Cord Blood in unrelated transplantation

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Cord Blood Transplantation at MSKCC: the First Ten Years

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Director, Cord Blood Transplant Program
Memorial Sloan-Kettering Cancer Center

CSA/ MMF
MSKCC CB Transplant Program

Searches – Clinical studies – Laboratories

- Starting a CB search: disease; donor status; urgency
- Performing a CB search: search algorithm; summary
- Selecting CBU for transplantation: final graft; back-up
- Clinical studies - transplant protocols
- Stem Cell Laboratory: procedures
- Infusion of CB grafts: procedures
- Related laboratory studies
- Clinical Outcomes
Who gets a formal CB search at MSKCC?

Patients with hematologic malignancies
No related donor:
Assess urgency and likelihood of suitable URD

Urgent or few or no suitable URDs
Simultaneous URD and CB search

Not urgent and multiple URDs
Search becomes urgent or problems with URD availability
Formal URD search only

Strategy optimizes timely acquisition of HSC
Search, Evaluation and Acquisition of CBU for unrelated transplantation

- Well trained, dedicated transplant search coordinators
- Clear, step-by-step procedures for search, evaluation and CBU selection for transplant
- Communication between search coordinators, clinical teams and Stem Cell Lab

Formal searches (2014) N = 290 pts
244 adults ; 46 children
Unrelated Donor Searches: Results based on patient Ancestry

CB extends transplant access to patients of ethnic “minorities”

Barker et al, BBMT 2010; 16: 1541-1548
CBU selection for transplant: considerations

Quality - Potency of CBU
- TNC dose; CD34+ cell dose and viability, CFU assays

Patient - CBU HLA match level
- Interaction of TNC - HLA match
- Allele level matching (HLA-A, -B, -C, -DRB1)
- Selection of CBU with permissible mismatches

Other immunological considerations
- HLA and relapse; Donor-specific antibodies; KIR-L

CBU quality post-thaw
- Standardization of banking practices
- CBU stability studies and segment evaluation

Other CBU characteristics - Banking aspects
- RBC depletion - final hematocrit
- Cryopreservation volume/bag, storage time
HLA disparity of patient - CB unit based on 8 HLA allele level match (N=200 CBU)

Eligible for analysis: N= 200 CBU; double unit grafts for N= 100 patients with hematologic malignancies; single center analysis

Dahi et al, BMT 2014; 49: 1184-1186
CB unit selection for transplant: Steps

1. Search for domestic and international CBU

2. “Screen” CBU by TNC: Establish a TNC dose “threshold” depending on graft (single / combined / other sources / expansion)
   - minimum: 2-3 x10⁷/kg for single CBU
   - 1.5-2 x10⁷/kg for each of the CBU in a double graft

3. For CBU above the “threshold” TNC dose:
   - evaluate HLA match level (at 6 and 8 alleles preferably):
     - If fully matched CBU: best choice (CBU quality needs to be considered)
     - avoid CBU with < 3/8 allele match, if possible
     - consider “permissible” mismatches for hematologic malignancies (unidirectional HLA MM, maternal HLA phenotype for NIMA/IPA assignments)
     - do not limit selection based on unit-unit match
   - evaluate potency assays, if available; presence of CBU segment
   - evaluate CB Bank of origin; overall quality of products
   - consider other patient-related variables (DSA, RBCs, CBU volume)

4. Identify CBU for the graft and back-up

Scaradavou A, ASBMT 2014
# Patient CB Search Summary Report

**Pt Name:** Example, Patient  
**Weight:** 62.0  
**Weight Date:** 2/24/2014  
**MSKCC #** 01234567  
**ABO Rh:** O+  
**DOB** 1/1/1950  
**Diagnosis:** AML  
**Reviewed Date:** 2/24/2014  
**Ancestry:** Both Parents - India  
**Referred MD:** SMITH, P  
**BMT MD:** BARKER, J  
**Last Re-run:** 2/21/14  
**Best Donor:** 8/10 URD

<table>
<thead>
<tr>
<th>Rank</th>
<th>Donor ID #</th>
<th>Donor Bank</th>
<th>RBC-deplete</th>
<th>Final vol (ml)</th>
<th>ABO Rh</th>
<th>Birthdate</th>
<th>Sex</th>
<th>UCB Dose x10^7_TNC/kg</th>
<th>Corrected Dose</th>
<th>Attached Segments</th>
<th>HLA Match</th>
<th>HLA Tested</th>
<th>Comments</th>
<th>Licensed/Ineligible</th>
<th>IDM Complete</th>
<th>IDM_Hbopathy Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>1a</td>
<td>9999-8888-7</td>
<td>Domestic CBB 1</td>
<td>Yes</td>
<td>25.0</td>
<td>O+</td>
<td>8/3/2011</td>
<td>Female</td>
<td>125</td>
<td>2.02</td>
<td>Yes</td>
<td>5</td>
<td>6</td>
<td>6</td>
<td>C,DR,DQ</td>
<td>Yes</td>
<td>FACT 2005</td>
</tr>
<tr>
<td>back-up</td>
<td>333333P&amp;Q</td>
<td>Domestic CBB 2</td>
<td>Yes</td>
<td>50.0</td>
<td>A-</td>
<td>2/24/2010</td>
<td>Female</td>
<td>240.0</td>
<td>3.87</td>
<td>Yes</td>
<td>4</td>
<td>5</td>
<td>A, B, C - patient is homozygous at A</td>
<td>Yes</td>
<td>FACT 2003</td>
<td></td>
</tr>
<tr>
<td></td>
<td>DUCB123456</td>
<td>Intl CBB 1</td>
<td>Yes</td>
<td>53.2</td>
<td>A+</td>
<td>11/3/2009</td>
<td>Male</td>
<td>200</td>
<td>3.23</td>
<td>Yes</td>
<td>4</td>
<td>4</td>
<td>B,b,C,dr,DQ</td>
<td>No</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1b</td>
<td>334455P</td>
<td>Domestic CBB 2</td>
<td>Yes</td>
<td>25.0</td>
<td>B+</td>
<td>7/28/2013</td>
<td>Female</td>
<td>180.0</td>
<td>3.00</td>
<td>Yes</td>
<td>4</td>
<td>5</td>
<td>B,C,DR,DQ-unit is homozygous at B,CDR,DQ</td>
<td>Yes</td>
<td>FACT 2003</td>
<td></td>
</tr>
<tr>
<td>back-up</td>
<td>0876-5432-1</td>
<td>Domestic CBB 3</td>
<td>Yes</td>
<td>25.0</td>
<td>A+</td>
<td>7/27/2007</td>
<td>Female</td>
<td>178.0</td>
<td>2.87</td>
<td>Yes</td>
<td>4</td>
<td>5</td>
<td>A,C,DR,DQ,DQ - patient is homozygous at A</td>
<td>Yes</td>
<td>FACT 2006</td>
<td></td>
</tr>
<tr>
<td></td>
<td>445566P</td>
<td>Domestic CBB 2</td>
<td>Yes</td>
<td>25.0</td>
<td>B+</td>
<td>2/23/2007</td>
<td>Female</td>
<td>172.0</td>
<td>2.77</td>
<td>Yes</td>
<td>4</td>
<td>4</td>
<td>A,b,CDR,DQ,dq - patient is homozygous at A</td>
<td>No</td>
<td>FACT 2003 NAT HIV &amp; NAT HCV pending</td>
<td></td>
</tr>
</tbody>
</table>
Clinical studies
Transplant with a Double Unit CB Graft

Fludarabine 25 mg/m²/d x 3
Cyclophosphamide 60mg/kg/d x 2
TBI 1375 cGy

UCB #1
UCB #2

CSA - 3 to ≥ +100
MMF - 3 to + 45
G-CSF
# MSKCC Pediatric Acute Leukemia study (N=35)

## Demographics

<table>
<thead>
<tr>
<th>Male/Female</th>
<th>18/17</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median age-yrs (range)</td>
<td>7.5 (0.8-18)</td>
</tr>
<tr>
<td>Median weight-kg (range)</td>
<td>28 (8-75)</td>
</tr>
<tr>
<td>N(%) recipient CMV +</td>
<td>11 (31%)</td>
</tr>
<tr>
<td>N(%) non-european ancestry</td>
<td>24 (69%)</td>
</tr>
</tbody>
</table>

## Disease

<table>
<thead>
<tr>
<th>AML N (%)</th>
<th>17 (49%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CR1*</td>
<td>6</td>
</tr>
<tr>
<td>CR2</td>
<td>8</td>
</tr>
<tr>
<td>CR3</td>
<td>3</td>
</tr>
<tr>
<td>aplasia</td>
<td>2</td>
</tr>
<tr>
<td>ALL N(%)</td>
<td>17 (49%)</td>
</tr>
<tr>
<td>CR1#</td>
<td>10</td>
</tr>
<tr>
<td>CR2</td>
<td>4</td>
</tr>
<tr>
<td>CR3</td>
<td>3</td>
</tr>
<tr>
<td>CML N (%)</td>
<td>1 (2%)</td>
</tr>
</tbody>
</table>

## Cytoreduction

<table>
<thead>
<tr>
<th>TBI-containing (N%)</th>
<th>21 (60%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cy/Flu/TBI 1375cGy</td>
<td>21</td>
</tr>
<tr>
<td>chemotherapy only N(%)</td>
<td>14 (40%)</td>
</tr>
<tr>
<td>Clo-Mel-Thio</td>
<td>10</td>
</tr>
<tr>
<td>Bu-Mel-Thio</td>
<td>4</td>
</tr>
</tbody>
</table>

## Graft: median cell dose (range)

<table>
<thead>
<tr>
<th>Infused TNC/kg engrafting CBU</th>
<th>3.89 (0.9-12.8)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infused TNC/kg non-engrafting CBU</td>
<td>4.15 (1.3-19.5)</td>
</tr>
<tr>
<td>Infused CD34/kg engrafting CBU</td>
<td>1.38 (0.1-7.0)</td>
</tr>
<tr>
<td>Infused CD34/kg non-engrafting CBU</td>
<td>1.10 (0.2-6.4)</td>
</tr>
</tbody>
</table>

CBU: cord blood unit; TNC/kg x10^7; CD34/kg x10^5

* AML CR1: M7, sec. 5q- MDS, FLT-3 ITD, Ph+, Down s. MRD+, germline CEBP α

# ALL CR1: Ph+ (1 MRD+), 2 T-cell ALL, 1 MLL, 1 L3 disease, 3 multiple inductions
MSKCC Pediatric Acute Leukemia study: Double CB grafts

Although many young children may have “adequate” single CB unit grafts as per the CIBMTR definition: cryopreserved TNC >3.0x10^7/kg; 6-8/8 allele HLA-match, a significant minority will not….

Patient - CBU HLA allele level matching (N=70 CBU)

<table>
<thead>
<tr>
<th>Match</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>6</th>
<th>7</th>
<th>8</th>
<th>(N)</th>
</tr>
</thead>
<tbody>
<tr>
<td>6/6</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>25%</td>
<td>25%</td>
<td>25%</td>
<td>25%</td>
<td>4</td>
</tr>
<tr>
<td>5/6</td>
<td></td>
<td></td>
<td>5%</td>
<td>19%</td>
<td>26%</td>
<td>35%</td>
<td>16%</td>
<td></td>
<td>43</td>
</tr>
<tr>
<td>4/6</td>
<td>13%</td>
<td>26%</td>
<td>26%</td>
<td>30%</td>
<td>4%</td>
<td></td>
<td></td>
<td></td>
<td>23</td>
</tr>
</tbody>
</table>

- 10/33 (30%) pts engrafted with a unit with a pre-cryopreservation TNC <2.5x10^7/kg
- 17/33 (51%) pts engrafted with a unit that was ≤5/8 HLA-allele matched to the recipient (range 2-5/8)

Scaradavou et al, ASBMT 2015
Myeloablative double unit CB transplantation in children with high risk acute leukemia: encouraging DFS with both TBI and chemotherapy-only regimens.

Chemotherapy-only-based conditioning is an effective alternative to radiation, and further extends transplant access to children unsuitable for TBI.

Scaradavou et al, ASBMT 2015
High:
Cy 120
Flu 75
TBI 1375

Midi:
Cy 50
Thio 10
Flu 150
TBI 400

Mini:
Cy 50
Flu 150
TBI 200

• Midi: intermediate intensity for acute leukemia, MDS, aggressive NHL.

• Components have additive or synergistic immunosuppression.

• CSA/ MMF & no ATG.

Ponce et al, BBMT 2013
2-Yr DFS by Regimen Intensity (n = 92)

Hi Dose Ablative (n = 54): 70%
Median age 15 yrs (0.9-57)

Midi (n = 38): 64%
Median age 55 yrs (18-69)

P = 0.60

Acute leukemia in morpho remission / aplasia or MDS/MPD

Barker et al, unpublished 2013
Compare engraftment (speed, success, chimerism) to historical controls: Hi dose or midi myeloablative vs. single CB unit + TCD haplo support.

Fernandez (BMT 2009) & van Besien (Blood 2011) with single CB unit + TCD haplo support concept.

J. Barker, MD
HSCT for non-malignant diseases
Laboratory procedures and CBU quality evaluation studies
Method for CBU preparation for infusion: wash or albumin dilution - final CBU volume – validated method

MSKCC Practice: Wash for patients with wt <20 kg Albumin reconstitution (dilution 1:8) for all others

Post-thaw evaluation studies

Barker et al, BBMT 2009; 15: 1596-1602
Dahi et al, BBMT 2014; 20: 490-494
Transplant Center Stem Cell Lab

- Number of cryopreserved bags (1 or 2)
- Type of cryopreservation bag
- Cryopreservation volume
- RBC depleted product or not
- Thawing instructions
- Product final volume
Post-thaw CD34+ cell viability as indicator of CBU potency

Post-thaw CD34+, CD3+ and CD45+ cell viability and unit engraftment in 44 double unit CB grafts

Modified ISHAGE gating strategy for assessment of post-thaw cell viability

Scaradavou et al, BBMT 2010; 16: 500-508
Time to ANC engraftment by infused viable CD34+ cell dose

Purtill et al., Blood 2014; 124: 2905-2912
### Factors Associated with Low CD34+ Cell Viability

<table>
<thead>
<tr>
<th>Variable</th>
<th>N (%) &lt; 75% CD34+ Viability</th>
<th>OR* (95% CI)</th>
<th>Multivariate p value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Netcord-FACT accreditation</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes (n = 350)</td>
<td>15 (4%)</td>
<td>Reference</td>
<td>0.002</td>
</tr>
<tr>
<td>No (n = 52)</td>
<td>18 (35%)</td>
<td>4.9 (1.8-13.3)</td>
<td></td>
</tr>
<tr>
<td><strong>Cryopreservation year</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1997 – 2004 (n = 119)</td>
<td>17 (14%)</td>
<td>1.47 (0.6-3.7)</td>
<td>0.408</td>
</tr>
<tr>
<td>2005 – 2012 (n = 283)</td>
<td>16 (6%)</td>
<td>Reference</td>
<td></td>
</tr>
<tr>
<td><strong>Cryopreservation volume per bag (ml)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt; 24.5 (n = 14)</td>
<td>5 (36%)</td>
<td>8.8 (1.9-41.7)</td>
<td></td>
</tr>
<tr>
<td>24.5 – 26.0 (n = 298)</td>
<td>8 (3%)</td>
<td>Reference</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>26.1 – 30.0 (n = 45)</td>
<td>7 (16%)</td>
<td>8.5 (2.6-28.0)</td>
<td></td>
</tr>
<tr>
<td>&gt; 30.0 (n = 45)</td>
<td>13 (29%)</td>
<td>7.5 (2.5-22.0)</td>
<td></td>
</tr>
<tr>
<td><strong>Processing method</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Manual (n = 187)</td>
<td>24 (13%)</td>
<td>2.3 (0.8-6.5)</td>
<td>0.131</td>
</tr>
<tr>
<td>Automated + semi-automated (n = 215)</td>
<td>9 (7%)</td>
<td>Reference</td>
<td></td>
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</tbody>
</table>

*Odds Ratio with 95% Confidence Interval*
# Infusion Adverse Events

**Infusion Reactions if Dilution Thaw in 136 dCBT:**

119/136 (88%) had 158 Reactions

<table>
<thead>
<tr>
<th>Grade</th>
<th>HTN</th>
<th>N + V</th>
<th>Cardio Pulm*</th>
<th>Allergic**</th>
<th>Other***</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>8</td>
<td>22</td>
<td>12</td>
<td>-</td>
<td>4</td>
<td>46</td>
</tr>
<tr>
<td>2</td>
<td>38</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>2</td>
<td>47</td>
</tr>
<tr>
<td>3</td>
<td>63</td>
<td>-</td>
<td>-</td>
<td>1</td>
<td>-</td>
<td>64</td>
</tr>
<tr>
<td>4</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>1</td>
<td>-</td>
<td>1</td>
</tr>
<tr>
<td>5</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>0</td>
</tr>
<tr>
<td>Total</td>
<td>109</td>
<td>22</td>
<td>19</td>
<td>2</td>
<td>6</td>
<td>158</td>
</tr>
</tbody>
</table>

*Cardio-pulmonary: dyspnea, wheezing, hypoxia, cough, brady or tachy, chest pain.

**Allergic or anaphylaxis. ***Other: fever/chills, shoulder or abdominal pain.

Dilution thaw safe if RBC depleted & > 20 kg recipient.

Serious reactions uncommon but since analysis have increased pre-meds. Need intensive nursing monitoring.

*Dahi et al, BBMT 2014*
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  Emily Lauer
  Cladd Stevens

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  Sean Devlin

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  Eric Pamer

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