Transplantation for sickle cell disease: a review

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Objective

Not to convince you that transplant is the **only** way to treat sickle cell patients...

...but that it might be a good way to treat some sickle cell patients.
Case

A 34 year old Nigerian woman with severe sickle cell disease with multiple vaso-occlusive crises presented for consideration of nonmyeloablative HCT on clinical trial.
History of sickle cell disease

- 70000-100000 BC: Sickle trait appears
- 1910: Hemolysis and vaso-occlusion described
- 1924: Sickle RBCs noted in Grenadan dental student
- 1948: Abnormal electrophoresis of HbS
- 1951: HbS polymerization discovered
- 1951: Role of HbF
- 1980: Civil Rights movement draws attention to SCD
- 1995: TCD screening and transfusions to prevent stroke
- 1998: Clinical trial demonstrates efficacy of HU

Adapted from Rees et al. Lancet 2010
Pathophysiology

Single nucleotide polymorphism in 6th codon β globin gene

\[ GAG \rightarrow GTG \]

Gln\( \rightarrow \)Val

Unstable HbS; polymerizes with hypoxia, dehydration

Hemolysis \(\rightarrow\) Vaso-occlusion
Epidemiology

Most common inherited RBC disorder

>200,000 births/yr

~1000-2000/year in US

Piel et al. *Nature Communications*, 2010
Burden of disease

- Steep decline in the probability of survival of adults with SCD
- Estimated mean lifespan: ~40 years*
- End-organ damage common

Complications of SCD
Management of SCD

Covers:

- Health maintenance
- Management of acute complications
- Management of chronic complications
- Hydroxyurea & transfusion therapy
Disease modifying strategies

“Few would argue that hydroxyurea or bone marrow transplantation, as currently applied, is the final word in the treatment of patients with sickle cell disease.”

- Steinberg MH, *NEJM* 1997

1. Hydroxyurea
   - Indicated for essentially all patients
   - Push dose to maximum tolerated (ANC 2000-4000)
   - End organ complications due to drug failure or intolerance still possible

2. Stem cell transplantation

3. (Gene therapy)

Not mentioned in Guidelines

1\textsuperscript{st} transplant reported in 1984

- 8 year old girl with AML (CR1)
  - HbSS with 1-2 VOC requiring admission per year
  - Donor: 4 year old HLA-matched brother (HbAS)
  - Conditioning: Myeloblative Cy/TBI
  - Infused $2.2 \times 10^8$ nucleated marrow cells on day 0
  - GVHD prophylaxis: Methylpred + methotrexate
  - Developed aGVHD$\rightarrow$cGVHD; off IS by 6 months

Stem cell transplantation for SCD

- SCD symptoms resolved
  - No VOC
  - Transfusions during active GVHD only (aplasia)
- HbS at donor levels

• Karyotype 46,XY by day +30

HCT for SCD

- Restores normal erythropoiesis
- Relieves symptoms related to sickling
- Slows/halts end-organ damage
HLA-matched sibling BMT


• 59 patients from 27 centers
• Age 3.3 - 15.9 years (median 10.1)
• Donor: HLA-matched sibling marrow
• Conditioning:
  – Cyclophosphamide (200 mg/kg)
  – Busulfan* (14 mg/kg)
  – Anti-thymocyte globulin (90 mg/kg)
• GVHD prophylaxis:
  – CSP alone (n = 3) or w/ MTX (n = 54) or prednisone (n = 1)

*All but 2 N. Amer. patients had BU levels monitored since 10-94 [N=32]
Clinical Severity

Indications

• stroke (n = 29)
• other CNS disease (n = 1)
• recurrent ACS/pulm disease (n = 20)
• recurrent pain (n = 8)

Severity:

• 41% with ≥ 1 episode of ACS
• 38% with ≥ 3 VOC episodes per year
• 66% received chronic RBC transfusions:
  – 25% allo-immunized
  – 34% received iron chelation therapy

Walters et al. *BBMT*, 2010
Outcomes of HLA-Matched Sibling HCT

Walters et al. *BBMT*, 2010
Outcomes of HLA-Matched Sibling HCT

- 55 alive at median follow-up 6.5 years
  - 50 disease free
  - 4 transplant related deaths (3 GVHD, 1 IVH)

- Transfusion independent
- Protected from subsequent stroke (if no rejection)
- Stable pulmonary function

Walters et al. BBMT, 2010
Outcomes of HLA-Matched Sibling HCT

• Conclusions:
  – Outcomes good
  – Mortality, GVHD, and rejection rates low

• Caveats:
  – Only in young patients (<16 years)
  – Only with matched sib donors
Challenges

1. Finding a donor.
2. Balancing sustained engraftment and transplant-related mortality.
Challenges

1. Finding a donor.
2. Balancing sustained engraftment and transplant-related mortality.
Donor identification

- Matched sibling donor best.
- What about sickle cell trait?
  - Sickle cell trait does **not** preclude donating stem cells.
    - Recipient: RBC parameters similar to donor’s after HCT
    - Donor: GCSF mobilization safe

Kang et al. Blood 2002
Donor identification

• But...<20% have suitable matched sibling.

• Alternative donors may improve odds, but still challenging
  – Unrelated donor (URD) marrow or PBSC
  – Umbilical cord blood (UCB)
  – Haploidentical relative
Unrelated donor

Probability of finding 8/8 match

Year

Caucasian

Af Am

NMDP data. Figure courtesy of A. Woolfrey.
Likelihood of finding matched unrelated adult donor

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

Match likelihood

Race or ethnic group of searching patient for hematopoietic cell transplantation

- 8/8 HLA match
- ≥7/8 HLA match

Unrelated donor

Challenges of finding unrelated donor in SCD:
1. High level of HLA diversity
2. Underrepresentation in registry
3. Lower donor availability
Umbilical cord blood: HLA-matched sibling

Multicenter EUROCORD/EBMT (1994-2005)
- 485 children (0.7-20 years)
- Indication: SCD (~30%) or thal major
- Matched-sib BMT or matched-sib UCB
- Conditioning: Varied
  - all myeloablative and Bu-based
- GVHD prophylaxis: CSP +/- MTX

Locatelli et al. Blood 2013
Umbilical cord blood: HLA-matched sibling

OS

EFS

Locatelli et al. Blood 2013
Umbilical cord blood: HLA-matched URD

BMT CTN phase 2 (single cohort)
• 8 children (7-16 years), all SCD
• URD single cord blood unit (≥5/6 match)
• Conditioning (reduced intensity):
  – Alemtuzumab day −21 to -19
  – Fludarabine 30 mg/m²/day day -8 to -4
  – Melphalan 140 mg/m² on day -3
• GVHD prophylaxis:
  – CSP or tacro + MMF

Kamani et al. BBMT 2012
Outcomes

- GVHD: aGVHD grade I-II (n = 3); cGVD extensive (n = 1)
- RRT: IVH/seizures, PRES, grade IV liver toxicity (n = 4); 1 death
- No exacerbation of SC related complications
- 5/8 patients experienced graft rejection by day +42
Haploidentical related donor

17 SCD patients (15-46 years)
• 14 haplo; 3 matched sibling
• Reduced intensity:

Haploidentical related donor

- Engraftment:
  - Primary (n = 1) & secondary (n = 5) failure, all in haplos
- RRT: PRES (n = 3), CMV reactivation (n = 3), EBV viremia, MTB
- GVHD: 1 mild aGVHD (matched sib), no cGVHD
- SCD: No new SCD-related complications after engraftment
  - 11/11 transfusion independent
  - 7/11 no longer require narcotics

“Graft failure ...may be acceptable in a fraction of patients if the majority can be cured with limited serious toxicities.”

FHCRC Protocol 2032

Nonmyeloablative haploidentical HCT
Primary endpoint = safety

Inclusions:
1. <55 years old with nonmalignant inherited disorder treatable by allo-HCT
2. High risk for TRM*
3. No HLA-matched donor
4. Related donor with 1 identical haplotype

Burroughs, PI
## Protocol 2032: Characteristics/Outcomes

<table>
<thead>
<tr>
<th>Pt</th>
<th>Diag.</th>
<th>Pre HCT Risk Factors</th>
<th>Regimen</th>
<th>% Chim</th>
<th>GVHD</th>
<th>F/U</th>
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<tbody>
<tr>
<td>1</td>
<td>SCID</td>
<td>CMV</td>
<td>Flu/Cy/2 Gy</td>
<td>100</td>
<td>4</td>
<td>II + &gt; 8.5 yr</td>
</tr>
<tr>
<td>2</td>
<td>SCID</td>
<td>PJP</td>
<td>Flu/Cy/2 Gy</td>
<td>100</td>
<td>3</td>
<td>III + &gt; 5.9 yr</td>
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<tr>
<td>3</td>
<td>SCID</td>
<td>Metapneumovirus</td>
<td>Flu/Cy/2 Gy</td>
<td>91</td>
<td>0</td>
<td>III + †1.4 GVHD</td>
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<tr>
<td>4</td>
<td>HLH</td>
<td>Stroke, BIPAP</td>
<td>Flu/Cy/2 Gy</td>
<td>100</td>
<td>92</td>
<td>II + &gt; 7.0 yr</td>
</tr>
<tr>
<td>6</td>
<td>SAA</td>
<td>-</td>
<td>Flu/Cy/4 Gy</td>
<td>100</td>
<td>100</td>
<td>- - &gt; 1.2 yr</td>
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<tr>
<td>7</td>
<td>*SAA</td>
<td>CHF, Pulm Aspergillus</td>
<td>Flu/Cy/4 Gy</td>
<td>100</td>
<td>100</td>
<td>II + &gt; 11 mo</td>
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<tr>
<td>8</td>
<td>*SAA</td>
<td>Brain/Pulm Bleed</td>
<td>Flu/Cy/4 Gy</td>
<td>100</td>
<td>100</td>
<td>II + &gt; 6 mo</td>
</tr>
<tr>
<td>9</td>
<td>*SAA</td>
<td>-</td>
<td>Flu/Cy/4 Gy</td>
<td>100</td>
<td>100</td>
<td>- + &gt; 6 mo</td>
</tr>
<tr>
<td>10</td>
<td>*SCD</td>
<td>Stroke, Acute Chest</td>
<td>Flu/Cy/4 Gy</td>
<td>99</td>
<td>100</td>
<td>II + &gt; 8 mo</td>
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<tr>
<td>11</td>
<td>*SCD</td>
<td>Acute Chest</td>
<td>Flu/Cy/4 Gy</td>
<td>86</td>
<td>100</td>
<td>II - &gt; 3 mo</td>
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<tr>
<td>12</td>
<td>*Glanzmann</td>
<td>Life Threat. Bleeding</td>
<td>Flu/Cy/2 Gy</td>
<td>85</td>
<td>16</td>
<td>II - &gt; 4 mo</td>
</tr>
</tbody>
</table>

*MMF, Tac, Sirolimus

Slide courtesy of L. Burroughs.
## Treatment Plan: PBSC

<table>
<thead>
<tr>
<th>Pt</th>
<th>Diag.</th>
<th>Conditioning</th>
<th>Graft</th>
<th>% Chimerism</th>
<th>GVHD</th>
<th>F/U</th>
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</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Regimen</td>
<td>Source</td>
<td>CD3</td>
<td>CD33</td>
<td>Acute</td>
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<tr>
<td>1.</td>
<td>HLH</td>
<td>Flu/Cy/4 Gy</td>
<td>PBSC</td>
<td>100</td>
<td>100</td>
<td>II</td>
</tr>
<tr>
<td>2.</td>
<td>HLH</td>
<td>Flu/Cy/4 Gy</td>
<td>PBSC</td>
<td>100</td>
<td>99</td>
<td>II</td>
</tr>
<tr>
<td>3.</td>
<td>SCD</td>
<td>Flu/Cy/4 Gy</td>
<td>PBSC</td>
<td>100</td>
<td>100</td>
<td>III</td>
</tr>
<tr>
<td>4.</td>
<td>CGD</td>
<td>Flu/Cy/4 Gy</td>
<td>PBSC</td>
<td>0</td>
<td>0</td>
<td>III</td>
</tr>
</tbody>
</table>

Slide courtesy of L. Burroughs.
Donors: Conclusions

Umbilical cord blood:
• Good if HLA-matched sibling
• Not so good if unrelated

Haploidentical:
• Well tolerated
• Rejection may be problematic
Challenges

1. Finding a donor.
2. Balancing sustained engraftment and transplant-related mortality.
Engraftment & toxicity

Rejection
(= “relapse”)

Transplant-related
M&M
Indications for HCT & comorbidities

• Indication based on donor availability
  – Matched sib donor
    • Best & most well-established outcomes → least stringent indications
  – Mismatched URD/haplo/UCB
    • Less data → more stringent indications

• Least stringent: Have a donor & have HbSS or HbSβ0
• Most stringent: Severe progressive SCD symptoms & intolerance of supportive care (i.e., HU)

<table>
<thead>
<tr>
<th>HLA-matched sib</th>
<th>HLA-matched URD</th>
<th>Mismatched marrow, haplo, URD cord</th>
</tr>
</thead>
<tbody>
<tr>
<td>Consider early; highest priority for HbSS and HbSβ^0 thal!</td>
<td>Stroke</td>
<td>Recurrent stroke despite adequate chronic transfusions; progressive CNS changes</td>
</tr>
<tr>
<td>Stroke</td>
<td>Elevated TCD velocity</td>
<td>Severe SCD symptoms &amp; inability to tolerate supportive care</td>
</tr>
<tr>
<td>Elevated TCD velocity</td>
<td>Recurrent ACS</td>
<td></td>
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<tr>
<td>Recurrent ACS</td>
<td>Recurrent severe VOC</td>
<td></td>
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<tr>
<td>Recurrent severe VOC</td>
<td>RBC alloimmunization + established indication for chronic transfusions</td>
<td></td>
</tr>
<tr>
<td>RBC alloimmunization + established indication for chronic transfusions</td>
<td>Pulmonary hypertension</td>
<td></td>
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<tr>
<td>Pulmonary hypertension</td>
<td>Recurrent priapism</td>
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<tr>
<td>Recurrent priapism</td>
<td>Sickle nephropathy</td>
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<tr>
<td>Sickle nephropathy</td>
<td>Bone/joint involvement</td>
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<td></td>
<td></td>
</tr>
</tbody>
</table>
The conundrum of indication & TRM in SCD

End organ damage is a transplant indication

but

End organ damage increases risk of transplant-related morbidity & mortality

An example:

• Recurrent ACS $\rightarrow$ decreased DLCO $\rightarrow$ increased TRM
  – DLCO $<$ 65%* = 3 points on HCT-CI $\rightarrow$ HR 4 (validation set)

Sorror et al. Blood 2005
How best to do no harm?

1. Transplant at younger age
2. Reduce intensity of regimen?
Reduced intensity HCT

- NHLBI phase 1/2 feasibility study
- Young adults (>16 years)
- Inclusion:
  - HbSS or HbSC
  - Severe disease
    - End organ damage (CVA, sickle cell nephropathy, ↑tricuspid jet velocity)
    - Reversible complication (frequent vaso-occlusive crises, ACS, osteonecrosis, RBC alloimmunization)
  - HLA-matched family donor

Hsieh et al. NEJM 2009
Reduced intensity

- GCSF-mobilized PBSC

Hsieh et al. *NEJM* 2009
Reduced intensity

• 10 patients enrolled (16-45 years)
  – HU and/or transfusions
• Median follow up 30 months
• One lost graft → 1 year later successful 2\textsuperscript{nd} HCT
• Minimal infectious complications
  – CMV reactivation, C. diff colitis, fever
• No GVHD
• No exacerbation of SC related complications

Hsieh et al. NEJM 2009
Reduced intensity

Laboratory Measurements after Hematopoietic Stem-Cell Transplantation.

Hsieh et al. NEJM 2009
Reduced intensity

Donor chimerism after HCT
All patients remained mixed chimeras on IS at end of study period. HbS levels were similar to donor.

Hsieh et al. NEJM 2009
Mixed chimerism suppresses HbS

- Graft loss
- Prolonged immunosuppression

Unpublished data from Walters MC. Figure courtesy of A. Woolfrey.
Why is rejection such a problem?

- Immunologically intact
- Alloimmunized
- Highly active marrow
  - Hypercellular
  - Erythroid hyperplasia

- Better with “debulking”
  - Myeloablative conditioning
  - Lucarelli preparative regimen
Lucarelli preparative regimen (thal)

- Azathioprine 3 mg/kg/d
- HU 30 mg/kg/d
- Flu 20 mg/m2/d
- Deferoxamine 40 mg/kg Q24hrs
- Cy 40 mg/kg/d
- Bu 14 mg/kg po
- G + epo 2x/week*

- Developed for thalassemia
- Used with modification here for SCD*

How best to do no harm?

1. Transplant at younger age
2. Reduce intensity of regimen
3. Maintain intensity & reduce toxicity
“Need for other options…”

- Nonmalignant disorders with higher risk graft rejection but high TRM with myeloablative conditioning
  - Certain Primary Immunodeficiencies
  - Marrow Failure Syndromes
  - Hemophagocytic Diseases
  - Hemoglobinopathies
  - Metabolic Diseases

- “Reduced intensity regimen that incorporates myeloablative properties of BU without toxicities”
Treosulfan

- Medac International
- Widely used in Europe & under IND in US
  - Chemotherapeutic agent for solid tumors
  - Transplantation for malignant and nonmalignant
- Full intensity, reduced toxicity
- Encouraging preliminary results:
  - Successful engraftment
  - Decreased toxicity – less organ damage
  - Improved survival

Slide courtesy of L. Burroughs & A. Woolfrey.
US Treosulfan: Study Characteristics

Multicenter
Median age 6.4 years (0.2 - 32.5)

Diagnosis (n=47)
• Immune Deficiencies (20)
• Bone Marrow Failure (11)
• HLH (10)
• Sickle Cell Disease (6)

Cell source
• Unrelated (40) Related (7)
• BM (43) PBSC (4)

Burroughs et al, BBMT 2014
Conditioning Regimen
US Treosulfan Study: BM/PB

FLU 150 mg/m²
TREO 42 g/m²
BM or PBSC
rATG 6 mg/kg
Methotrexate
Tacrolimus

Burroughs et al, BBMT 2014
US Treosulfan Study – Survival (n=47)

Survival (%)

2.2 yrs

93%

Months after HCT

Burroughs et al, *BBMT* 2014
US Treosulfan Study: BM/PB

• GVHD:
  – aGVHD d +100: II-IV 62%; III-IV 10%
    • Grade III-IV only occurred prior to adding rATG
  – cGVHD 2 years 21%

• TRM:
  – GVHD (n = 1)
  – Recurrent CNS HLH (n = 1)
  – Surgical complication (n = 1)

Burroughs et al, BBMT 2014
Challenges

1. Finding a donor.
2. Balancing sustained engraftment and transplant-related mortality.
Timing of transplant
Evidence based recommendations

For patients with matched sibling donor:

• “Consider early, prior to or at onset of SCD symptoms, with the highest priority given to patients with HbSS and HbSβ0 thalassemia”

Start the conversation early.

Future directions in SCD therapy

• Gene therapy:
  – LentiGlobin BB305 = lentiviral vector containing an engineered $\beta^{A-T87Q}$-globin gene (*bluebird bio, Inc*)
  – Transduce autologous CD34+ cells
  – Reinfuse after Bu myeloablation
  – 1 severe SCD, 3 thalassemia major
    • Multiple VOC, ACS, silent infarct, chronic RBCs
  – At day +88:
    • 48.5% HbS/48% HbA$^{T87Q}$ ("anti-sickling" Hb)
    • Off chronic RBC transfusions
    • No hospitalizations for SCD-related events

Cavazzana et al. *ASH Annual Meeting*, 2015 abstract #202
Summary

- HCT is potentially curative for SCD.
- Best outcomes in young patients w/ HLA-matched sibling.
- HCT challenging for patients >16 or without sibling donor:
  - Identifying a donor
  - Balancing engraftment and toxicity
- Advances in haploidentical HCT & reduced intensity conditioning regimens are promising.
- Since transplant indication depends on donor, consider early referral to transplant team.
  - Especially for HbSS or HbSβ0 or complications of SCD.
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- All the sickle cell patients I’ve cared for