Stem cell therapies
For Sickle Cell Disease

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“additional research is still needed that addresses the potential risks of this therapy (e.g., failure of engraftment and chronic graft-versus-host disease) before HCT can become a widely used therapy”

HCT in SCD: indications and management recommendations from an international expert panel

Young patients with symptomatic SCD who have an HLA-matched sibling donor should be transplanted as early as possible, preferably at pre-school age.

Unmanipulated BM or UCB (whenever available) from matched sibling donors are the recommended stem cell source.

BMT for SCD (N=59)

Median follow-up - 5.8 years (range, 1.4 – 12.4)

- Survival: 93%
- Event-free survival: 85%
- Cumulative incidence of graft rejection: 9%

Event = death, graft rejection, or disease recurrence.
# Summary of HLA-ID sib HCT for SCD

<table>
<thead>
<tr>
<th>Center</th>
<th>Regimen</th>
<th>n</th>
<th>Age range (years)</th>
<th>Death (mos)</th>
<th>GvHD</th>
<th>Follow up (yrs)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rome</td>
<td>BU14 mg/kg, CY 200 mg/kg/rATG 10 mg/kg, ± Flu 150 mg/m²</td>
<td>40</td>
<td>2-17</td>
<td>3 (2.5, 6, 15)</td>
<td>17.5% acute, 5% chronic</td>
<td>1 - 10</td>
</tr>
<tr>
<td>Brussels</td>
<td>BU 13-18 mg/kg, CY 200 mg/kg, ± rATG (10 – 20 mg/kg), ± HU</td>
<td>50</td>
<td>1.7 – 15.3</td>
<td>2 (0.5, 6.6 yrs)</td>
<td>20.5% acute, 20% chronic</td>
<td>0.4 – 21.3</td>
</tr>
<tr>
<td>NYC</td>
<td>BU 12.8 – 16 mg/kg, Flu 180 mg/m², Alem 54 mg/m²</td>
<td>18</td>
<td>2.3 – 20.2</td>
<td>none</td>
<td>17% acute, 11% chronic</td>
<td>0.4 – 7.5</td>
</tr>
<tr>
<td>Mississippi</td>
<td>BU 14 mg/kg, CY 200 mg/kg, ATG 90 mg/kg</td>
<td>10</td>
<td>2.8 – 16.3</td>
<td>1</td>
<td>40% acute, 10% chronic ext</td>
<td>2.9 – 9.9</td>
</tr>
<tr>
<td>Atlanta</td>
<td>BU 14 mg/kg, CY 200 mg/kg, ATG 90 mg/kg</td>
<td>27</td>
<td>3.3 – 17.4</td>
<td>1 (3)</td>
<td>12% acute, 1 death from chronic GVHD</td>
<td>0.1 - 10</td>
</tr>
<tr>
<td>Pavia</td>
<td>BU 16 mg/kg, TT 10 mg/kg, Flu 160 mg/m² or Treo 14 gm/m², TT 10 mg/kg, Flu 160 mg/m², ATG</td>
<td>30</td>
<td>1.7 – 18.8</td>
<td>none</td>
<td>7% Gr I-II aGVHD, 7% cGVHD in BU group, none in treo group</td>
<td>0.5 – 14</td>
</tr>
</tbody>
</table>
Survival summary

• 195 pediatric HLA-ID sibling allograft recipients treated at 7 US and European centers
• 188/195 survive after HCT – 96%
• 180/195 survive free of SCD – 92%
• At last follow-up, 3 of 180 survivors were receiving IST for cGVHD – 1.7%

CIBMTR – OS 91%
N=412

EBMT – OS 95%
N=487

Registry Data between 1994 - 2005

HbSS and HbSβ° patients, overall survival at 18 years of age is estimated to be 93.9% in the Dallas cohort; NB 1% mortality at 20y in East London
SCD Survival from birth in Belgium 2008 - 2012 (N=469)

P=0.07
P=0.01 (HSCT Vs. HU)
P=0.66 (HSCT Vs. supportive rx)

Le PQ et al, Ped Blood Canc, June 2015
Barriers to Transplant for SCD

- Only 14% of families have HLA-identical sibling donor
- Only 19% have well-matched unrelated donor
- Clinicians do not refer patients because of GVHD and risk of dying
Multi-center clinical trials

- STRIDE – pilot trial of HLA-matched BMT for adults with SCD, 22 enrolled, 21 surviving free of SCD (R34 NIH funding)
- BMT-CTN 1503 (STRIDE2) comparison of HLA-matched BMT and std care in adults with SCD (U01 NIH funding)
- BMT-CTN 1507: Haplo-ID BMT in adults and children with SCD
Objective

- Determine the safety of HCT in patients aged 15-40 years with severe SCD defined as 1-year disease-free survival ≥75%

Trial period: 10/2012 – 06/2015; N = 8 centers; 19 of 23 enrolled in 01/2014 – 06/2015

N = 23 enrolled (results for N = 22)

Median age 22 years

Donors: 17 HLA-matched sibling; 5 HLA-matched URD

Results

- N = 20 alive; median follow-up: 9.7 months
- OS and EFS 95% (90% CI 76%; 99%)
Overall and Disease-free Survival

Kaplan-Meier estimation of OS by donor group for the 22 STRIDE patients

Overall survival

Months from transplantation

Patients at risk
matched-related
matched-unrelated

Matched-related
Matched-unrelated
Eligibility Criteria – BMT CTN 1503

- Age 15 – 40 years
- CNS event: stroke or deficit lasting >24 hours
- ≥ 2 episodes of acute chest syndrome (ACS) in preceding 2 years despite adequate supportive care measures
- ≥ 3 episodes of pain crisis (VOC) in preceding 2 years despite adequate supportive care measures
- ≥ 8 transfusions per year for ≥ 1 year to prevent SCD-related complications (VOC, ACS, stroke)
- Tricuspid valve regurgitant jet (TRJ) ≥ 2.7 m/sec
## Conditioning Regimen – BMT CTN 1502

<table>
<thead>
<tr>
<th>Day</th>
<th>Regimen</th>
</tr>
</thead>
<tbody>
<tr>
<td>-8</td>
<td>IV busulfan 3.2 mg/kg</td>
</tr>
<tr>
<td>-7</td>
<td>IV busulfan 3.2 mg/kg, fludarabine 35 mg/m²</td>
</tr>
<tr>
<td>-6</td>
<td>IV busulfan 3.2 mg/kg, fludarabine 35 mg/m², thymoglobulin 0.5 mg/kg</td>
</tr>
<tr>
<td>-5</td>
<td>IV busulfan 3.2 mg/kg, fludarabine 35 mg/m², thymoglobulin 1 mg/kg</td>
</tr>
<tr>
<td>-4</td>
<td>IV fludarabine 35 mg/m², thymoglobulin 1.5 mg/kg</td>
</tr>
<tr>
<td>-3</td>
<td>IV fludarabine 35 mg/m², thymoglobulin 1.5 mg/kg</td>
</tr>
<tr>
<td>-2</td>
<td>IV thymoglobulin 1.5 mg/kg</td>
</tr>
<tr>
<td>-1</td>
<td>Rest</td>
</tr>
<tr>
<td>0</td>
<td>Infuse bone marrow graft</td>
</tr>
<tr>
<td>Day</td>
<td>Regimen</td>
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<tr>
<td>-----</td>
<td>---------</td>
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<tr>
<td>-3</td>
<td>tacrolimus through day +180; taper per institutional standards; may use cyclosporine if unable to tolerate tacrolimus</td>
</tr>
<tr>
<td>0</td>
<td>Bone marrow infusion</td>
</tr>
<tr>
<td>+1</td>
<td>IV methotrexate 7.5 mg/m²</td>
</tr>
<tr>
<td>+3</td>
<td>IV methotrexate 7.5 mg/m²</td>
</tr>
<tr>
<td>+6</td>
<td>IV methotrexate 7.5 mg/m²</td>
</tr>
<tr>
<td>+11</td>
<td>IV methotrexate 7.5 mg/m²</td>
</tr>
</tbody>
</table>
Study Design - BMT CTN 1503

Consultation with HCT physician

- Clinically Eligible; Consent
  - Register in AdvantageEDC℠

- ERC: Confirm Clinical Eligibility
  - HLA typing
    - Re-register in AdvantageEDC℠ for Biologic Assignment
      - No Donor
      - Donor

- Off study
  - Comparison Cohort
    vs.
    - HCT not Performed
    - HCT

ITT Analysis
Reduced Intensity Conditioning before HLA-Haploidentical Bone Marrow Transplantation in Patients with Symptomatic Sickle Cell Disease

BMT CTN protocol development
Michael R. DeBaun MD MPH
Mark Walters, MD
Robert Brodsky, MD
Haplo-ID BMT for SCD - Hopkins

• Conditioning regimen
  – ATG, CPM 14.5 mg/kg x 2, Flu with post-BMT CPM

• Replaced tacrolimus with sirolimus to avoid posterior reversible encephalopathy syndrome

29 consecutive patients treated
First cohort; 8/14 (57%) engrafted
Second cohort; 10/15 (67%) engrafted
Overall engraftment 62% with 97% survival

Haplo-ID BMT for SCD – St. Mary’s, London

- 12 patients (11 with SCD and 1 with thal major)
- Flu 150 mg/m$^2$, CPM 29 mg/kg, Thiotepa 10 mg/kg, rATG 4.5 mg/kg, TBI 2 Gy with HU/azathioprine 2 months before prep

11/12 have full or partial donor chimerism (92%)
1/12 had graft rejection (8%) and also died

Delafuente, et. al EBMT 2015.
Haplo-ID BMT for SCD – BMT CTN proposal June 2015

HU 30 mg/kg day -51 to -9

BMT 0.5

Day -9 -8 -7 -6 -5 -4 -3 -2 -1 0 5 10 20 30 40 365

Donor BM harvest

MMF 15 mg/kg p.o. t.i.d.
sirolimus

Cy 50 mg/kg/day

Marrow infusion

ATG

Fludarabine 30 mg/m²/day

Thiotepa 8 mg/kg x 1 day

Cy 14.5 mg/kg/day

TBI 200 cGy

Donor BM harvest

Rx

Donor

BMT

2

2 mg/kg

0.5

HU 30 mg/kg day -51 to -9

Primary Objective – Ph II study to define an optimal regimen for HaploID BMT

- Two co-primary end-points for power analysis: Overall survival (OS) and event-free survival (EFS) at 1 year
- Events for EFS: Death, severe GVHD, 1° or 2° GF with (or without) disease recurrence, or sickle complications by 1 year
Study populations

• 2 strata
  – Children <16 years of age who have had a cerebral infarction (clinically overt or silent)
  – Adults 16-45 years of age with severe symptoms

• Analyzed together for two co-primary endpoints of OS and EFS at 1 year
Clinical Trial of Stem Cell Gene Therapy for Sickle Cell Disease

- **Autologous Bone Marrow Harvest**
- **Isolate BM Stem Cells**
- **Add a Normal B-globin Gene**
  - **Condition with chemotherapy**
  - **Transplant BM Cells Back to Patient**
  - **Follow: Safety Efficacy**

Test Cells. Freeze.
Gene therapy for SCD

Table 1. Demographics and Transplantation Outcomes

<table>
<thead>
<tr>
<th>Subject</th>
<th>Age (years)</th>
<th>Gender</th>
<th>Genotype</th>
<th>BB305 Drug Product (VCN)</th>
<th>CD34+ cell dose (x10^6 per kg)</th>
<th>Day of Neutrophil Engraftment</th>
<th>Drug Product-related Adverse Events</th>
<th>Day of last pRBC transfusion</th>
<th>Last Study Visit</th>
<th>Hb amounts at last visit (g/dL)</th>
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<tbody>
<tr>
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<tr>
<td>Subjects with β-thalassemia major</td>
<td></td>
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<td></td>
<td></td>
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<tr>
<td>1201</td>
<td>18 F</td>
<td></td>
<td>β^{0}/β^{E}</td>
<td>1.5</td>
<td>8.9</td>
<td>Day +13</td>
<td>None</td>
<td>Day +10</td>
<td>12M</td>
<td>7.7/11.0</td>
</tr>
<tr>
<td>1202</td>
<td>16 M</td>
<td></td>
<td>β^{0}/β^{E}</td>
<td>2.1</td>
<td>13.6</td>
<td>Day +15</td>
<td>None</td>
<td>Day +12</td>
<td>9M</td>
<td>9.4/13.2</td>
</tr>
<tr>
<td>Subject with severe sickle cell disease</td>
<td></td>
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<td></td>
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<td></td>
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<tr>
<td>1204</td>
<td>13 M</td>
<td></td>
<td>β^{s}/β^{s}</td>
<td>1.2 / 1.0</td>
<td>5.6</td>
<td>Day +37</td>
<td>None</td>
<td>Day +88</td>
<td>45M</td>
<td>2.9/4.0/0.9/12.0</td>
</tr>
</tbody>
</table>

As of February 2015

* VCN, vector copy number; F=female; M= Male for gender, and months for day of last follow-up
^these authors contributed equally

* At 4.5 mos post infusion, no sickle-related events and tapering RBC txns

Cavazzana et al, ESH abstract, 2015
Summary

• HCT for SCD in children is performed rarely, and generally used only in children with significant complications.

• However, if one chose to apply HCT more broadly in the children with a suitable sibling donor, survival after HCT and with supportive care is similar.

• Studies that might expand HCT to adults and haploidentical donors are under development.