Hematopoietic Stem Cell Transplant in Adults with Sickle Cell Disease: the changing landscape

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Outline

• Sickle cell disease morbidity
• Hematopoietic stem cell transplant in SCD – *what we have learnt so far*
• The challenges in the adult patient
• Transplant approach in the adult patient
• Future directions
Case

• 51 year old AAM, lawyer, with sickle cell disease (SCD), Hb SS, h/o recurrent pain episodes, ACS, depression, DVT, cholecystectomy, chronic fatigue and poor QOL. Treatment in the past included: hydrea (1995-2007), decitabine, thalidomide, on chronic transfusion, presented for transplant consultation

• Other medical problems:
  - Transfusional iron overload
  - Sickle cell nephropathy
  - AVN of the Left femoral head
  - Priapism with secondary impotence
Outcome of sickle cell anemia: A 4-decade observational study of 1056 patients

- Childhood survival improved from 79% to 89%
- 73% had 1 or more clinically recognized forms of irreversible organ damage.
- By the fifth decade, 48% had documented irreversible organ damage.
  - ESRD 11.6%
  - Sickle cell chronic lung disease 16% (often associated with pulmonary hypertension)
  - Cerebrovascular accident 11%

Improved survival of sickle cell disease

Quinn et al. Blood. 2010 Apr 29;115(17):3447-52
Age at death for individuals with SCD from CDC compressed mortality reports

Factors associated with survival in a contemporary adult SCD cohort

OS curves by genotype

Survival by pain crises/yr

## Factors associated with survival in a contemporary adult SCD cohort

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Hazard ratio</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pulmonary hypertension</td>
<td>2.34</td>
<td>0.0036</td>
</tr>
<tr>
<td>Leg ulcer</td>
<td>1.66</td>
<td>0.0118</td>
</tr>
<tr>
<td>Proteinuria</td>
<td>1.86</td>
<td>0.0014</td>
</tr>
<tr>
<td>Cerebrovascular event</td>
<td>1.95</td>
<td>0.0005</td>
</tr>
<tr>
<td>Stroke</td>
<td>1.64</td>
<td>0.0335</td>
</tr>
<tr>
<td>Seizure</td>
<td>2.54</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Pain crisis in past year</td>
<td>1.74</td>
<td>0.0054</td>
</tr>
<tr>
<td>Antihypertensive</td>
<td>1.74</td>
<td>0.0168</td>
</tr>
<tr>
<td>Short-acting narcotics (daily)</td>
<td>1.55</td>
<td>0.0395</td>
</tr>
<tr>
<td>sVCAM-1</td>
<td>2.03</td>
<td>0.0003</td>
</tr>
</tbody>
</table>

Factors associated with survival in a contemporary adult SCD cohort

OS by organ severity score

Other end-points

- Effect of organ severity score was additive (p < 0.001)
- Median OS - 61 years
- HbSS and HbS$\beta^0$ - 58 years
- HbSC and HbS$\beta^+$ - 66 years
- HU and HbF had no effect on survival

Let’s look at the impact of sickle cell disease on a specific organ, the brain.
Direct effects of sickle cell disease on the brain

- Overt stroke
- Silent stroke
- Anemia
Overt strokes

- Most widely recognized cause of brain injury in SCD
- Occur in 5 – 10% of children with SCD
- Highest incidence of first stroke: ages 2 – 5
- Rate of stroke recurrence is around 70%
- Blood transfusion therapy can decrease recurrence to around 10%
Stroke free interval versus sickle cell phenotype
Hemorrhagic Stroke

- Most common in adults
- Peak incidence between 20 to 29 years of age
- Subarachnoid hemorrhages most common
- The hemorrhagic predominance may reflect the development of "moya-moya" syndrome years after an earlier thrombotic stroke
- Angiography reveals the complex filamentous structure of the moya-moya lesion
Secondary prevention of overt strokes

• Therapies for prevention of second strokes:
  – Chronic blood transfusion therapy
  – Allogeneic stem cell transplant
  – Hydroxyurea
  – Revascularization
Summary of treatment of stroke

• Recurrence Rate
  – 22% (2.2 per 100 pt yrs) with transfusion (J Pediatr. 2002;140(3):348-54)
  – 50% with cessation of transfusions (J Pediatr 1991; 118(3):377-82.)
  – *Risk higher in first 2 yrs after initial stroke

• Initial treatment should include exchange transfusion (J Pediatr. 2006,149(5):710-2)

• Approximately 45% of the patients that are rigorously transfused will have progressive disease (overt or silent strokes) Blood. 2011 Jan 20;117(3):772-9
  – Progressive CNS lesions based on progressive vasculopathy
Event-free interval of new overt or silent cerebral infarcts in children with SCD while on transfusion therapy for secondary stroke prevention.

- 11/40 with new SCI
- 7/40 new over strokes
- 45% with progressive cerebral infarcts, mean follow-up of 5.2 years

Hulbert et al, 2011
Given the rate of cerebral infarcts in children (37% before 18 years of age), coupled with the high rate of cerebral hemorrhage in adults, we elected to introduce as standard of care MRI and MRA imaging evaluation in adults.
Rationale

• High pre-test probability > 37%
• Detection of either silent cerebral infarcts or moya moya would significantly alter medical care
  – Cognitive testing
    • Alter expectations
  – Consideration for blood transfusion therapy or Hematopoietic stem cell transplant (HSCT)
  – Ongoing CNS imaging surveillance
Preliminary findings of MRI/MRA result in adult patients with SCD

- Implemented as standard of care in 2011
- n=69 (predominantly HbSS -57)
- 9% with aneurysms (~ 5% in general population); 6 patients with moyamoya
  - 6 patients were recommended to have a neurological procedure
  - 2 agreed to the neurosurgical procedure
Consequence of stroke in SCD

- High recurrence rate (progressive)
- Motor, speech, sensory impairment
- **Cognitive impairment**
- Excessive iron stores secondary to transfusions
  - Burden of chelation due to transfusion therapy
- Death
Neurocognitive functioning in a clinical sample of adult patients with sickle cell disease (n = 41)
Clinical Cognitive Assessment Program

• 2.5-hour battery of tests and questionnaires that measures:
  ~ General Intelligence (IQ)
  ~ Memory
  ~ Executive Function
  ~ Psychosocial Adjustment

• Goal: to identify signs of impairment and assist medical team in developing plan of care
## Patient scores on cognitive tests compared to population mean

<table>
<thead>
<tr>
<th>Domain/Test</th>
<th>Patient Mean (SD)</th>
<th>Population Mean (SD)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>IQ (Wechsler Adult Intelligence Scale-IV)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Full Scale IQ</td>
<td>85.5 (13.9)</td>
<td>100 (15)</td>
<td>&lt; .001</td>
</tr>
<tr>
<td>Verbal Comprehension Index</td>
<td>89.2 (13.5)</td>
<td>100 (15)</td>
<td>&lt; .001</td>
</tr>
<tr>
<td>Perceptual Reasoning Index</td>
<td>89.8 (15.8)</td>
<td>100 (15)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Working Memory Index</td>
<td>86.6 (11.7)</td>
<td>100 (15)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Processing Speed Index</td>
<td>85.1 (13.7)</td>
<td>100 (15)</td>
<td>&lt;.001</td>
</tr>
</tbody>
</table>
Cognitive test scores in patients with overt strokes vs no overt strokes

<table>
<thead>
<tr>
<th>Test</th>
<th>Overt Stroke</th>
<th>No Overt Stroke</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Full Scale IQ</td>
<td>83.7 (22.9)</td>
<td>85.8 (11.9)</td>
<td>Not Significant</td>
</tr>
<tr>
<td>Total Memory Recall</td>
<td>30.1 (8.8)</td>
<td>40.5 (11.1)</td>
<td>.026</td>
</tr>
<tr>
<td>Executive Functioning</td>
<td>5.3 (3.7)</td>
<td>7.7 (2.5)</td>
<td>.033</td>
</tr>
</tbody>
</table>
### Relation between cognitive functioning and employment status

<table>
<thead>
<tr>
<th>Test</th>
<th>Employed/In School</th>
<th>Unemployed</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Full Scale IQ</td>
<td>93.1 (12.6)</td>
<td>78.9 (11.6)</td>
<td>.001</td>
</tr>
<tr>
<td>Total Memory Recall</td>
<td>41.1 (11.8)</td>
<td>36.8 (10.9)</td>
<td>Not Significant</td>
</tr>
<tr>
<td>Delayed Memory Recall</td>
<td>43.9 (13.3)</td>
<td>35.5 (12.0)</td>
<td>.04</td>
</tr>
<tr>
<td>Executive Functioning</td>
<td>8.1 (2.5)</td>
<td>6.7 (3.0)</td>
<td>Not Significant</td>
</tr>
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</table>
Given the high rate of CNS morbidity, and progressive organ dysfunction, can we abate progression of the disease?
Outcome after transplantation for 50 children with advanced, symptomatic SCD

An event is defined as death, graft rejection or recurrence of sickle cell disease

Late effects evaluation

- 55 long-term survivors >2yrs post-BMT
- Median age 9.4 year (range 3.3-14.0)
- No patient had an additional stroke or SCI
- All patients had abrogation of SCD related clinical symptoms such as pain and ACS
- Significant gonadal toxicity >females
- Unchanged or improved pulmonary function

Outcome of patients with hemoglobinopathies given either cord blood or BMT from an HLA-identical sibling: Eurocord-EBMT

Overall survival

Other outcomes
• Median age 6yrs and 8yrs
• Median year 2001 vs 1999 for CBT v BMT respectively
• Median follow-up 70 months
• DFS did not differ in both
• GVHD: BMT > CBT
• Graft failure: CBT > BMT
• Outcomes were comparable

Long-term outcome and evaluation of organ function in Pediatric patients with SCD following HSCT- St. Judes experience

Matched related donor (n=14)  Haploidentical (n=8)

Dallas et. al Biol Blood Marrow Transplant 19 (2013) 820-830
**Late effects: MRD or Haplo**

- Indication: stroke, recurrent ACS and VOE
- Median follow-up: $9.0 \pm 2.3$yrs / $7.4 \pm 2.7$yrs
- Greater risk of GVHD in both arms
- Higher risk of graft rejection in Haplo arm
- Beneficial outcomes similar in both arms
  - No recurrent stroke or SCI, MRI improved
  - Stable NCT with no change in IQ post-HSCT
  - Decline in DLCO, renal and cardiac function in MRD cohort, likely due to conditioning

Dallas et. al Biol Blood Marrow Transplant 19 (2013) 820-830
Health related quality of life in children with SCD and thalassemia following HSCT

Benefits and risks of HSCT

**Benefits**
- Curative in SCD
- Halts and reverses chronic end-organ damage
- Improved overall QOL

**Risks**
- Early and Late regimen related toxicities
- Increased risk of infertility
- Growth disturbance in children
- 5% long term increased risk of secondary cancer
<table>
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<tbody>
<tr>
<td>Total</td>
<td>611</td>
<td>627</td>
</tr>
<tr>
<td>Type of donor</td>
<td></td>
<td></td>
</tr>
<tr>
<td>HLA identical</td>
<td>487</td>
<td>430</td>
</tr>
<tr>
<td>CB related and unrelated</td>
<td>73</td>
<td>71</td>
</tr>
<tr>
<td>Haploidentical donor</td>
<td>34</td>
<td>61</td>
</tr>
<tr>
<td>Other unrelated donor</td>
<td>17</td>
<td>65</td>
</tr>
<tr>
<td>Overall survival</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1 year</td>
<td>95% + 1%</td>
<td>96% + 2%</td>
</tr>
<tr>
<td>2 year</td>
<td>94% + 1%</td>
<td>94% + 1%</td>
</tr>
</tbody>
</table>
The challenges

• Severely shortened life span in adults with SCD (mean age of death 38.2 years 1994-2004, unchanged from the early 90s)

• Improved survival into adulthood has uncovered true natural history of adult SCD with progressive organ damage with significant morbidity and mortality

• Goal: sustained donor engraftment with minimal toxicity using novel approaches
Other concerns

• Need to avoid the high morbidity and mortality associated with conventional bone marrow transplantation (BMT)
• What level of hematopoietic chimerism alleviates both disease related morbidity, and prevents silent organ damage
• The scarcity of acceptable stem cell donors
• No hard & fast indications for transplant
Approach to HSCT in the adult patient ..... 
“Primum non nocere”  
(first do no harm)
## Summary of earlier non-myeloablative transplant experience

<table>
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</thead>
<tbody>
<tr>
<td><strong>Number</strong></td>
<td>2</td>
<td>2</td>
<td>6</td>
<td>1</td>
<td>7</td>
<td>18</td>
</tr>
<tr>
<td><strong>Conditioning</strong></td>
<td>Flu, Mel, ATG</td>
<td>Flu, Mel, campath</td>
<td>Flu, 200 TBI, ATG</td>
<td>Flu, Cy</td>
<td>Flu, Bu, ATG, TLI</td>
<td></td>
</tr>
<tr>
<td><strong>Immunosupp</strong></td>
<td>Tacro, MTX</td>
<td>Tacro or CSA, MMF</td>
<td>CSA, MMF</td>
<td>CSA</td>
<td>CSA</td>
<td></td>
</tr>
<tr>
<td><strong>Age</strong></td>
<td>40, 56</td>
<td>19, 24</td>
<td>3 to 20</td>
<td>8</td>
<td>6 to 18</td>
<td></td>
</tr>
<tr>
<td><strong>Engraftment</strong></td>
<td>2</td>
<td>2</td>
<td>5</td>
<td>1</td>
<td>1</td>
<td>6</td>
</tr>
<tr>
<td><strong>Rejection</strong></td>
<td>0</td>
<td>1</td>
<td>6</td>
<td>0</td>
<td>1</td>
<td>8</td>
</tr>
<tr>
<td><strong>Acute GvHD</strong></td>
<td>2</td>
<td>0</td>
<td>1 (Gr 2)</td>
<td>0</td>
<td>1 (Gr 2)</td>
<td>8</td>
</tr>
<tr>
<td><strong>Chronic GvHD</strong></td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>1 (limited)</td>
<td></td>
</tr>
<tr>
<td><strong>Mixed chimerism</strong></td>
<td>0</td>
<td>1</td>
<td>6</td>
<td>1</td>
<td>6</td>
<td></td>
</tr>
<tr>
<td><strong>Death</strong></td>
<td>2 (GvHD)</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td></td>
</tr>
</tbody>
</table>
In the adult patient with an HLA identical sibling
NIH protocol 03-H-0170
non-myeloablative stem cell transplant

- Alemtuzumab (1 mg/kg total)
- TBI 300 cGy
- Unmanipulated G-CSF mobilized PBSC infusion
- Red cell exchange to lower HbS ~ 30%
- Platelet transfusion threshold is 50k/uL (to prevent CNS bleeding)
- Taper immunosuppression planned at 1 year post transplant, if CD3 donor chimerism is >50%

- Hydroxyurea is continued through day -8

Update on protocol 03-H-0170

Overall survival, 100%
Disease free survival, 87%

30 SCD patients transplanted
22 patients with white cell engraftment
21 patients with donor red cell engraftment
1 patient with delayed red cell engraftment (anti-donor RBC antibody)
No GvHD

- Median f/up >3 yrs
- Age 17-65 yrs
- GCSF primed PBSC
- Graft failure 3/26
How about the adult SCD patient without an HLA identical sibling?
Haplo-identical Transplant for Sickle Cell Disease and other Hemoglobinopathies
**Proof of principle**

- Non-myeloablative regimen, suggests that the procedure can be performed in patients who are ineligible for myeloablative alloBMT
- Expands the donor pool for eligible patients
- Immune suppression approach reduces risk of graft rejection and minimizes GVHD
Mechanism of tolerance induction by high dose cytoxan

Leo Luznik, Paul O'Donnell and Ephraim Fuchs, Semin Oncol. 2012
Conditioning schema

- First 2 pts were transplanted w/o ATG
- Sirolimus replaced tacrolimus w/ 11 pt to reduce the incidence of PRES

Outcomes data

• 19 patients screened, 17/19 were transplanted (89%)
• 14 -haploidentical; 3 -HLA-matched related donors.
• Eleven patients engrafted durably.
• After median follow-up of 711 days (minimal follow-up 224 days), 10 patients are asymptomatic, and 6 patients are off immunosuppression.
• Only 1 patient developed skin-only acute GVHD that resolved without any therapy.
• No mortality

Limitations

- No assessment of whether there was attenuation of end organ disease, specifically CNS, lung or kidneys
- Graft failure, 43% in haploidentical pairs, remains a major obstacle
## Pros and cons of three existing alloBMT approaches in patients with SCD

<table>
<thead>
<tr>
<th></th>
<th>Myeloablative matched alloBMT</th>
<th>Non-myeloablative matched alloBMT</th>
<th>Non-myeloablative mismatched (haplo) alloBMT</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Pros</strong></td>
<td>Curative</td>
<td>Does not exclude SCD patients with end-organ damage</td>
<td>Does not exclude SCD patients with end-organ damage</td>
</tr>
<tr>
<td></td>
<td>Large experience</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Good rates of engraftment</td>
<td>More available to adults with SCD (30%)</td>
<td>Available to most SCD patients (&gt;50%)</td>
</tr>
<tr>
<td></td>
<td>May attenuate end-organ damage</td>
<td>TRM &lt; 5%</td>
<td>TRM &lt; 5%</td>
</tr>
<tr>
<td></td>
<td>EFS 85%; OS 97%</td>
<td>EFS 79%; OS 95%</td>
<td>EFS 58%; OS 96%</td>
</tr>
<tr>
<td><strong>Cons</strong></td>
<td>Limited availability ~10%</td>
<td>Limited experience</td>
<td>Limited experience</td>
</tr>
<tr>
<td></td>
<td>Limited to children less than 16 yrs old</td>
<td>Graft rejection (11– 50%)</td>
<td>Graft rejection (40-50%)</td>
</tr>
<tr>
<td></td>
<td>TRM 7%</td>
<td>Acute and chronic GVHD</td>
<td>No GVHD</td>
</tr>
</tbody>
</table>
International Consortium

- Vanderbilt team
  - Haydar Frangoul
  - Michael Debaun
  - Adetola Kassim

- Johns Hopkins team
  - Robert Brodsky
  - Kenneth Cooke

- UAB team
  - Racquel Shelton

- UK Team
  - Josu de la Fuente
  - Baba Inusa
  - Paul Telfer

- French team
  - Nathalie Dhedin
  - Francoise Bernaudin
  - Mariane Demontal
  - Mathieu Kuentz
Update on collaborative effort

- Created both pediatric and adult transplant consortium for haplo-identical transplant in SCD
- Common entry criteria and protocol
- Signed memorandum of understanding
- To date: 4-patients at VUMC; 3-patients in France
- JHC - 10/12 (83%, all haplos) engrafted with GCSF mobilized donors; 1 death (TRM 4%) - ?IPD; 1-GVHD (4%)
- Enrollment pending in UAB and UK
HSCT approach for the adult patient

Adult SCD patient with organ dysfunction (?severity score or CI)

- HLA identical sibling available
  - Non-myeloablative BM or PBSC*

- No HLA identical sibling
  - Related non-myeloablative haploidentical BM

Other approaches being evaluated: Unrelated cord blood, expanded cord strategies, MUD
* Using the haploidentical approach with high dose cytoxan
Case: follow-up

- Patient had no HLA matched sibling
- Underwent a Haplo-BMT from 58yr old sister
- Indication: SCD with multiple comorbidities
- Data D+100: RFLP 100% donor; sorted chimerism
  CD3 / CD 33 100% donor; HPLC: nl hemoglobin
- Presently: >D +120 from Haplo-BMT
- Complications: AKI due to sirolimus, and rash
  (suppurative folliculitis) - resolved
Special dedication

“I never thought that this could happen in my lifetime. I still have lingering issues from living with SCD for so long; but no NEW organ damage or bone damage will occur to me because I am cured”.
Conclusions

- Haplo-BMT approach has low toxicity, applicable to adults with severe organ damage
- Less than full engraftment sufficient to revert the sickle phenotype
  - no acute or chronic GvHD
  - data suggest operational tolerance to donor blood cells
- Longer follow-up and further accrual to ascertain
  - stable chimerism off immunosuppression
  - reversal of end-organ damage
- Amended protocol to enroll pediatric patients
Acknowledgements

• Patients and their families
• Michael Debaun, MD
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• Nicoll Hannaway, LCSW
• Members of the Vanderbilt-Meharry-Matthew Walker Center of Excellence for Sickle Cell Disease