Advances in HSC Transplantation for Myelodysplasia: Cord Blood Transplantation & RIC

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Acknowledgements

**MSKCC**

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Debbie Wells, Kathleen Doshi, Sinda Lee
**Cytotherapy Lab:** esp Allison Schaible
**CB Research Staff:** Marissa Lubin
Anne Marie Gonzales, Katie Evans
**Cellular Immunology Lab:** Kathy Smith
Malcolm Moore
Machi Scaradavou
Nancy Kernan & Richard O’Reilly
Doris Ponce
Marcel van den Brink & Sergio Giralt

**U of Minnesota**
John E. Wagner

**NYBC**
Pablo Rubinstein
Cladd Stevens
Machi Scaradavou
Allo Transplant for Acute Leukemia & MDS

**PROS:** Curative.

**CONS:** Limited by:

1) **Access**
   - 75%: no matched sibling.
   - URD: 8/8 HLA-A,B,C + DRB1 or 10/10 HLA-A,B,C + DRB1,DQ allele matching limits access.
   - Majority non-Europeans: no matched URD.
   - Lengthy URD searches (2-4 months).

2) **Transplant-related mortality**
   - Especially if mismatch.
Patient Related Factors

- **Biology of Malignancy**: determines need for hi dose prep vs reliance on GVL
- **Patient Characteristics** (age, extent of prior therapy, comorbidities): determines ability to tolerate hi dose prep, tac/CSA, GVHD.
Variables that Determine Outcome

**Transplant Related Factors**
- **Conditioning:**
  - High eg Cy/ Flu/ TBI 1375
  - Midi eg Cy/ Thio/ Flu/ TBI 400
  - Mini eg Cy/ Flu/ TBI 200

- **HSC source:**
  - HLA-identical sibling (25%)
  - URD: availability depends on ancestry
  - CB: > 90% (patient weight & ancestry)

- **Immunosuppression** (rejection/ GVHD)
- **Supportive care:** infection, bleeding, nutrition etc

**Patient Related Factors**
- **Biology of Malignancy:** determines need for hi dose prep vs reliance on GVL
- **Patient Characteristics** (age, extent of prior Rx, comorbidities): determines ability to tolerate hi dose prep, tac/CSA, GVHD.
CB: Promising Alternative HSC Source
Unlimited Supply (?)

- Collect from all racial groups
- Current inventory:
  - NMDP: 200,000
  - NYBC: 50,000
  - Global: 600,000
- Limitation: $$$$$
Unrelated Donor CB: Cryopreserved Product

Admit revolves around patient, not donor.
Easy to reschedule.
Easy shipment.
Easy thaw.
Less Than Expected Incidence of GVHD for Degree of HLA-Mismatch of CB Grafts

Naïve immune system = reduced GVHD = permits marked HLA disparity.

(Biology not well understood).
University of Minnesota: One Strategy to Improve Outcome By Augmenting Cell Dose: Use 2.

**MSK Double Unit CBT: Engraftment & Survival**

N = 54, median 42 yrs (range 7-66), high risk heme malignancies

![Graph showing engraftment and survival rates](image)

**One unit wins. High rates of sustained neutrophil engraftment despite low cell dose of engrafting unit.**

- **NMA (n=19): 94%**
- **Ablative (n=35): 94%**

**Promising survival.**

- **OS: 65% @ 1 yr**
- **DFS: 56% @ 1 yr**

*Barker et al, BBMT 2009*
Further Benefit of Double CBT: Reduced Relapse?
Myeloablative CBT for Acute Leukemia, U of MN

Supported by other US & Eurocord analyses. Due to unit vs unit interactions?

Verneris et al, Blood 2009
MSK Allo for Heme Malignancies 2005-2009: 2 Year PFS After Double-Unit CB vs RD vs URD Transplant

P = 0.573

CB (n = 75)  
RD (n = 108)  
URD (n = 184)

2 Year PFS after CBT: comparable to RD or URD transplant.

Ponce, BBMT 2011
Why is This Remarkable?
Comparison of Donor-Recipient HLA-Match:
CB (n = 75, 150 units) vs URD (n = 184)

CB grafts: marked degree of HLA-disparity.

CD34+ cell dose also much lower:
RD 7.9, URD 6.0, CB 0.09 (p < 0.001).

Ponce, BBMT 2011
CBT with high dose myeloablative conditioning associated with relatively high early TRM risk: Is NMA ("mini") prep the answer?
Lack of prior therapy strongly associated with risk of graft failure: likely due to rejection.

Barker, Blood 2004, 104; 235a
Added ATG to Augment Engraftment After NMA CBT = EBV Risk

High incidence of EBV-related complications after NMA CBT with ATG*.

ATG may also increase relapse risk.

* Equine ATG 15 mg/kg q12 hrs x 6 doses

Brunstein et al, Blood 2006
Non-Myeloablative CBT, U of M (n = 110)

Relapse is significant: approx one third patients.

Brunstein, Blood 2007
Problem: need intermediate intensity prep that ensures engraftment without ATG, has low toxicity, & protects against relapse.

High:
Cy 120
Flu 75
TBI 1375

Mini:
Cy 50
Flu 150*
TBI 200

CB #1
High:  
Cy 120  
Flu 75  
TBI 1375

Midi:  
Cy 50  
Thio 10  
Flu 150  
TBI 400

Mini:  
Cy 50  
Flu 150  
TBI 200

**Midi:** built on mini platform, but added thiotepa & increased TBI to 400 cGy.
To augment engraftment & GVL: everyone gets 2 units.
**Midi Prep & Immune Suppression**

-7 -6 -5 -4 -3 -2 -1 0

- **CB #1**
- **CB #2**

▲ Cyclophosphamide 50 mg/kg
- Red □ Fludarabine 30 mg/m² x 5
- Light □ Thiotepa 5 mg/kg x 2
- Yellow ⚡ TBI 200 cGy x 2

GVHD prophylaxis from -3:
- CSA 200-400/
- MMF 1 gm IV q8 hours

6 day prep, no ATG.
Sibling typing → simultaneous URD & CB search

**Suitable Sibling**
(match/ donor health)

**Suitable URD**
(match/ availability):

- **Suitable CB Graft**
  (match/ dose):
  4-6/6 A,B antigen, DRB1 allele
  2 units: each ≥ 2 x 10^7 NC/kg

- **Hi Dose Prep**
  Children (Young adults)

- **Midi/ Mini**
  + 10/10 donor
  TCD 9-10/10 donor

- **Hi Dose +**
  TCD 9-10/10 donor

**Midi or Mini (Unmodified)**

**Disease specific protocols**

**MSKCC Donor Algorithm**
**DCBT for Acute Leukemia/ MDS/ MPD (n = 75):**

### Demographics

<table>
<thead>
<tr>
<th></th>
<th>Adults (n = 52)</th>
<th>Children (n = 23)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Median Age</strong></td>
<td>41 yrs (range 16-69)</td>
<td>9 yrs (range 0.9-15)</td>
</tr>
<tr>
<td><strong>Median Weight</strong></td>
<td>69 kg (range 47-105)</td>
<td>37 kg (range 7-72)</td>
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</tbody>
</table>
| **Diagnosis***       | 63% AML  
27% ALL  
10% MDS/ MPD | 43% AML  
52% ALL  
4% MDS/ MPD |
| **Conditioning Intensity** | 50% high  
50% midi | 100% high |
| **Recipient CMV+**   | 69% CMV+ | 26% CMV+ |
| **Unit-Recipient HLA-match** | 3% 6/6  
47% 5/6  
50% 4/6 | 2% 6/6  
63% 5/6  
35% 4/6 |
| **Median Inf. TNC Dose/Unit x 10^7/kg** | 2.7 + 1.9 | 3.3 + 2.6 |

*All received CNI (predominantly CSA) & MMF & no ATG.*

* Morpho. CR 1-4 or aplasia, or MDS/ MPD ≤ 5% blasts  
  Barker et al, ASH 2011
**DCBT for Acute Leukemia/ MDS/ MPD (n = 75):**

**Outcomes**

<table>
<thead>
<tr>
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<th>Adults (n = 52)</th>
<th>Children (n = 23)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Engraftment</strong></td>
<td>94%</td>
<td>91%</td>
</tr>
<tr>
<td><strong>Neut Recovery</strong></td>
<td>26 days</td>
<td>20 days</td>
</tr>
<tr>
<td><strong>Day 180</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>II-IV aGVHD</td>
<td>58%</td>
<td>44%</td>
</tr>
<tr>
<td><strong>Day 100 TRM</strong></td>
<td>19%</td>
<td>9%</td>
</tr>
<tr>
<td><strong>2 yr Relapse</strong>*</td>
<td>6%</td>
<td>9%</td>
</tr>
</tbody>
</table>

*Median f/u survivors 26 months (range 4-70)

**Barker et al, ASH 2011**

Low relapse incidence is striking. **Enhanced GVL from unit-unit interactions?**

(Eldjerou, Blood, 2010; Gutman, Blood 2010).

*Median f/u survivors 26 months (range 4-70)
DCBT if Acute Leuk/ MDS/ MPD: 2-yr DFS

Low incidence of relapse translates to relatively high survival rates.

Barker et al, ASH 2011
DCBT for Acute Leuk/ MDS/ MPD: DFS by Age

Barker et al, ASH 2011

Disease-Free Survival

Age > 45 (n = 24): 61%
Age 16-44 (n = 28): 67%
Age < 16 (n = 23): 78%

P = NS

Time Post Transplant (Months)
DFS for Adults by Disease Status (n = 50)

CR1 (n = 41): 69%

All others (n = 34): 67%

P = 0.663

Barker et al, ASH 2011
DFS by Conditioning Intensity: High vs Midi (n = 75)

High dose (n = 49): 71%
Midi (n = 26): 62%

*p = NS*
DFS in Adults by Recipient CMV Status (n = 50)

Disease-Free Survival

Time Post Transplant (Months)

Negative (n = 16): 88%
Positive (n = 36): 54%

Barker et al, ASH 2011
Disease-Free Survival
Time Post Transplant (Months)

≥ 3.0 x 10^7/kg (n = 19): 77%

< 3.0 x 10^7/kg (n = 56): 65%

P = 0.307

2 Year DFS by Infused TNC/kg of Engrafting Unit (n = 75)
2 Year DFS by Engrafting Unit 10 Allele Match (n = 75)

7-10/10 (n = 34): 73%
2-6/10 (n = 41): 64%

P = 0.418
Why are These Results Important?
CB Extends Transplant Access to “Minorities”: URD vs CB vs No Graft by Ancestry (n = 385)

Barker et al 2010, BBMT
Greater than 50% of CBTs had non-European ancestry

Barker et al, 2010, BBMT

Patient Ancestry if Transplanted or No Graft (n = 385)

<table>
<thead>
<tr>
<th>Group</th>
<th>No.</th>
<th>NW Europe</th>
<th>East Europe</th>
<th>South Europe</th>
<th>Mix: Europe</th>
<th>Asian</th>
<th>African</th>
<th>White Hispanic</th>
<th>Middle Eastern</th>
<th>Mix: Non Europe</th>
</tr>
</thead>
</table>
DCBT if Acute Leuk/ MDS/ MPD: 2-yr DFS

- Children 0-15 yrs (n = 23): 78% (Europeans 86%, Non-Europeans 75%)
  - Adults 16-69 yrs (n = 52): 64% (Europeans 62%, Non-Europeans 66%)

No difference between European & non-European patients.

In multivariate analysis only CMV serostatus was significant.

Barker et al, ASH 2011
Conclusions

- CBT extends transplant access to patients of all racial & ethnic backgrounds. Lack of donor is rare (< 5%).

- Preliminary analyses: DFS after DCBT comparable to non-cords. In acute leukemia patients DCBT associated with high rates of engraftment, low relapse & promising survival. DFS in Europeans & non-Europeans similar.

- Future efforts: speed count recovery, reduce toxicity, new prophylaxis & treatment for GVHD.
Challenges for MDS Patients Remain

- T-replete transplants challenging for older patients (> 60 years).
- Significant comorbidities (esp. in older patients, esp. renal impairment) may preclude CBT or greatly increase TRM risk.
- Heavy transfusion history increases sensitization & iron overload.
- Evolution to refractory AML precludes effective allograft.