Post Transplant Management for Sickle Cell

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Thank you for this opportunity to present this information ...

• I have no financial interests to disclose.
Goal of Transplant for Sickle Cell Disease...

- Replace the making of sickle hemoglobin with normal hemoglobin

Minimal Toxicity

- Autologous: ✗
- Allogeneic: ✓

Some Donor Engraftment

Few Late Effects
Learning Objectives

• Awareness of the role HCT has played in the treatment of SCD in the past
• Awareness of specific medical challenges with HCT in the SCD patient
  – Awareness of recommended supportive care
• Awareness of current studies for patients with SCD
Indications for Hematopoietic Stem Cell Transplants in the US, 2013

- Allogeneic (Total N=8,197)
- Autologous (Total N=11,258)

Number of Transplants

- Myeloma / PCD
- AML
- ALL
- CML
- NHL
- HD
- MDS / MPD
- CLL
- Aplastic Anemia
- Other Non-Malignant Disease
- Other Cancer

CIBMTR
Center for International Blood & Marrow Transplant Research
The Past ...

[Diagram showing the history of bone marrow transplantation and related events from 1955 to 2010.]

The First Successful Transplant for SCD

- 8 year old girl with Hgb SS
  - 1-2 hospitalizations/ year for pain crisis
- 1982: She developed acute myeloid leukemia (AML)
- Matched sibling donor identified (brother)
  - Presence of sickle trait
- Preparative regimen:
  - 11.5 Gy TBI/ Cyclophosphamide 120 mcg/kg
  - GVHD Prophylaxis: Methylprednisolone and Methotrexate

Johnson FL. et al. NEJM. 1984; 311: 780-783
The First Successful Transplant for SCD

• Engraftment occurred with recovery of white count by day +12

• Developed acute graft-versus-host disease (GVHD) that evolved into chronic GVHD

• 16 months after transplant:
  – Remission from AML
  – Karyotype: XY, suggesting donor engraftment
    • Hemoglobin electrophoresis: A1, S, A2 (trait pattern)
  – No signs of sickle cell disease (a potential cure!)

Johnson FL. et al. NEJM. 1984; 311: 780-783
Which patients with SCD should be considered for HCT?

- Historically..., Hgb SS, Hgb SC, Hgb Sβ° thalassemia AND severely symptomatic
  - Prior history of neurological/ cerebrovascular complication, i.e. stroke or neurological event lasting > 24 hours – OR-
  - Elevated TCD velocity that exceeds 200cm/sec by non-imaging technique (or > 185 cm/sec by imaging technique) measured at 2 separate occasions 1 month or more apart – OR-
  - Minimum of 2 episodes of acute chest syndrome within the preceding 2 years – OR-
  - 3 or more severe pain episodes per year within the preceding 2 years
  - AND...
Historically... Who is considered?

- Eligible HLA-matched sibling donor (Hgb AA or AS)

  ![Family Tree Diagram](Image)

  **Chance of matched sibling donor: 25%**

  **Most do NOT have this option**
A cure is available to these recipients...

• Between September 1991 - April 1997
  – 34 children (age < 16 years) with symptomatic SCD were transplanted with HLA matched sibling donor.
    • Stroke: 17
    • Recurrent acute chest syndrome: 10
    • Recurrent vaso-occlusive crisis: 7
  – 21 receiving regular red cell transfusions
  – Preparative regimen: myeloablative
    • Busulfan/Cyclophosphamide based
    • Horse ATG, Rabbit ATG or CAMPATH-1H

Walters MC, et al. NEJM. 1996; 335: 369-376
Results: Matched Sibling Donor Trial

- Median follow-up: 26.5 months (range, 0.2-66.9 months)
- 32 of 34 patients survived
  - 28 with stable donor engraftment
  - 4 had graft rejection or sickle cell disease recurrence
  - 2 died from intracranial hemorrhage or GVHD
  - OS 93%
  - EFS 79%

Walters MC, et al. NEJM. 1996; 335: 369-376
Summary of MSD Results from CIBMTR

• 67 recipients of MSD for SCD between 1989-2002
• Most common indications:
  – Stroke: 38%
  – Recurrent vaso-occlusive crisis: 37%
• Median age: 10 years
• 94% received busulfan/cyclophosphamide
• Most achieve hematopoietic recovery
• Acute GVHD 10%
• Chronic GVHD 22%
• Disease free survival: 85%
• Overall survival: 97%
• 9 experienced graft failure with autologous recovery = recurrence of sickle cell disease

Key points:
- High survival rate after MSD for SCD
- Few transplant related complications
- Elimination of sickle-related complications

As Few Have a MSD & HCT Cures SCD...

Future Opportunities & Challenges
What Do You Think Should Be Future BMT Goals? (Audience response)

• 1. Unrelated donor transplants
• 2. Reduce the intensity of the conditioning regimen
• 3. Improve supportive care
• 4. Tolerate mixed chimerism
• 5. All of the above
New Goals...

Expanding the Donor Pool

Reducing Late Effects

Reducing Acute Toxicities

Maintaining Donor Engraftment
Next Directions...

- Alternative Donors?
  - Matched unrelated donor
  - Umbilical cord unit

- Preparative Regimen?
  - Reduce the intensity?
Next Directions...

- **Alternative Donors?**
  - Matched unrelated donor
  - Umbilical cord unit
Likelihood of finding matched unrelated adult donor

Range 66-97%: Available suitable match, by race/ethnic group, Be The Match Registry®

Race or ethnic group of searching patient for hematopoietic cell transplantation

- 8/8 HLA match
- ≥7/8 HLA match

Likelihood of finding an unrelated cord blood unit

Range 95-99%: patients <20 years, adequate cell dose, Be The Match Registry®

Race or ethnic group of searching patient for hematopoietic cell transplantation

- 6/6 HLA match
- ≥5/6 HLA match
- ≥4/6 HLA match

Likelihood of finding unrelated donor or cord blood

Range 98-99%: patients <20 years, when searching for adult donor, then cord blood
Blood and Marrow Transplant Clinical Trials Network: 0601

• Unrelated Donor Reduced Intensity Bone Marrow Transplant for Children with Severe Sickle Cell Disease / The SCURT Study
  – Enrolled participants with matched unrelated donors and umbilical cord donors
  – Reduced intensity preparative regimen
BMTCTN 0601: SCURT

• Primary Goal:
  – Determine EFS 1 year after unrelated BM or UCB transplant
    • Goal: EFS ≥ 75%
• Estimated Accrual: 45 patients in 4 years
• Eligibility:
  – Age: 3-19.75 years
  – Sickle cell disease
  – History of stroke or neurologic event lasting > 24 hours & accompanied by infarct noted on brain MRI
  – Minimum of 2 episodes of acute chest syndrome within preceding 2 years
  – History of 3 or more severe pain crises/year in the past 2 years despite adequate supportive care (hydroxyurea and compliant)

Other end organ and performance status requirements as well
BMTCTN 0601: SCURT

• Donor Requirements:
  – Suitable 8/8 HLA allele matched unrelated donor
  – ≥ 5/6 unrelated cord blood unit
    • HLA-A & B: matched at the low/intermediate resolution molecular typing
    • HLA DRB1: high resolution molecular typing (allele level)
    • Minimum cell dose: 3 x 10^7 TNC/kg (pre-cryopreservation)
BMTCTN 0601
Treatment Regimen

**Day** | **Treatment**
--- | ---
-22 | Alemtuzumab test dose 3 mg IV*
-21 | Alemtuzumab 10 mg IV*
-20 | Alemtuzumab 15 mg IV*
-19 | Alemtuzumab 20 mg IV*
-18 | Fludarabine 30 mg/m² IV
-17 | Fludarabine 30 mg/m² IV
-16 | Fludarabine 30 mg/m² IV
-15 | Fludarabine 30 mg/m² IV
-14 | Fludarabine 30 mg/m² IV
-13 | Melphalan 140 mg/m² IV
-2 | Rest
-1 | Rest
0 | Bone marrow infusion
+1 | Methotrexate 7.5 mg/m² IV
+3 | Methotrexate 7.5 mg/m² IV
+6 | Methotrexate 7.5 mg/m² IV
+7 | Methylprednisolone 1 mg/kg/day IV until d+28 and then taper

**Total doses:**
- Campath-1H: 48 mg
- Fludarabine: 150 mg/m²
- Melphalan: 140 mg/m²

**Notes:**
- Hgb S ≤ 45% 7 days prior to the start of alemtuzumab
- Iron chelation &/or hydroxyurea: d/c 48 hrs prior to alemtuzumab
- Alemtuzumab: May be given between days -22 and -18 but required to be given 3 consecutive days. Test dose given 24 hours prior to 1st dose
- Cord GVHD Prophylaxis: CSA/Tacrolimus: until d+100 and then taper through d+180
  - MMF: Day -3 until day d+45 or 7 days after engraftment, whichever was later
  - G-CSF 5 mcg/kg/day IV until ANC ≥ 0.5 x 10⁹/L for 3 consecutive days
SCURT Trial Results: Umbilical Cord

- 8 recipients of umbilical cord graft
  - 1: 6/6 match
  - 7: 5/6 match
- Median age: 13.7 years (range, 7.4-16.2)
- Median weight: 35 kg (range, 25.2-90.2)
- Median cell dose: $6.4 \times 10^7$ TNC/kg (range, 3.1-7.6)
- All achieved neutrophil recover by day +33
  - 5 experienced graft rejection & had autologous recovery
  - 1 died 14 months after transplant from respiratory failure and extensive chronic GVHD
- Cord arm met stopping rules and was closed early due to graft failure

SCURT Trial Results: Unrelated Donor

• Manuscript just accepted to *Blood*
• 30 children between the ages of 3-19 years enrolled between 2008-2014
  – 29 evaluable
• Indications
  – Stroke: 12
  – Elevated TCD: 2
  – Vaso-occlusive pain crisis: 12
  – Acute chest syndrome: 4
• Median TNC: $3.5 \times 10^8$/kg (range, 1.3-6.8)
• Median CD34 dose: $2.9 \times 10^6$/kg (range, 0.3-9.2)
• Median follow-up: 26 months (range, 12-62)
SCURT Trial Results: Unrelated Donor

- 27/29 engrafted
- Median ANC recovery: 12 days (range, 6-16)
- Median platelet recovery: 24 days (range, 7-90)
- Graft rejection: 10%
  - 2 primary (day 39 & day 91)
  - 1 secondary (day 49)
  - All 3 recovered host hematopoiesis

All engrafted recipients (>90% donor) at 3 months: sustained engraftment at 1 and 2 years in those evaluable

Shenoy S, et al. Blood, accepted for publication
SCURT Trial Results: Unrelated Donor

• 1-year EFS: 76%
  – 95% CI 56-88%
• 2-year EFS: 69%
  – 95% CI 48-82%
• 1-year OS: 86%
  – 95% CI 67-95%
• 2-year OS: 79%
  • 95% CI 59-90%
• Day 100 grade II-IV acute GVHD: 28%
  – 95% CI 13-45%
• 1-year chronic GVHD: 69%
  – 95% CI 41-77%
  – 38% extensive

Shenoy S, et al. Blood, accepted for publication
Deaths: 7 & GVHD related

<table>
<thead>
<tr>
<th>#</th>
<th>Age (years)</th>
<th>Time of death (days)</th>
<th>Complications at the time of death</th>
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<tbody>
<tr>
<td>1</td>
<td>17</td>
<td>231</td>
<td>Acute GVHD (gut), opportunistic infection, ARDS</td>
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<td>2</td>
<td>16</td>
<td>539</td>
<td>Chronic GVHD, CMV infection, encephalomyelitis, cardiorespiratory failure</td>
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<td>Acute GVHD (gut), respiratory and renal failure</td>
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<td>Chronic GVHD</td>
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<td>507</td>
<td>Chronic GVHD, VRE and HSV infections</td>
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<tr>
<td>6</td>
<td>14</td>
<td>199</td>
<td>Acute GVHD, Candida and CMV infections, respiratory and renal failure</td>
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<td>7</td>
<td>18</td>
<td>143</td>
<td>Acute GVHD (gut), pulmonary hemorrhage, <em>Staphylococcus aureus</em> pneumonia</td>
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</tbody>
</table>

GVHD- graft-versus-host-disease; ARDS-Acute respiratory distress syndrome; CMV-cytomegalovirus; VRE- Vancomycin resistant *enterococcus*; HSV-herpes simplex virus
Key Points of BMTCTN 0601 (SCURT):

• Children with sickle cell disease can engraft after an unrelated donor transplant utilizing a reduced intensity preparative regimen.

• Specifically for this trial, although the goal of the EFS was met, the high incidence of GVHD and the associated mortality, compromises the safety for our patients.
Sickle Cell Disease Overall Survival
Transplantation with Bone Marrow, PBSC and Cord Blood for Pediatric Patients Unrelated Transplants Facilitated by NMDP/Be The Match (2004-2013)

SOURCE: CIBMTR®, the research program of NMDP/Be The Match
Next Directions...

- *Preparative Regimen?*
  - Reduce the intensity?

*Conditioning Regimens??*
Reducing the Intensity in MSD BMT for Severe SCD: The CHOA Study

- **Goal:** Decrease exposure to busulfan (50%) and cyclophosphamide (55%) by adding fludarabine
  - Decreasing busulfan and cyclophosphamide in a step wise fashion.
- **The Hope:**
  - Fewer acute and late side effects from HCT
  - Obtaining stable donor chimerism
    - Day +28 chimerism predominantly donor
- Multi-institutional study

Results of the De-escalation Trial

• The first 2 de-escalation steps were completed without difficulty
  – 6 participants enrolled on Level 1
  – 6 participants enrolled on Level 2
  – Reduced cyclophosphamide from 200 mg/kg to 90 mg/kg

• Level 3: 2 participants enrolled
  – Busulfan decreased from 12.8 mg/kg to 9.6 mg/kg
  – Both had T cell chimerism < 50% donor on Day +28
  – Triggered stopping rules

• No regimen related toxicities observed
• All 14 participants are surviving and disease free

Summary: This could be an effective but less toxic regimen
So what lessons have we learned from past studies? (Audience response)

1. Transplant does not prolong survival for children with SCD.
2. Fertility is often preserved after a myeloablative transplant.
3. Mixed chimerism can be tolerated in BMT for SCD.
4. SCD patients are not at an increased risk of PRES.
5. Transfusion requirements are the same as other patients undergoing BMT for malignant diseases.
Improvement in Long-term Outcomes

- Spleen: Recovered function
- Pulmonary: Stable to improved function
- Neuroimaging: Stable to improved
- Renal/cardiac: stable to normal function
- Reproductive: Normal to gonadal dysfunction to primary amenorrhea & HRT

Lessons Learned from the Early Trials...

• *Increased neurological consequences*
  – Seizures
  – Intracranial hemorrhage
  – Subarachnoid hemorrhage

• *From SCURT: Increased incidence of PRES*
  – 10 patients developed PRES
  – 1-year incidence: 34% (95% CI 18-52)
  – Related to use of GVHD meds, such as steroids and cyclosporine
  – Typically witness an increase in blood pressure
  – Characterized by headache, visual changes or loss, and seizures

Walters MC, et al. NEJM. 1996; 335: 369-376
Shenoy S, et al. Blood, accepted for publication
Changes in Clinical Management

• Platelets > 50K
  – Reduce risks of intracranial bleeds
  – If no history of cerebrovascular disease, may consider lowering platelet threshold to 30K

• Hemoglobin between 9-11
  – Avoid higher hemoglobin to minimize risks associated with blood hyperviscosity

• Mixed chimerism
  – With the use of reduced intensity, increased concerns for mixed chimerism
  – Encouraged not to discontinue or rapidly taper immunosuppression as may induce GHVD
  – If on a study, encouraged to contact study PIs if mixed chimerism or falling chimerism occurs
Changes in Clinical Management

• Anticonvulsant medications
  – Reduce risk of seizures from busulfan and calcineurin inhibitors
  – Begin 1-2 weeks prior to admission and continue for the duration of calcineurin inhibitor therapy

• Magnesium level normalized
  – Hypomagnesium can be induced by calcineurin inhibitor therapy
  – Hypomagnesium has been associated with seizures
  – Consider empirically beginning magnesium supplementation to maintain normal levels

• PRES
  – Removal of offending agents and control B/P
Changes in Clinical Management

• Control of B/P
  – Calcineurin inhibitors can induce hypertension, which can contribute to post-transplant neurologic events
  – Know the baseline B/P of your patient and try to keep post transplant B/P close to baseline
  – Empirically begin an anti-hypertensive medication on the day beginning calcineurin inhibitor
  – Key: often patients with SCD have lower than normal B/P for age
**B/P Levels for Pediatric Patients**

- Charts based on gender, age, and height
- Charts are for pediatric patients ages 1-17 years

**NIH Blood Pressure Tables for Children and Adolescents**

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<th>Age (Year)</th>
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*Blood Pressure Levels for Boys by Age and Height Percentile*
Other Lessons Learned...
Reproductive Late Effect Challenges

- Gonadal failure and delayed sexual development occurred.
  - Most receiving a myeloablative Busulfan/ Cyclophosphamide containing preparative regimen
- **Females:** In the multicenter study, 6 of 7 evaluable females developed primary amenorrhea
  - Another study 50% (2 patients) had ovarian failure and other 2 had normal menstrual cycles
- **Males:** The majority of evaluable males had normal sexual development
  - 4 of 9 recipients had evidence of hypogonadism
- New studies addressing preservation of fertility

Other Lessons Learned...

Growth Challenges

• Through serial height and weight measurements of 53 children & adolescents transplanted for SCD
  – Growth was NOT impaired in the young children
  – Growth may be diminished if occurs near or during the adolescent growth spurt
  – St. Jude observation: Those recipients with delayed bone growth had normalization of this after HCT, if not complicated by chronic GVHD

Do Not Forget...

• Post transplant immunizations
• While most SCD patients who have not had a splenectomy recover splenic function, this is gradual
• Remember post- transplant immunizations
  – Specifically pneumococcal (PCV13 & PPV23)
  – Consider continuing antimicrobial prophylaxis until patient is fully re-vaccinated
Future Directions

Moving Forward
Open protocols through STAR: Sickle Transplant Alliance for Research

• Retrospective registry
• Transplant for children with less severe disease & MSD
• Transplant for children & adolescents with severe disease using abatacept for GVHD prophylaxis

STAR is a multi-institutional consortium whose mission is to enhance the lives of children suffering from sickle cell disease through blood and marrow transplantation.
A Multi-Center Retrospective Registry of Children with Sickle Cell Disease following Hematopoietic Cell Transplantation

• Specific aims:
  – Aim 1: To establish a multi-center retrospective registry of pediatric sickle cell disease patients who have undergone allogeneic hematopoietic cell transplantation.
  – Aim 2: To describe long term health related outcomes in children with sickle cell disease following allogeneic hematopoietic stem cell transplantation.
Transplant for Children with Less Severe Disease SCD & MSD

• Specific Aims
  – To prospectively assess safety and efficacy of HLA MSD HCT using a reduced intensity conditioning regimen - fludarabine, alemtuzumab and melphalan - in children with less severe SCD.
  – To address current gaps in understanding of the long term effects of HSCT in children with SCD, by longitudinally assessing ovarian reserve, sickle cell related cerebrovascular disease, sickle cell related nephropathy and health related quality of life.
Transplant for Children with Less Severe Disease & MSD: Inclusion Criteria

- Must be at least 2 years and less than 10 years old and have HbSS or Sβ₀ thalassemia
- Must have an HLA identical sibling donor who is less than 10 years old.
- Must meet criteria for less severe disease
  - Asymptomatic cerebrovascular disease, as evidenced by one the following:
    - Silent cerebral infarction with at least one lesion measuring at least 3 mm in one dimension on the most recent MRI scan.
    - Cerebral arteriopathy, as evidence by conditional TCD testing (TAMMV>170cm/sec but <200cm/sec) on two separate scans >2 weeks apart.
  - ≥ 2 painful vaso-occlusive episodes (in lifetime) requiring hospitalization or outpatient treatment with parenteral opioids.
  - ≥ 2 episodes of acute chest syndrome (in lifetime) irrespective of therapy administered.
  - Any combination of ≥ 3 acute chest syndrome episodes and vaso-occlusive pain episodes (defined as above, lifetime).

Hope to begin enrollment by Fall 2016
Enrollment Goal: 50 recipients
Abatacept for Graft Versus Host Disease Prophylaxis after Hematopoietic Stem Cell Transplantation for Pediatric Sickle Cell Disease

• Specific Aims
  – To assess the tolerability of the costimulation blocking agent abatacept (CTLA4-Ig) when added to the standard graft versus host disease (GVHD) prophylaxis regimen of a calcineurin inhibitor and methotrexate in patients receiving early alemtuzumab (completed by day -18) followed by fludarabine and melphalan (FAM) for conditioning.
  
  • Goal: Reduce risk of GVHD
  – To characterize the elimination of alemtuzumab and immune reconstitution in patients receiving this therapy.
Abatacept for GVHD Prophylaxis: Inclusion Criteria

- Patients with Hgb SS or Sβ⁰ thalassemia between the ages of 3 and 20.99 years who are at least 10 kg & receiving an HLA matched bone marrow transplant.
- Patients consider to be at an increased risk for GVHD:
  - Are between 10 and 20.99 years & receiving their transplant from an HLA matched related donor.
  - Are between 3 and 9.99 years & receiving their transplant from an HLA matched related donor who is at least 10 years.
  - Are between 3 and 20.99 years & receiving their transplant from an HLA matched unrelated donor. Donors must be matched at the A, B, C and DRB1 loci at the allele level.
- Patients meeting the definition of severe SCD disease.

Enrollment has begun! Pilot study of 10 recipients
BMTCTN 1503

• Study to compared BMT to standard of care (SOC) in adolescents & young adults with severe sickle cell disease
• Primary Aim: Compare OS at 2 years after BMT or SOC
• Secondary Aim: Compare SCD related events (e.g., pulmonary HTN), functional outcomes, cardiac & pulmonary function, & mean pain intensity (diary) from baseline to 2 years
• Standard transplant secondary objectives as well for those that undergo BMT
BMTCTN 1503

• Eligibility:
  – Age between 15-40.99 year
  – Severe sickle cell disease
  – Adequate physical function

• If identified donor: BMT
  – Busulfan, fludarabine, rATG
  – GVHD prophylaxis: tacrolimus, methotrexate

• If no identified donor: SOC

• Followed for 2 years
BMTCTN 1503

• Enrollment goals:
  – BMT arm: 60 participants
  – SOC (no donor) arm: ~140 participants

• Protocol has been released to participating centers
Summary

• Exciting time for transplant for patients with sickle cell disease.
  – Improving outcomes with increased supportive care
  – Trying to reduce intensity of preparative regimens to decrease risk of acute and late toxicities
  – Expanding transplant to those with less severe disease and adults
Thank you!