Emerging Therapies in Sickle Cell Disease: Bone Marrow Transplantation As A Curative Therapy

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The Clinical Course of Sickle Cell Disease is Highly Variable and Unpredictable.

1. Dead of Pneumococcal Sepsis < 2yrs
2. Stroke at 10 yrs, hemiplegia. Transfusion and chelation, early death from iron overload.
3. Numerous Pain Crises. >/= 1 bout of acute chest. below-avg. life expectancy.
4. Average incidence of symptoms. Dies in her 40s.
5. Relatively few symptoms. Longer life expectancy, but continued clinical issues.

But significant barriers exist…

Currently the only curative therapy for sickle cell disease is allogeneic bone marrow transplant.

Toxicities of Allogeneic BMT and the Lack of HLA-matched Donors Represent Significant Barriers to Transplant for SCD

The two major barriers are
1. Toxicity associated with myeloablation. Graft rejection after allo-BMT, and GvHD.
2. Lack of HLA-identical donors.

Can we Design a Strategy for Non-toxic BMT That Would Still Cure Sickle Cell Disease?

The answer may lie in mixed chimerism using both allogenic and autologous BMT Approaches…

Key Terms in Transplant for SCD

- Allogeneic Transplant: Using Bone Marrow from a Donor to Cure SCD
  - HLA Matched Sibling
  - Unrelated Donor Transplant
  - HLA Mismatched Family Member

- Gene-Corrected Autologous Transplant

- Mixed Chimerism: The Phenomenon by which both sickle and normal stem cells co-exist after transplant.
Mixed WBC Chimerism Results in Full Replacement With Normal RBC and Cure of Murine SCD

Sustained Mixed Chimerism Is Beneficial To SCD Patients

Can We Translate The Results in SCD Animal Models to Our Patients?
- Safer Allogeneic HSCT
- Gene Therapy Linked with Autologous HSCT

The Standard

Results With Matched Sibling Transplants In Children Have Been Very Encouraging

**And For Children, Are Improving…**

French Multicenter

![Graph showing event free survival](image)

**Event Free Survival**

- **Years:** 0, 3, 6, 9, 12, 15
- **Percent Survival:** 96.3%
- **Percent Survived:** Children's Healthcare of Atlanta

**The New Frontier for Adults with SCD: Non-Myeloablative Transplantation**

*Allogeneic Hematopoietic Stem-Cell Transplantation for Sickle Cell Disease*

Hsieh MM, et al.

*N Engl J Med 2009; 361:2309-2317*

- Adults
- TBI (300 cGy), Alemtuzumab
- PBSC
- Sirolimus (indefinite)

**Other Recent Successful Attempts at Reduced Intensity Conditioning for Patients with Hemoglobinopathies**


- Results suggest that reduced intensity conditioning is feasible.
- But, that the rate of graft rejection may be as high as 15-20% in the absence of chronic immune suppression.

**Sustained Engraftment in 9 of 10 Patients**

<table>
<thead>
<tr>
<th>Patient</th>
<th>Coombing of Donor Cells</th>
<th>Coombing of Recipient Cells</th>
<th>Donor Leukocyte Chimerism</th>
<th>Donor Colonies</th>
<th>Colony Growth</th>
<th>Donor DNA</th>
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*Results are from the non-myeloablative approach. CD34+ cells were obtained from bone marrow and PBSC, and last evaluate recipients were transplanted.*

**Despite Successes, Patients Continue to Face Significant Toxicities of HSCT:**

- Rejection—SCD patients are at increased risk.
- Graft-versus-host disease
- Neurologic Complications: Intracranial hemorrhage and encephalopathy with seizures.
  - Implementation of specific supportive measures, has reduced the incidence of hemorrhage.
  - Seizures are an ongoing risk
- Most common complication: hypogonadism and infertility

**For Children, An Opportune Time to Develop a Safer, Yet Still Highly Effect Approach to BMT**

- An approach that....
- Maintains a Sustained Engraftment Rate of at least 95%.
- Decreases the rate of Neurological Complications to less than 10%.
- Decreases the rate of infertility to less than 25%.
The Safe BMT for SCD Trial:
PI: John Horan, Children's Healthcare of Atlanta

Primary Objective:
• Determine the feasibility of reducing
  Cytoxan: From 200 mg/kg → to 90 mg/kg
  Busulfan: From 12.8 mg/kg → 9.6 mg/kg
By incorporating Fludarabine:
A non-vasculopathic, non-gonadotoxic, yet potent T cell depleting agent into the BMT.

For the SCD Patient
Without an HLA Matched Sibling:
The Outlook is More Complicated

• BMT is More High-Risk
  ◦ Rejection Rates are Higher
  ◦ Risk of Graft-versus-host disease increases
  ◦ Immune Dysfunction Post-transplant Increases

Cord Blood Transplant Trial Closed Due to High Rates of Rejection

• Several Novel Approaches are Now Being Designed For Adults and Children With HLA-mismatched Related Donors.

• Significant Efforts Underway to Understand The Immune Effects of Sickle Cell Disease So That Targeted Therapies Can Be Designed.

• Remains a Critical Area of Unmet Need For Our Patients.

On The Horizon: Autologous BMT:
Gene Correction of A Patient’s Own Stem Cells
To Cure Their SCD:
Curing SCD without the need for a matched-sibling donor or Allogeneic BMT

Question: What Level of Gene Correction Will Cure Sickle Cell Disease?
Or
Would This Approach Really Be A Feasible Cure?

Strategy:
• Without myeloablation, transplant increasing amounts of normal, healthy stem cells into Sickle Cell Disease Mouse

Goal:
• Create low level Stem Cell Correction and Determine the Degree of RBC Replacement with Low Levels of Bone Marrow Chimerism

These results suggest that gene correction of 1-5% could cure Sickle Cell Disease.
• Provides the rationale for the gene correction strategy currently being pursued by multiple research groups.
Emerging Therapies for SCD: Conclusions:

- Bone Marrow Transplantation is Currently the Only Curative Therapy for Sickle Cell Disease.
- Transplants, especially from matched-sibling donors, are getting safer, and new data supports reduced intensity transplants and cure with mixed-chimerism is feasible.
- Several trials ongoing, with mechanisms for financial aid for eligible patients, with matched sibling donors.
- Intense efforts to apply HSCT to patients without matched siblings are underway.
- The survival advantage of normal RBC compared to Sickle RBC means that even low levels of stem cell correction can cure disease.
- This has inspired several new initiatives designed to manipulate the genes that result in SCD and cure SCD by gene therapy and autologous transplant.

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Survival isn’t everything

- Neurologic:
  - 93% stroke-free survival
  - 1 pt had second stroke as S fraction rose after rejection, 1 had ICH
  - Many MRI’s stable to improved, including most silent stroke patients
  - CNS events and vascular disease progression are arrested after BMT for SCD in this series
  - Efficacy of stroke prevention favorable compared to chronic transfusion
Key issues in BMT for non-malignant disease

- Relative risks and benefits to weigh
- Stable mixed chimerism an acceptable goal
- Graft-versus-host not helpful

The DONOR: Who?

- HLA testing and matching
- Healthy matched sibling
  - Can have sickle trait
  - Gender doesn’t matter
  - Blood type doesn’t matter
  - Age generally doesn’t matter
- “Alternate” donors
  - Partially mismatched family member
  - Unrelated donors from registries

Human Leukocyte Antigen

- Determines self vs non-self
- Inherited on short arm of chromosome 6
- Class I
  - HLA-A, HLA-B, HLA-C
- Class II
  - HLA-DR, HLA-DQ, HLA-DP
- Haplotypes
  - Inherit one from each parent

Human Leukocyte Antigen

Extended family typing usually not helpful unless there is consanguinity

Difficulty finding African American donors

- Few otherwise eligible SCD patients have suitable matched sibling donor
- NMDP currently has over 5 million donors
  - Only about 400,000 (8%) are African American
- NMDP minority recruitment efforts
  - www.marrow.org or 1-800-MARROW
  - No-fee donor registration

Waiting for engraftment

For every BMT patient
- Isolation
- Low blood counts
- Transfusions
- Infection prevention/treatment
- GVHD prevention
- Controlling symptoms
- Coping with acute illness
- Staying busy, staying active
- Treatment of complications
- Individualized psychosocial support

Special for SCD
- Keep platelets >50,000
- Keep hgb goal 9-11 g/dl
- Suspicion for pneumococcus
- More aggressive GVHD prevention
- More vigilant control of hypertension
- Prolonged seizure prophylaxis
- Maintain serum Mg >2

0 100 1000
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Outpatient recovery

**For every BMT patient**
- Polypharmacy
- Transfusions
- Tests
- Regaining strength
- Coping with body changes
- Avoiding infection
- Treatment of complications
- BMT clinic visits
- Re-hospitalization
- Psychosocial support

**Special for SCD**
- Keep platelets >50,000
- Keep hgb goal 9-11 g/dl
- Prophylaxis for pneumococcus
- Slow CSa taper
- Vigilant control of hypertension
- Prolonged seizure prophylaxis
- Maintain serum magnesium >2
- Looking for SCD complications

Did it work?

- Engraftment studies
  - The counts
  - Chimerism
- Hemoglobin electrophoresis
- Arrest of clinical sickle events

Dosing

- Fludarabine 35 mg/m²/day for 3 doses (-4 to -2)
- ATG 30 mg/kg/day for 3 doses (-4 to -2)
- Busulfan and Cyclophosphamide
  - Dose level 1:
    - Busulfan 12.8 mg/kg IV (16 doses)
    - Cyclophosphamide 135 mg/kg (3 doses)
  - Dose level 2:
    - Busulfan 12.8 mg/kg IV (16 doses)
    - Cyclophosphamide 90 mg/kg (2 doses)
  - Dose level 3:
    - Busulfan 9.6 mg/kg IV (12 doses)
    - Cyclophosphamide 90 mg/kg (2 doses)

What can be done about sickle cell?

**Supportive**
- Diagnose early (newborn)
- Education
- Prophylactic PCN
- Recognize complications
- Treatment of pain
- Empiric antibiotics

**Interventions**
- Drugs to increase HbF
- Chronic transfusions and chelation
- Erythrocytapheresis

**Cure**
- Gene therapy
- Transplant
  - Matched sib
  - Alternate donor

Who has had BMT for sickle cell?

- First BMT in 1984: leukemia patient with sickle cell
- Since then
  - Over 200 patients worldwide
    - Pesaro n=19
    - France n=60
    - Multicenter n=59
    - Belgium n=50
    - Other Europe/US n=10
  - Overall survival is 91% (n=201)
  - Rejection 8%
  - Stable mixed chimerism 11%
  - Chronic GVHD 13%

Myeloablative Matched Sibling SCD BMT

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<th>Walters et al</th>
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<tr>
<td><strong>Total</strong></td>
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NIH/NHLBI Workshop, 2003
Survival isn’t everything

- Median 4 year follow-up
- Of the 50 engrafted patients
  - No VOC, ACS, sequestration or RBC transfusion
  - QOL appears good, though no formal study
- Growth: grew better after an initial lag
- Endo: Most girls had primary amenorrhea

A Year After Transplant: The “new” normal

- Elimination/decrease of sickle complications.
- Dealing with transplant-specific issues
- Stable grafts
- The Cured Patient: “Ex-sickle”!