Improved Outcome Following Unrelated Donor Allografts: When Should BMT Be Considered for Adults and Children with Severe Aplastic Anemia?

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Marrow Failure: Sustained decrease in at least two of the three major parts of BM: WBC, blood or platelets

First Risk Stratification: Rule out Inherited Marrow Failure Disease

- Acquired Aplastic Anemia
  - Loss of hematopoietic stem cells via immune attack or toxin exposure
  - Non-vs. Severe Aplastic Anemia: Camitta Criteria
    - ≥2 lines down: ANC < 500/μL, Plts < 20K/μL, Retic < 1%
    - BM cellularity <25% or 25-50% with 30% hematopoietic cells
    - “Very Severe AA” ANC < 200/μL
  - Treated with immune suppression or BMT
- Hereditary BM Failure Syndromes
  - Genetic disorders resulting in BM or single lineage failure
  - Disorders often associated with phenotypic abnormalities
  - Propensity to develop secondary MDS/Leukemia
Hereditary Marrow Failure Syndromes

• Fanconi Anemia (FA)
• Shwachman-Diamond Syndrome (SDS)
• Dyskeratosis Congenita (DC)
• Congenital Amegakaryocytic Thrombocytopenia (CAMT)
• Thrombocytopenia with Absent Radii (TAR)
• Diamond-Blackfan Anemia (DBA)
• Severe Chronic Neutropenia (Kostmann’s Syndrome)
• Seckel Syndrome
• Pearson Syndrome (mitochondrial disorders)

What BMF Patients should be further evaluated?

• Patients who are short or have phenotypic abnormalities such as
  – Radial anomalies (abnormal or missing thumbs, abnormal radius) (FA)
  – Metaphyseal chondrodysplasia, narrow chest (SDS)
  – Café au lait (FA), reticular upper chest pigmentation (DC)
  – Small HC, hypo/hypertelorism, small eyes (FA)
  – Abnormal ear shape & location, poor hearing
  – Abnormally ridged and small nails, esp. toenails (DC)
  – Leukoplakia (DC)
  – Square blockish head (DBA)
  – Developmental delays, school issues, ADHD (FA, SDS, Seckel)
  – Neurological findings (mtDNA disorders)
  – Hypospadius, cryptorchidism

• Patients with unusual findings on testing
  – Cardiac anomalies (FA, DC)
  – Horseshoe kidneys (FA)
  – Pulmonary fibrosis (DC)
  – Elevated LFTs (SDS)
  – Liver fibrosis, cirrhosis, esophageal varices (DC)
  – Small or fatty pancreas (SDS)
  – Osteopenia in a young patient (SDS, DC)
  – Severe dental anomalies (SDS)

• Patients with unusual cancers or response to treatment
  – SCC in young patient (H&N, vulva, cervix)
  – AML or MDS with unusual or with unexpected cytogenetics (3q gain, isochromosome 7, 20q del)
  – Unexpectedly severe response to chemo or radiation (severe toxicity, prolonged pancytopenia) - exp. Alkylators (FA, ?SDS), Actino-D (?SDS), radiation for H&N cancer
  – MOF with BMT Prep – too late to find out!
**Initial therapeutic decision**

- **Age**
  - 40-50yr
  - > 40-50yr

- **Transfusion dependent**
  - Yes
  - No

- **HLA identical sibling donor**
  - Yes
  - No

- **BMT**
- **ATG + CSA**
- **ATG + CSA**
- **Watch and wait**

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If I get sibling transplant up front, what are keys to success?

- Don’t wait!
- Bone marrow is best
- Give me ATG or Campath
- Age is a high price to pay for maturity. ~Tom Stoppard

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**EBMT--Sib HCT in SAA: Factors that Improve Outcome**

<table>
<thead>
<tr>
<th></th>
<th>Univariate RR</th>
<th>p</th>
<th>Multi-variate RR</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age ≥20 years</td>
<td>2.4 &lt;0.0001</td>
<td></td>
<td>2.0 (1.5-2.5)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Wt, DaT ≤114 lb</td>
<td>1.7 .001</td>
<td>1.3 (1.04-1.7)</td>
<td>.005</td>
<td></td>
</tr>
<tr>
<td>No ATG in w/s</td>
<td>1.6 .001</td>
<td>1.6 (1.2-1.9)</td>
<td>.004</td>
<td></td>
</tr>
<tr>
<td>Cond. Reg. other than Gy200</td>
<td>1.47 .004</td>
<td>1.3 (1.04-1.6)</td>
<td>.007</td>
<td></td>
</tr>
<tr>
<td>Use of PB vs BM</td>
<td>2.1 &lt;0.0001</td>
<td>1.6 (1.2-2.0)</td>
<td>&lt;0.0001</td>
<td></td>
</tr>
<tr>
<td>CyA+MTX vs other</td>
<td>0.76 .004</td>
<td>0.9 (0.7-1.1)</td>
<td>0.3</td>
<td></td>
</tr>
<tr>
<td>Radiation conditioning</td>
<td>1.3 .001</td>
<td>1.7 (1.0-1.4)</td>
<td>0.3</td>
<td></td>
</tr>
<tr>
<td>Fem Don in Male Recipient</td>
<td>1.0  .7</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Previous IST</td>
<td>1.2 .51</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CMV D+/R+</td>
<td>0.8 .93</td>
<td></td>
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</table>

SAA = aplastic anaemia; Cond. Reg. = conditioning regimen; PB = peripheral blood; BM = bone marrow.
Acute and Chronic GVHD: Sib BMT

Young patients treated right . . .

What if I’m Over 40? Sangiolo et al Seattle
23 patients, 40-68 (median 49)—11 previously failed IS therapy

I was treated with IS, when would I need unrelated donor BMT?

- Outcome varies based upon timing, donor, approach, and possibly other factors
  - Initial failure of IS when good donor available?
    - Most agree!
  - Failure of two attempts at IS with any donor?
    - Relapse after weaning IS?
      - Many can have CSP dependence and do well
    - Failure if IS with short telomeres with any donor?

ATG and cyclosporine for severe aplastic anemia: association between hematologic response and long-term outcome

Rosenfeld JAMA 2003;289:1130

Treatment of severe aplastic anemia after failure to respond to first line ATG+CSA

Late events

Relapse 35% at 5yr

11% MDS & 10% PNH

Telomere Length, ARC and Survival

Response same--Telomere Length Related to Clonal Evolution

Telemore Length and Relapse
Telomere Length and Survival

Other Issues: Predicting Response to IS

- Camitta Criteria do not predict response
- Low ANC (<200), high risk for early death
  - Patients with low ANC at 1 month on G-CSF → survival
- ALC and ARC combine to predict response/survival
- Age predicts response
- Presence of PNH clone unsure
- Many markers require further validation
- Telomere length does not predict response, but does predict relapse, clonal evolution and survival

Current Status of Unrelated Donor BMT

- BM is the best source
- Reduced intensity approaches have increased survival significantly
- Patients transplanted within 1-2 years of diagnosis do better
- Recipients of mismatched donors/haplo/cords have worse outcomes
  - Small studies hint at progress

Excellent outcome of matched unrelated donor transplantation in paediatric aplastic anaemia following failure with immunosuppressive therapy: a United Kingdom multicentre retrospective experience

- Samarasinghe et al.
- BJH 2012
- N=44 for transplant with this package
  - Also evaluated those receiving IST first with rabbit ATG/CSA
  - All donors matched at A,B,C,DRB1,DQB1
- Fludarabine 150 mg/m²
- Cyclophosphamide
  - 11: CY 200; 33: CY120
- Alemtuzumab (Campath)
  - 14: 0.3 mg/kg/day x3
  - 30: 0.2 mg/kg/day x5
Samarasinghe et al. BJH 2012

<table>
<thead>
<tr>
<th>MUD HSCT</th>
<th>Numbers</th>
<th>44</th>
</tr>
</thead>
<tbody>
<tr>
<td>Medium age at HSCT (range)</td>
<td>2006 (2006–2019)</td>
<td></td>
</tr>
<tr>
<td>Gender (Male:Female)</td>
<td>8:1 (3:4)</td>
<td></td>
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<tr>
<td>SAA vs SAA</td>
<td>19 (43.2%):25 (56.8%)</td>
<td></td>
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<tr>
<td>FFM IST (median of IST course)</td>
<td>8 x 2 IST, 1 x 3 IST</td>
<td></td>
</tr>
<tr>
<td>OS and FFS following HSCT</td>
<td>95.01% (95% CI 81.38 to 98.74)</td>
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(A) Children with Idiopathic SAA who received Rabbit ATG/Ciclosporin as first line therapy. The 5-year estimated failure-free survival (FFS) following immunosuppressive therapy was 13.3% (95% CI 4.0 to 27.8) and overall survival (OS) was 94.2% (95% CI 78.7 to 98.6). \((n = 43)\).

(B) OS and FFS following matched unrelated donor-haematopoietic stem cell transplantation with the FCC (fludarabine, cyclophosphamide, alemtuzumab) regimen. The estimated 5-year OS/FFS following HSCT was 95.01% (95% CI 81.38 to 98.74). \((n = 44)\)

Samarasinghe et al. BJH 2012

<table>
<thead>
<tr>
<th>MUD HSCT</th>
<th>Total N = 296</th>
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<tbody>
<tr>
<td>5-year cumulative incidence of acute GVHD</td>
<td>38-45% (95% CI 19-49-19-74)</td>
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<tr>
<td>5-year cumulative incidence of chronic GVHD</td>
<td>11-55% (95% CI 6-92-16-43)</td>
</tr>
<tr>
<td>5-year cumulative incidence of graft failure</td>
<td>0%</td>
</tr>
<tr>
<td>Medium donor chimerism at last follow-up (n = 42)</td>
<td>100% (88-100%)</td>
</tr>
<tr>
<td>5-year cumulative incidence of clonal evolution</td>
<td>0%</td>
</tr>
</tbody>
</table>

Use of Peripheral Blood (PB) instead of Bone Marrow (BM) Grafts

- Total N = 296
- 225 BM and 71 PB
- Donor-recipient pairs matched
- HLA-A, -B, -C, -DRB1 (allele-level)
- Interval from diagnosis to HCT
  - 13 months in the BM group
  - 11 months in the PB group
- Median follow-up: 3 yrs
PB vs BM Unrelated Donor Transplants for Aplastic Anemia

<table>
<thead>
<tr>
<th>BM vs PB</th>
<th>Neutrophil recovery</th>
<th>Platelet recovery</th>
<th>Acute GVHD</th>
<th>Chronic GVHD – Age &lt; 20</th>
<th>Chronic GVHD – Age 20+</th>
<th>Survival</th>
</tr>
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Impact of HLA-Matching in Unrelated Donor Transplantation for Aplastic Anemia

M Eapen, et al. Presentation #213, Monday, Dec 6, 7:15 am

- N = 388 unrelated donor HCT
- Bone marrow grafts
- Age, median 20 years
- Good performance score: 70%
- 56% transplanted > 12 mo after
- 60% matched at HLA-A, -B, -C, -DRB1

Cumulative Incidence of Grades II-IV Acute GVHD after Unrelated Donor Bone Marrow Transplantation for Aplastic Anemia

Cumulative Incidence of Chronic GVHD after Unrelated Donor Bone Marrow Transplantation for Aplastic Anemia
Probability of Survival After Unrelated Donor Bone Marrow Transplantation for Aplastic Anemia

BM, matched, 78% @ 3-yrs
BM, mismatched, 58% @ 3-yrs
P-value < 0.001

EBMT Data: URD Outcome Has Improved Bacigalupo Haematologica 2010

Shorter Time from Diagnosis to BMT Improves Survival Bacigalupo Haematologica 2010

Reduced Intensity Regimens with Fludarabine Improve Survival Bacig Haematol 2010
What is the best preparative regimen?

- BMT CTN 0301—Flu/Cyt/ATG/low dose TBI (200cGy)
  - Designed to optimize dose of cyclophosphamide
  - 4 cohorts: 0, 50, 100, and 150 mg/kg
  - To date, 0 and 150 closed for excessive rejection and toxicity respectively
  - Study ongoing accruing to 100 and 50 mg cohorts

What about SAA Patients Without HLA-matched Donors?

- Haploidentical donors?
  - Anecdotal experiences
  - Requires further study, high rejection rate
- Cord Blood?
  - European, Japanese and CIBMTR outcomes in the 40% range
  - Some promising approaches on the horizon, but require development
Adult Cord Match Rates in the Cord Blood Registry, Cell Dose ≥2.5/Kg

Umbilical Cord Blood Transplants for Aplastic Anemia

<table>
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<tr>
<th></th>
<th>N</th>
<th>Survival</th>
<th>Citation</th>
</tr>
</thead>
<tbody>
<tr>
<td>CIBMTR 2000-2008</td>
<td>45</td>
<td>35%</td>
<td>Unpublished</td>
</tr>
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Cell Dose Important in UCB for SAA

Overall survival after UCBT
Overall survival after UCBT

Small Japanese Cohort Yamamoto Blood 2011

- Fludarabine 125/m2 + melphalan 80mg/m2 + 400cGy TBI
- 12 adult patients
- Median cell dose 2.5 x 10^7 TNC/kg
- 11/12 engrafted, one late secondary graft failure (3 yrs)
  - Both graft failures underwent successful re-transplant
- 2pts died of IPS

Combined Cord Blood and CD34+
Haploidentical Transplant for SAA
(NHLBI, ASH 2011)

- Eligibility Criteria
  - Severe aplastic anemia between ages 6-55
  - ANC < 500 cells/ul
  - Intolerance or failure to respond to standard immunosuppressive therapy x 2
  - No available HLA matched donor (related or unrelated)
  - Availability of at least one ≥ 4/6 HLA-matched cord blood unit with TNC ≥ 1.5 x 10^7 cells/kg
  - Availability of at least one HLA- haploidentical family donor
SAA Patient Characteristics

<table>
<thead>
<tr>
<th>All Patients (n=11)</th>
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<tbody>
<tr>
<td>Median age years (range)</td>
</tr>
<tr>
<td>Sex</td>
</tr>
<tr>
<td>Median ANC prior to transplant (range)</td>
</tr>
<tr>
<td>Number HLA-alloimmunized</td>
</tr>
<tr>
<td>Median prior transfusions:</td>
</tr>
<tr>
<td>RBC (range)</td>
</tr>
<tr>
<td>Platelets (range)</td>
</tr>
<tr>
<td>CMV at risk</td>
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Allograft Characteristics

<table>
<thead>
<tr>
<th>All Patients (n=11)</th>
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<tbody>
<tr>
<td>Median Cord TNC dose (range)</td>
</tr>
<tr>
<td>Cord HLA match</td>
</tr>
<tr>
<td>6/6</td>
</tr>
<tr>
<td>5/6</td>
</tr>
<tr>
<td>4/6</td>
</tr>
<tr>
<td>Haplo Donor</td>
</tr>
<tr>
<td>Father</td>
</tr>
<tr>
<td>Mother</td>
</tr>
<tr>
<td>Aunt/ Uncle</td>
</tr>
<tr>
<td>Sister</td>
</tr>
<tr>
<td>Median Haplo CD34+ cell dose (range)</td>
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</tbody>
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Transplant Outcomes

<table>
<thead>
<tr>
<th>All Patients (n=11)</th>
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</thead>
<tbody>
<tr>
<td>Engraftment</td>
</tr>
<tr>
<td>Day ANC&gt;500, median (range)</td>
</tr>
<tr>
<td>Day Platelet count &gt; 20</td>
</tr>
<tr>
<td>Acute Grade II-IV GVHD</td>
</tr>
<tr>
<td>grade II</td>
</tr>
<tr>
<td>grade III</td>
</tr>
<tr>
<td>grade IV</td>
</tr>
<tr>
<td>Steroid refractory GVHD</td>
</tr>
<tr>
<td>Chronic GVHD</td>
</tr>
<tr>
<td>Mild</td>
</tr>
<tr>
<td>Moderate</td>
</tr>
<tr>
<td>Severe</td>
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Transplant Outcomes

<table>
<thead>
<tr>
<th></th>
<th>All Patients (n=11)</th>
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<tbody>
<tr>
<td>CMV reactivation</td>
<td>8</td>
</tr>
<tr>
<td>disease</td>
<td>1 (pneumonitis/fatal)</td>
</tr>
<tr>
<td>EBV reactivation</td>
<td>7</td>
</tr>
<tr>
<td>EBV disease (LPD)</td>
<td>0</td>
</tr>
<tr>
<td>Transfusion independence</td>
<td>11</td>
</tr>
<tr>
<td>Median follow-up days (range)</td>
<td>339 (28-1434)</td>
</tr>
<tr>
<td>Survival</td>
<td>10/11 (91%)</td>
</tr>
</tbody>
</table>

Combined Haploidentical/UNR Cord Experience

MLC data shows that the cord blood eventually rejects the haplo graft leading to full cord blood donor chimerism.

Next Steps—Future research focuses

- Decreasing GVHD—Campath and other approaches
- Improving Engraftment of Alternative sources
  - Haploidentical approaches
  - Haplo/cord
  - Cord
- Improving immune reconstitution after BMT
Late effects among pediatric patients followed for nearly 4 decades after transplantation for Severe Aplastic Anemia Sanders et al Blood 2011

Percent survival among 152 children surviving at least 1 year after transplantation for severe AA. Survival of the 137 with acquired AA (solid line) is 82% and for the 15 Fanconi anemia patients (dashed line) is 58% at 30 years (P = .01).

Percent survival among 35 children who had chronic GVHD (dashed line) and 117 children without chronic GVHD (solid line) at 1 year after transplantation for severe AA (P = .02).

Growth in Children after BMT

Pregnancies after BMT for SAA
Quality of Life

- 49 adult survivors assessed with Short Form-36 physical function
  - Survivors vs. controls (n = 197) were not significantly different from each other.
  - Educational, work or school status, financial situation, or marital status of the of patients vs. controls similar.
  - In contrast, insurance issues were significantly different
    - Nine of 49 (18%) transplant recipients had been denied health insurance vs. 3 of 197 (2%) control patients.
    - Life insurance—A total of 10 of 49 (20%) survivors had been denied life insurance vs. 2 of 197 (1%) of control patients.

Summary: BMT for SAA

- Aplastic Anemia can be treated with immune suppression or BMT
  - Patients transplanted early with BM from Matched Sibling Donors do very well
  - Patients without sibling donors who fail IS require careful judgment in choosing when to do URD BMT
  - Well matched, early BMT results in good outcomes
    - GVHD is rare, but remains a problem
  - Alternative donor approaches look promising
    - Further study of haplo or cord sources ongoing

Acknowledgements

- BMT CTN 0301 protocol group
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  - Jeff Lipton
  - David Margolis

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