Haplotypes

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<td>DR</td>
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</table>

History of HCT for SCA

- First HCT for SCA performed for AML
- Cured AML but also cured SCA

Public Health and HCT for SCD

- 2,000 born in US each year with SCD
- Estimated 6,000 could be eligible
- 1137* US patients have been transplanted for SCD
  - (~600 in Europe)

* Data obtained from Statistical Center of the Center for International Blood and Marrow Transplant Research (CIBMTR). The data presented here are preliminary and have not been reviewed or approved by the Statistical or Scientific Committees of the CIBMTR.
**Indications for HCT**

- Stroke/elevated flow on TCD
- Recurrent VOC
- Recurrent ACS
- Significant end organ damage
- Allo-immunization
  - Infers chronic transfusion therapy


**Transplant Toxicities**

**SHORT TERM**
- Seizures, CVA, PRES
- Mucositis
- Veno-occlusive disease of the liver

**Acute Graft Versus-Host Disease**

**Infections**

**LONG TERM**
- Learning Disability
- Bronchiolitis Obliterans
- Cardiac Dysfunction
- Liver Dysfunction

Finding a Donor

- HLA-identical sibling or family member
  - Vs.
- Alternative donor
  - Unrelated donors
  - Partially matched family member

**HLA-matched sibling HCT for SCD**

- Good engraftment
- Low rates of GVHD
- Stable mixed chimerism cures SCD
HLA-matched sibling HCT 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-Cyclophosphamide +/- ATG
- Bone marrow


Survival in SCD after MRD

- 84% bone marrow grafts
- 5 year EFS was 91%
- 5 year OS 93%


Summary of HLA-matched sibling HCT

- Large retrospective cohort from US and Europe
- Myeloabative (n=873)
- Reduced intensity (n=125)
- 84% bone marrow grafts
- 5 year EFS was 91%
- 5 year OS 93%


Summary of HLA-matched sibling HCT

- 92-94% overall survival, 82-91% EFS
- Graft rejection 7-10%
- Graft-versus-host disease (GVHD)
  - Acute grade II-IV 15-20%, Chronic 12-20%
- Transplant-related mortality 6-7%

Survival in SCD

Quinn CT et al. Improved survival of children and adolescents with sickle cell disease. Blood. 2010
Michlitsch et al. Recent advances in bone marrow transplantation in hemoglobinopathies. Current Molecular Medicine. 2008

Late Effects of Myeloablative BMT

• Bu/Cy ATG follow-up of 10 years 95% survival
• Pulmonary function tests:
  – FEV1 pre-BMT 88%±10%, post-BMT 86%±11% (p=0.6)
  – FVC pre-BMT 78%±16%, post-BMT 81%±12% (p=0.4)
• Gondal toxicity:
  – Males <25% had normal testosterone
  – Females >50% had primary ovarian failure

Michlitsch et al. Recent advances in bone marrow transplantation in hemoglobinopathies. Current Molecular Medicine. 2008

Non-myeloablative Conditioning

• HLA-matched PBSC
• Conditioning: Alemtuzumab (Campath) + low dose TBI (total body irradiation)
• GVHD prophylaxis with Rapamycin
• Outcomes in adults:
  – No transplant related mortality (TRM)
  – Mixed donor chimerism only with continued immune suppression


Pediatric Experiences with Reduced Intensity/NMA Conditioning

• Trial (n=1) → Bu/Flu+ATG → 1 death, GVHD
• Trial (n=6) → TBI/Flu → 6, transient engraftment in 5
• Trial (n=2) → Flu/Mel+ATG → none remain alive without SCD
• Trial (n=7) → Bu/Flu+ATG → 6 of 7 alive without SCD

Eckrich et al. Reduced-intensity allogeneic stem-cell transplantation for sickle cell disease in pediatrics: A single institution experience. Biology of Blood and Marrow Transplantation. March 2018

Reduced Intensity- Matched Sibling

• Campath, Fludarabine, Melphalan→MSD
  – OS 94%
  – EFS 92%
• aGVHD 23%
• cGVHD 13%

Eckrich et al. Reduced-intensity allogeneic stem-cell transplantation for sickle cell disease in pediatrics: A single institution experience. Biology of Blood and Marrow Transplantation. March 2018

Reduced Intensity- Matched Sibling

• N=13
• Six patients with severe SCD
• Amongst matched sibling:
  – OS 100%
  – aGVHD <20%

Barriers to HCT in SCD

- Only 14-18% with matched sibling
- Lack of HLA-matched donor: 85% do NOT have donor available
  - Only 40% had HLA-typing performed
  - Lack of psychosocial support - 10%
  - Parental refusal - 10%
  - Physician referral to transplant refusal - 4%

Walters et al. Barriers to bone marrow transplantation for sickle cell anemia. Biology of Blood and Marrow Transplant. 1996

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Alternative Options for SCD

- Alternative Donor: Unrelated cord blood
  - 50% 5/6 cords - with cell doses of 5 x 10 cells/kg
  - 46% 5/6 cords (Stevens-ASH abstract 2012)

Approximately 50% will have suitable cord unit available

Alternative donor HCT for SCD

- Preliminary data:
  - Conditioning: Campath/Fludarabine/Melphalan
  - Used related or unrelated marrow
  - n=14
  - OS of 95%, EFS 79%

S.C.U.R.T. trial

European Conditioning (Cord)

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

Engraftment Outcomes (Cord)

- 9 SCD achieved hematopoietic recovery
- 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)

Outcomes (Cord)

- Disease free survival (DFS):
  - 50% for SCD
- DFS higher in CB units >5x10^7/kg
- Effect of TNC on DFS:
  - Independent of disease

Cord Barriers

- Historically, cords matched at three alleles
- Increased TRM unless matched at four alleles
- Further reduces suitable cord units
Cord Conclusions

• Only UCB units containing >5 x 10^7/kg should be considered for transplantation of hemoglobinopathy
• Associated with 50% DFS
• Associated with high rates of graft rejection
• Largest U.S. trial of unrelated cord transplant for SCD was closed

Recent Cord for SCD

• Recent experience with novel reduced intensity regimen (phase I)
• (n=9) age 3-10 years, with CVA complications received Campath, Fludarabine, Melphalan, Thiotepe
• 7/9 engrafted, 2 autologous recovery
• Disease free survival of 78%
• Acute GVHD in 3 (33%)
• Chronic GVHD in 3 (33%)

Results of Phase II MUD

• N=29
• One and 2-year EFS were 76% and 69%, respectively
• Overall survival (OS) was 86% and 79%
• The day-100 incidence of grade II-IV acute GVHD was 28%; 1-year incidence of chronic GVHD was 62%; 38% classified as extensive
• There were 7 GVHD-related deaths

Summary of Phase II MUD

• Cannot be considered sufficiently safe for widespread adoption without modifications to achieve more effective GVHD prophylaxis

Other Alternative Donor Trials

• Conditioning: Fludarabine, Melphalan, Campath
  – 2 marrow (7/8 allele matched)
  – 6 cord (4/6 cord)
• Addition of mesenchymal cells (MSC)
Other Alternative Donor Trials

• Only 3/6 patients engrafted
• 2/3 engrafted patients developed GVHD
• 4/6 patients died
  -2 infectious (CMV, toxoplasmosis)
  -GVHD
  -Intra-ventricular hemorrhage

Result: Pilot study prematurely terminated


Mismatched Related (Haploidentical) Donor Transplant

• Almost every child will have a donor
• Rapid engraftment → short hospital stay
• High risk of GVHD and graft rejection can potentially be overcome
• Major challenge is delayed immune recovery and infection after transplant

Alternative Donor Transplant

• Engraftment, No GVHD, low regimen-related toxicity
  – 1. In vivo graft manipulation
  – 2. Graft Engineering

T Cells

• Coordinate response to infection
• Fight viral and fungal infection
• Cause Graft-Versus-Host disease

For patients needing alternative donor transplant...

In vivo graft manipulation
Vs.
T-depletion

Alternative Donor Transplant

• Engraftment, No GVHD, low regimen-related toxicity
  – 1. Graft Engineering
  – 2. In vivo graft manipulation
**Patient Characteristics**

<table>
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<tr>
<th>Age (y)</th>
<th>Sex</th>
<th>Indications</th>
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**Chimerism**

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* Required second transplant from a second haploidentical donor.

**SCD Outcomes Post-HCT**

- Recovery of donor CD4+ T Cells
- CD4+ less than 200 requires anti-viral and anti-fungal prophylaxis
- Prolonged immune suppression

**Outcomes**
Complications

- Graft failure in one; engrafted after second SCT
- 2 pts developed PRES (posterior reversible encephalopathy); one seizure
- PRES resolved by four weeks in both
- 4 PTLD (post-transplant lymphoproliferative disorder)
  - One treated XRT and with EBV specific T cells and low dose TBI
  - 2 treated with 4 doses of IV rituximab- resolved
  - One died as consequence of treatment for PTLD

Outcomes

- OS 90%
- EFS 90%
  - aGVHD 20%
  - cGVHD 10%

Alternative Donor Transplant

- Engraftment, No GVHD, low regimen-related toxicity
  - 1. Graft Engineering
  - 2. In vivo graft manipulation

In vivo Graft Manipulation

- HLA-haploidentical bone marrow transplantation with post-transplant cyclophosphamide

Post-HCT Cyclophosphamide Outcomes

- 11/17 Durable engraftment
- 10/17 Remain asymptomatic
- 1/17 Developed GVHD (skin only)
- 5/11 Remain on immune suppression
- 6/17 Graft rejection

Limitations

- Graft failure
- Many need prolonged or indefinite immune suppression
The Future of HCT Trials for SCD

- **Stride II Trial**: Eligibility will be determined on the biological assignment of HLA-identical siblings or well-matched unrelated donors.
  - Those lacking an eligible donor for HCT serving as a comparison group
- **BMT 1507**: Alternative donor SCT for SCD using reduced-intensity conditioning and haploidentical donors

Summary

- HLA-matched sibling donor transplant may be considered standard of care for SCD
- Alternative donor transplant options are available
- A reduced-intensity conditioning regimen followed by T cell depleted transplant provides:
  - Reliable engraftment
  - Low GvHD
  - Low transplant-related mortality
- Haploidentical transplant expands the donor pool

References


Gene Therapy

- Lentiviral vector gene insertion
  - Phase III expected to open in 2018
- CRISPR single nucleotide mutagenesis
  - Phase I opening soon

Moving Beyond SCD...

References

- Walters et al. Barrier to bone marrow transplantation for sickle cell anemia. BMJ. 1996 Vol. 2; 100-104.