Sickle Cell Disease-
chronic illness or curable disease?
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Objectives

- To review the general principles of hematopoietic stem cell transplantation (HSCT), including risks of morbidity and mortality.
- To understand that allogeneic HSCT is a curative therapy of increasing interest to those with sickle cell disease.
- To learn the techniques of HSCT as applied to sickle cell disease, with a focus on highly effective and safe reduced intensity approaches and future directions.

Why would a family ask about cure for SCD?

www.sicklecelldisease.org
What is hematopoietic stem cell transplantation (HSCT)?

- HSCT is the procedure of infusing blood stem cells from a donor into a recipient.
- Allogeneic HSCT
  - Stem cells from another individual are infused into the recipient after she or he receives preparatory chemotherapy, immunotherapy and/or radiation therapy.

Why not call it BMT?

- Blood stem cells can be donated from
  - Bone marrow (harvested)
  - Peripheral blood stem cells (apheresis procedure)
  - Umbilical cord blood collection
    - Public banks (vast majority)
    - Private banks (1/2 700 to 1/250 000 privately banked cord blood products are used for HSCT)
Risks of myeloablative allogeneic HSCT

- Death
- Infection/Sepsis
- End organ dysfunction
- Veno-occlusive disease of liver
- Renal insufficiency
- Sepsis
- Calcineurin inhibitor (eg cyclosporin)
- Infertility (85%)
- Cancer (5-8%)

[Thomas, 2004]

History of HSCT for SCD 101

BONE-MARROW TRANSPLANTATION IN A PATIENT WITH SICKLE-CELL ANEMIA

F. LEONARD JOHNSON, M.B.B.S.,
A. THOMAS LOWE, M.D., JON GUCKERMAN, M.D.,
MARY R. RUGIERO, P.N.P.,
LUZIANO DALLA-POZZA, M.B.B.S.,
AND FREDERIC T. BILLINGS III, M.D.

[Johnson et al., 1984]

Bone marrow transplantation in sickle cell anaemia

- 12 patients aged 11 months to 23 years
- Median 4 years
- All matched-sibling donors
- Busulphan/cyclophosphamide conditioning
- All alive, all cured
- 1 re-transplanted due to graft failure

[Youngblood, S. et al., 1986; Youngblood et al., 1991]
Bone Marrow Transplantation for Sickle Cell Disease

22 children less than 16 years at HSCT
Symptomatic SCD
- Typically stroke, acute chest syndrome or recurrent pain crises
Busulphan/cyclophosphamide/ATG
Sibling donors with S trait (HgAS) or HgAA were acceptable

Clinical Trial
Inclusion Criteria
These criteria make sense, especially in the context of uncertain outcomes in a clinical trial for a disease with variable phenotypes.
However, they seem to have persisted as the criteria to proceed to HSCT with a matched-sibling donor outside of the research context.

Results of Landmark Study
- 20/22 alive
- 1 died of CNS hemorrhage
- 1 died of GVHD
- 16 had stable donor engraftment
  - ¼ who rejected graft had aplasia, the others autologously reconstituted
- Event-free survival (EFS) 73%
- Overall survival (OS) 91%

(Walters et al., 1996)
Myeloablative HSCT with busulphan and cyclophosphamide
ATG later added due to graft rejection events
Almost all bone marrow stem cell source
Event-free survival (alive with a graft) using ATG was 95.3%
3% graft failure rate with ATG
2% mortality with ATG
22.6% graft failure rate without ATG (Bernaudin et al., 2007); www.commons.wikipedia.org

What are some unique aspects of HSCT for SCD?
- HbS should be <30% prior to conditioning
- To avoid a crisis or CNS event during recovery from HSCT
- Either simple or exchange transfusion can achieve this goal
- Hydroxyurea for 3-6 months prior to HSCT
- To reduce marrow cellularity and facilitate engraftment
- Magnesium must be kept normal
- Risk of seizures
- Cyclosporin will lower Mg

Other supportive care precautions
- BP must be kept normal for age
- Risk of CNS events
- Hg must be maintained 90-110 g/L post HSCT
- Avoid high (hyperviscosity)
- Avoid low (hypoxia)
- Platelets must be kept > 50 x 10^9/L

(Walters et al., 1996)
What about the long-term outlook?
- Generally accepted that complications are minimal
- GVHD is greatest cause of treatment-related mortality (TRM)
- No new CNS events in those who engraft
- Those who had strokes prior to HSCT did not have new CVA’s
- 2 patients with graft loss had subsequent strokes
- Cerebral velocities lowered significantly

What about the status of other organs in the long run post HSCT?
- Majority showed no worsening of pulmonary function
- Of 11 patients with baseline restrictive lung changes
  - 5 showed improvement
  - 6 had stable findings
- Of 2 patients with obstructive changes, one improved and one worsened
- Significant gonadal toxicity, with very high rates of infertility (especially in females)
- Myeloablative busulphan exposure

What about neurocognitive function?
An important question to be answered
"More than twice as many parents of children with non-malignancies compared to parents of those with malignancies reported moving forward with HSCT because they desired a more normal and better quality of life for the patient and family."

(Pelletier et al., 2014)

**Sickle Cell Specific Decision-Making (Southern Georgia)**

- There is a growing body of literature that suggests that HSCT is indicated for children with SCD but, families are not always informed of the option for HSCT and there is some controversy around timelines for offering HSCT, and when it is most appropriate to proceed [15,20]. This controversy may also reflect why no patients with non-malignant diagnoses or their family members identified HSCT being part of the upfront treatment plan as being a theme important in proceeding with HSCT. HSCT may not be offered upfront in this setting.

(Pelletier et al., 2014)

**But not everyone has a choice...**

- Only 25% of children have an HLA-matched sibling donor (10/10)
- 25% of siblings of those with SCD also have SCD
- 0.25 x 0.75 = 0.1875
- Therefore only 18-19% of those with SCD have an unaffected MSD
- Other donor options must be explored in the future...
- NB unrelated HSCT for SCD remains experimental due to relatively high rates of graft failure, GVHD and mortality
Unrelated HSCT

- Unrelated cord blood trials had unacceptably high rates of graft failure
- SCURST trial had only 3/8 subjects who engrafted
  - 37.5% EFS
  - Lower intensity conditioning
- Columbia University experience similar
  - 8 subjects received lower intensity conditioning
  - 50% had grades II-IV aGVHD
  - EFS 50%, OS 62.5%

(Kamani et al., 2012); (Radhakrishnan et al., 2013)

Unrelated HSCT

- Inadequate data to even comment on live-donor unrelated HSCT for sickle cell disease
- Data forthcoming from Nationwide Children’s Hospital
- Alberta Children’s Hospital opened this multi-centre trial
- Study met accrual goals just prior to enrolment of first patient locally

(Angelucci et al., 2014)

How many African-Americans can find unrelated donors?

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<td><strong>Live-donor HSCT</strong></td>
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<td><strong>African American</strong></td>
<td>33</td>
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<td><strong>Not African American</strong></td>
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(Angelucci et al., 2014)
Meet RIC...

- Reduced Intensity Conditioning

  - Lower intensity chemotherapy ± radiation therapy to allow for engraftment yet minimize risks of morbidity and mortality
  - Often lower rates of GVHD
  - Less tissue damage with subsequent antigen presentation for immune reaction

Conditioning

(Hsieh et al., 2009)
What does it mean to get this conditioning?

- ~ 1 week in hospital
- Minimal malaise and mucositis
- Transient hair loss
  - OTHERWISE YOU WOULDN’T KNOW THEY HAD AN HSCT
- No fertility compromise
  - Pregnancy post conditioning described
  - Negligible risk of malignancy

NIH results

- 30 adult subjects
- Many with major SCD co-morbidities
- 87% engrafted to reverse SCD phenotype
- Graft failure related to non-adherence to sirolimus
- One death
  - Sickle cell complication in a person who did not sustain their graft
- No aGVHD
- No cGVHD

European Expert Panel Recommendations

[Hsieh MM et al., 2014]

[Angelucci et al., 2014]
ACH results

- 4 patients have undergone MSD HSCT for SCD
- 1 with myeloablative conditioning
- 3 with reduced intensity conditioning
- All alive
- No GVHD
- No major complications
- ALL CURED!
- No children have received the NIH protocol in published literature
- ACH has done 3 such procedures
- 3-4 more planned in next 6 months
- We recommend the NIH protocol

To summarize:

- SCD has a natural history of morbidity and mortality
- One might argue risks similar to sibling donor HSCT
- SCD can be cured with acceptable risk
- AND FERTILITY PRESERVATION
- Only those with unaffected matched sibling donors (18%) are routinely offered HSCT
- Unrelated donor HSCT remains experimental for SCD