Stem Cell Transplantation to Cure Adults with Sickle Cell Disease
Disclosure Statement

I have no financial interest or other relationship with any manufacturer/s of any commercial product/s which may be discussed at this activity.
Biology of Sickle cell disease (SCD)

- Low Oxygen
- Vaso-occlusion
- Hemolysis
- Anemia

- Stroke
- Retinopathy
- Acute Chest Syndrome
- Pulmonary Hypertension
- Cardiac Disease
- Spleen Infarcts
- Priapism
- Avascular necrosis
- Leg Ulcers
- Kidney Disease
- Gall-Stones
- Severe pain episodes
- Dactylitis
SCD-Related Complications

Vaso-occlusive Crises
- #1 cause for hospitalization and negatively impacts quality of life
- ~50% of SCD patients had ≥3/year acute visits for VOC1

Acute Chest Syndrome
- #2 cause for hospitalization and can become rapidly fatal

Stroke
- Lifetime risk: 30% overt stroke, 44% silent infarctions2
- Transfusion therapy: 18% and 28% risk of overt or silent infarcts3

1. Lanzkron S et al, Blood Adv 2018
2. WY Wong et al, Hematol Oncol Clin N Am 2005
3. Hulbert ML et al, Blood 2011
# Current Therapies for SCD

## Hydroxyurea

<table>
<thead>
<tr>
<th>Outcome</th>
<th>HU</th>
<th>Placebo</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pain crises</td>
<td>1.0/year</td>
<td>2.4/year</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Acute Chest Syndrome</td>
<td>25%</td>
<td>51%</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Transfusions</td>
<td>336 U</td>
<td>586 U</td>
<td>0.004</td>
</tr>
</tbody>
</table>

Charache S et al, NEJM 1995  
Niihara et al., ASH Abstract #1318, 2014  
NHLBI Expert Panel Report 2014

## L-glutamine

<table>
<thead>
<tr>
<th>Outcome</th>
<th>L-glutamine</th>
<th>Placebo</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pain crises</td>
<td>2 events</td>
<td>3 events</td>
<td>0.005</td>
</tr>
<tr>
<td>Hospital days</td>
<td>6.5 days</td>
<td>11 days</td>
<td>0.02</td>
</tr>
<tr>
<td>Acute chest syndrome</td>
<td>11.9%</td>
<td>26.9%</td>
<td>0.006</td>
</tr>
</tbody>
</table>

## Transfusion

- **Stroke prevention**
- **Acute complications:**
  - acute chest syndrome, intrahepatic cholestasis, splenic sequestration
- **Preoperative management**
What Year did the following take place?
BONE-MARROW TRANSPLANTATION IN A PATIENT WITH SICKLE-CELL ANEMIA

F. Leonard Johnson, M.B.B.S.,
A. Thomas Look, M.D., Jon Gockerman, M.D.,
Mary R. Ruggiero, P.N.P.,
Luciano Dalla-Pozza, M.B.B.S.,
and Frederic T. Billings III, M.D.

First HSCT performed in an SCD patient in 1984
8 year old girl with Hb SS and AML
  • HLA-matched brother with sickle cell trait
Myeloablative conditioning regimen:
  • Cyclophosphamide (60mg/kg x 2 days) + TBI (11.5 Gy)
Complications:
  • Acute and Chronic GVHD
  • Pneumococcal bacteremia

Johnson Fl et al, NEJM 1984
## Transplant Outcomes:
### Myeloablative/intense regimens in Children

<table>
<thead>
<tr>
<th>Center</th>
<th>N</th>
<th>Rejection</th>
<th>TRM</th>
<th>Cure Rate</th>
<th>Acute GVHD</th>
<th>Chronic GVHD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Belgium</td>
<td>50</td>
<td>10%</td>
<td>7%</td>
<td>83%</td>
<td>20%</td>
<td>20%</td>
</tr>
<tr>
<td>US/Europe</td>
<td>59</td>
<td>10%</td>
<td>6%</td>
<td>84%</td>
<td>15%</td>
<td>12%</td>
</tr>
<tr>
<td>French</td>
<td>87</td>
<td>7%</td>
<td>7%</td>
<td>86%</td>
<td>20%</td>
<td>14%</td>
</tr>
<tr>
<td>Belgium</td>
<td>50</td>
<td>8%</td>
<td>6%</td>
<td>86%</td>
<td>22%</td>
<td>20%</td>
</tr>
<tr>
<td>USA</td>
<td>43</td>
<td>2%</td>
<td>7%</td>
<td>91%</td>
<td>23%</td>
<td>13%</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td>289</td>
<td>8%</td>
<td>7%</td>
<td>86%</td>
<td>20%</td>
<td>16%</td>
</tr>
</tbody>
</table>

References:
- Vermylen et al. BMT 2007
- Walters et al. BMT 2001
- Dedeken et al. BJH 2014
- King et al. AJH 2015
Transplant Outcomes: Improvements with Time

<table>
<thead>
<tr>
<th>Variable</th>
<th>Before 1/2000 ( N = 43 )</th>
<th>After 1/2000 ( N = 44 )</th>
</tr>
</thead>
<tbody>
<tr>
<td>Used ATG</td>
<td>27 (63%)</td>
<td>42 (96%)</td>
</tr>
<tr>
<td>Cord Blood</td>
<td>1 (2%)</td>
<td>11 (25%)</td>
</tr>
<tr>
<td>Deaths</td>
<td>6 (14%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>Rejection</td>
<td>5 (12%)</td>
<td>2 (5%)</td>
</tr>
<tr>
<td>aGVHD ( \geq ) Grade 2</td>
<td>12 (28%)</td>
<td>5 (11%)</td>
</tr>
<tr>
<td>cGVHD</td>
<td>9 (21%)</td>
<td>2 (5%)</td>
</tr>
</tbody>
</table>

## Transplant Outcomes: by Disease Status

<table>
<thead>
<tr>
<th>Variable</th>
<th>Symptomatic N = 36</th>
<th>Asymptomatic N = 14</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (median, range)</td>
<td>8.6 (1.7 – 23)</td>
<td>2 (0.9 – 15)</td>
</tr>
<tr>
<td>Deaths</td>
<td>2 (6%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>Failed Engraftment/Rejection</td>
<td>4 (12%)</td>
<td>1 (7%)</td>
</tr>
<tr>
<td>aGVHD</td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Grade 1 or 2</td>
<td>14 (39%)</td>
<td>5 (36%)</td>
</tr>
<tr>
<td>- Grade 3 or 4</td>
<td>1 (3%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>cGVHD</td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Limited</td>
<td>5 (14%)</td>
<td>2 (14%)</td>
</tr>
<tr>
<td>- Extensive</td>
<td>3 (8%)</td>
<td>0 (0%)</td>
</tr>
</tbody>
</table>
Transplant Outcomes: Long-Term Improvements

<table>
<thead>
<tr>
<th>Organ System</th>
<th>Outcomes Post-transplant</th>
</tr>
</thead>
<tbody>
<tr>
<td>Brain/CNS</td>
<td>· Stable/Improved MRI/MRA</td>
</tr>
<tr>
<td></td>
<td>· No episodes of stroke</td>
</tr>
<tr>
<td>Pulmonary</td>
<td>· Improvement in restrictive pattern 25% of evaluated patients</td>
</tr>
<tr>
<td></td>
<td>· No episodes of acute chest syndrome</td>
</tr>
<tr>
<td>Liver</td>
<td>· Resolution of liver changes in 3 of 3 pts</td>
</tr>
</tbody>
</table>

Walters MC et al. BBMT 2010
Dallas MH et al. BBMT 2013
Green NS et al. BBMT 2017
Transplant Outcomes: Improved Quality of life

When to consider stem cell transplantation

<table>
<thead>
<tr>
<th>HLA-Matched</th>
<th>Standard-of-care</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Stroke or silent stroke with cognitive impairment</td>
<td>• Stroke or silent stroke with cognitive impairment</td>
</tr>
<tr>
<td>• Pain crises (≥2/year)</td>
<td>• Pain crises (≥2/year)</td>
</tr>
<tr>
<td>• Acute chest syndrome (≥2/lifetime)</td>
<td>• Acute chest syndrome (≥2/lifetime)</td>
</tr>
<tr>
<td>• Recurrent priapisms</td>
<td>• Recurrent priapisms</td>
</tr>
<tr>
<td>• Pulmonary hypertension</td>
<td>• Pulmonary hypertension</td>
</tr>
<tr>
<td>• Osteonecrosis (AVN) of joints</td>
<td>• Osteonecrosis (AVN) of joints</td>
</tr>
<tr>
<td>• Kidney damage</td>
<td>• Kidney damage</td>
</tr>
<tr>
<td>• Multiple red blood cell antibodies</td>
<td>• Multiple red blood cell antibodies</td>
</tr>
</tbody>
</table>
Transplant for SCD
Global Experience (1986-2013)

1000 SCD recipients with HLA-matched sibling donor

- 106 Centers/23 Countries (CIBMTR, EBMT, Eurocord databases)
- Median age 9 years old (range: 1 – 54 years)
- 87% received a myeloablative regimen

At 5 years:

- 91% cure rate
- 15% had acute GVHD
- 14% had chronic GVHD
# Transplant for SCD
## Global Experience (1986-2013)

<table>
<thead>
<tr>
<th></th>
<th>Children (n = 846, median age 8)</th>
<th>Adults (n = 154, median age 19)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Myeloablative regimen</td>
<td>90%</td>
<td>73%</td>
</tr>
<tr>
<td>Bone marrow cells</td>
<td>86%</td>
<td>72%</td>
</tr>
<tr>
<td>GVHD-free survival</td>
<td>86%</td>
<td>77%</td>
</tr>
<tr>
<td>Overall survival</td>
<td>95%</td>
<td>81%</td>
</tr>
</tbody>
</table>

For every 1 year increase in age:
- 4% increased risk for acute GVHD
- 9% increased risk for graft failure
- 10% increased risk for death
Transplant for SCD: Experience in adults

**Reduced Intensity Conditioning:**
Fludarabine 30mg/m2 x 4 days
Melphalan 140mg/m2 x 1 day
ATG 30mg/kg x 4 days

1) Hb SS, Age 40, Frequent VOC, ESRD
   Deceased at Day +335 from Lung GVHD complications

2) Hb SC, Age 56, Frequent VOC, AVN, Retinopathy
   Deceased at Day +147 from GI GVHD complications

van Besien et al. BMT 2000
Mixed chimerism

Goal of Stem Cell Transplant

- Therapeutic efficacy → reduce SCD complications
- Minimize toxicity → reduce GVHD & mortality

Is there a chimerism % that can:

1) Avoid toxicity of intense regimens
2) Reverse SCD phenotype
Mixed chimerism

Mouse Model:
Transplanted varying Sickle : Normal marrow

SCD Patients:
Efficacy: No SCD-related complications
Toxicity: No GVHD

<table>
<thead>
<tr>
<th>Donor</th>
<th>Chimerism</th>
<th>Hb (g/dL)</th>
<th>HbS %</th>
</tr>
</thead>
<tbody>
<tr>
<td>AA</td>
<td>11%</td>
<td>11.3</td>
<td>7</td>
</tr>
<tr>
<td>AA</td>
<td>67%</td>
<td>14.2</td>
<td>0</td>
</tr>
<tr>
<td>AA</td>
<td>74%</td>
<td>11.3</td>
<td>0</td>
</tr>
<tr>
<td>AS</td>
<td>60%</td>
<td>11.3</td>
<td>37</td>
</tr>
<tr>
<td>AS</td>
<td>25%</td>
<td>11.8</td>
<td>36</td>
</tr>
</tbody>
</table>

Iannone R et al. Blood 2001
Walters MC et al. BBMT 2001
SCD Adults (median age 26, range 16 – 45 y.o.)
Transplant Regimen:
  - Alemtuzumab/TBI 300 cGy for conditioning
  - Sirolimus for GVHD prophylaxis/graft rejection

- 90% engraftment
- No mortality
- No GVHD

Hsieh M et al. NEJM 2009
Transplant for SCD: NIH Experience

Hemoglobin:

<table>
<thead>
<tr>
<th></th>
<th>Pre-HSCT</th>
<th>Post-HSCT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Female</td>
<td>8.8 ± 0.3</td>
<td>12.6 ± 0.6</td>
</tr>
<tr>
<td>Male</td>
<td>9.3 ± 0.5</td>
<td>12.7 ± 1.1</td>
</tr>
</tbody>
</table>

Hemolytic Markers:

- Reticulocyte Count (x10^9/liter)
  - Before HSCT: 300, >1 Yr: 100
  - Comparison: P=0.004

- Total Bilirubin (mg/dl)
  - Before HSCT: 8, >1 Yr: 2
  - Comparison: P=0.01

- LDH (U/liter)
  - Before HSCT: 500, >1 Yr: 200
  - Comparison: P=0.08

Hsieh M et al. NEJM 2009
Chemotherapy-Free transplant Regimen

Alemtuzumab
- Antibody targeting CD52
- Depletes T and B immune cells
- Does not affect stem cells
- Major risk is reactivation of a virus, CMV

Sirolimus
- Inhibits T-cell activation and proliferation
- Mouse transplant model: sirolimus vs. cyclosporine
  - Only sirolimus treated mice showed long-term engraftment
Chemotherapy-Free Transplant regimen

-10: RBC Exchange Transfusion
-8: Discontinue Hydroxyurea
-7: Alemtuzumab 1mg/kg Total Dose divided over 5 days
-6: Start Sirolimus
-5: TBI 300cGy
-4: Stem Cell Infusion
-3: D0
-2
-1

Diagrams showing the timeline and clinical steps involved in the Chemotherapy-Free Transplant regimen.
Screening process

Time Period: 9/2011 – 12/2017

152 Patients Referred

- 36 lacked full siblings
- 20 declined further evaluation
- 14 denied by insurance

82 SCD Patients with 161 Full Siblings

31 Patients HLA-matched Siblings

- 2 RBC alloimmunized to donor RBC antigen
- 2 declined evaluation

27 (18%) Patients Transplanted
# Patient & TRANSPLANT Characteristics

<table>
<thead>
<tr>
<th>Variable</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>33 (17 – 55)</td>
</tr>
<tr>
<td>Gender (Female: Male)</td>
<td>13 : 14</td>
</tr>
<tr>
<td>SCD Genotype:</td>
<td></td>
</tr>
<tr>
<td>Hb SS</td>
<td>24</td>
</tr>
<tr>
<td>Hb SC</td>
<td>2</td>
</tr>
<tr>
<td>Hb Sβ+-thalassemia</td>
<td>1</td>
</tr>
<tr>
<td>RBC Alloimmunized</td>
<td>6</td>
</tr>
<tr>
<td>ABO Major Mismatched</td>
<td>3</td>
</tr>
<tr>
<td>Donor β-Hemoglobin Status:</td>
<td></td>
</tr>
<tr>
<td>Hb AA</td>
<td>20</td>
</tr>
<tr>
<td>Hb AS</td>
<td>7</td>
</tr>
<tr>
<td>CD34+ Cell Dose (x106 cells/kg)</td>
<td>8.1 (5.1 – 15.3)</td>
</tr>
<tr>
<td>Duration of Follow-Up (months)</td>
<td>49 (2 – 79)</td>
</tr>
</tbody>
</table>
21/27 patients developed ANC < 500

- Median duration 5 days (range: 1-14)
- 5 patients had a neutropenic fever
Engraftment

- All 27 patients initially engrafted
- 3 (11%) subsequently rejected (1 noncompliant, 2 intolerant of sirolimus)
- Chimerism in 24 non-rejected patients:
hemoglobin concentration

P < 0.0001

N: 24 21 19 17 16

Months Post-HSCT

Hemoglobin (g/dL)
cardiopulmonary Improvements

Heart Function:

Lung Function:
SF-36 Health Survey

* 50 is the general US population norm
TOXICITY

• GVHD: 0%

• Rejection: 3/27 (11%)

• Sirolimus: Lung toxicity 2/27 (7%)
  Increased urine protein 3/27 (11%)
  Low blood counts 1/27 (4%)
  Mouth inflammation 4/26 (15%)
  Ankle/knee pain 10/26 (38%)
Post-Transplant Health Care Utilization

**Emergency Care Use**

- **Year One**:
  - Transplanted: [Graph A]
  - Non-transplanted: [Graph B]
  - P = 0.02

- **Year Two**:
  - Transplanted: [Graph C]
  - Non-transplanted: [Graph D]
  - P = 0.007

**Inpatient Hospital Days**

- **Year One**:
  - Transplanted: [Graph E]
  - Non-transplanted: [Graph F]
  - P = 0.001

- **Year Two**:
  - Transplanted: [Graph G]
  - Non-transplanted: [Graph H]
  - P = 0.008
# Transplant for SCD: Chemotherapy-free REgimen

<table>
<thead>
<tr>
<th>Center</th>
<th>N</th>
<th>Age Range</th>
<th>Rejection</th>
<th>Cure Rate</th>
<th>Acute GVHD</th>
<th>Chronic GVHD</th>
</tr>
</thead>
<tbody>
<tr>
<td>NIH</td>
<td>30</td>
<td>16 – 65</td>
<td>13%</td>
<td>87%</td>
<td>0%</td>
<td>0%</td>
</tr>
<tr>
<td>UIC</td>
<td>27</td>
<td>17 – 55</td>
<td>11%</td>
<td>89%</td>
<td>0%</td>
<td>0%</td>
</tr>
<tr>
<td>Calgary</td>
<td>8</td>
<td>&lt; 18</td>
<td>0%</td>
<td>100%</td>
<td>0%</td>
<td>0%</td>
</tr>
</tbody>
</table>

- Hsieh et al. JAMA 2014
- Saraf et al. BBMT 2016
- Guilcher et al. EBMT Abstract # 287 2017
Transplant for SCD: Current Challenges

- 1/3 of SCD patients meet eligibility criteria
  - 14% have an HLA-matched sibling donor

- Potentially all SCD patients should have a haploidentical related donor
  - Parents & Children
  - Siblings (including half-siblings)
  - Aunts/Uncles, Cousins
Haploidentical HSCT: University of Illinois

Chemotherapy:
- Fludarabine
- Cyclophosphamide

TBI 300cGy

Peripheral Stem Cell Infusion

Cyclophosphamide

MMF + Sirolimus*

-6 -5 -4 -3 -2 -1 D0 +3 +4 +5

* MMF until day+35
Sirolimus for 1 year

PMID: 29656137
Screening process

Time Period: 1/2016 – 1/2018

50 SCD Patients Referred

- 10 Denied by insurance

40 SCD Patients & 73 Relatives Screened

- ~60% had available haplo-donor
- 4 No haploidentical donor identified
- 12 Donor specific antibodies (DSA) (MFI > 2000)

24 Eligible SCD Patient-Haploidentical Pairs

- 14 Deferred or declined transplantation

10 (20%) Patients Transplanted
### Haploidentical HSCT: University of Illinois

<table>
<thead>
<tr>
<th>Variable</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>28 (20 – 37)</td>
</tr>
<tr>
<td>Gender (Female: Male)</td>
<td>2 : 8</td>
</tr>
<tr>
<td>SCD Genotype:</td>
<td></td>
</tr>
<tr>
<td>Hb SS</td>
<td>9</td>
</tr>
<tr>
<td>Hb Sβ+-thal</td>
<td>1</td>
</tr>
<tr>
<td>Donor β-Hemoglobin Status:</td>
<td></td>
</tr>
<tr>
<td>Hb AA</td>
<td>3</td>
</tr>
<tr>
<td>Hb AS</td>
<td>7</td>
</tr>
<tr>
<td>Donor Source:</td>
<td></td>
</tr>
<tr>
<td>Parent</td>
<td>5</td>
</tr>
<tr>
<td>Sibling</td>
<td>4</td>
</tr>
<tr>
<td>Child</td>
<td>1</td>
</tr>
<tr>
<td>Follow-Up (months)</td>
<td>12 (4 – 32)</td>
</tr>
</tbody>
</table>
Stable engraftment in 9/10 (90%) of SCD patients
Transplant-related toxicity

- 2 patients with small brain hemorrhages when platelets low
  - Both had history of strokes
  - Both fully recovered and are working full time

- 2 had acute GVHD
  - 1 noncompliant with sirolimus → acute on chronic GVHD
  - 1 acute Grade 2 gut GVHD
    - Resolved with prednisone therapy

Haploidentical HSCT: University of Illinois
Summary

• Stem cell transplantation should be considered for SCD patients w/ complications + HLA-matched sibling
  • >85% cure rate
  • No GVHD observed with alemtuzumab/TBI regimen

• Special circumstances for Haploidentical HSCT in SCD
  • Recent regimens demonstrate >80% cure
  • Chemotherapy → more toxicity
  • GVHD risk
Acknowledgements

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- Ana Gordan, MS

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- 8 West/BMT Nursing Staff