Update on Unrelated Cord Blood Transplantation

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State of the art: UCBT

• Eurocord Registry update

• Indications

• Survey on outcomes in children and adults

• New criteria for Cord Blood Unit Choice

• Conditioning regimen

• Complications (engraftment and infections)
UCBT

- Registry update
- Indications
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Eurocord Registry Update

- 12,066 CBU shipped for transplantation (283, 2%, not used):
  - 11,783 CBU used for:

- 9,883 CBT from 1988 to 2012 in 51 countries and 577 centres

<table>
<thead>
<tr>
<th>Type</th>
<th>Cases</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>293 EBMT</td>
<td>6,958</td>
<td>75%</td>
</tr>
<tr>
<td>267 Non-EBMT</td>
<td>2,379</td>
<td>25%</td>
</tr>
</tbody>
</table>

- Related: 708 (8%)
- Unrelated: 8,618 (92%)
- Children: 5,071 (54%)
- Adult: 4,265 (46%)
Eurocord Registry

N° of European CBUs shipped by year*

<table>
<thead>
<tr>
<th>Year of shipment</th>
<th>N of CBUs</th>
</tr>
</thead>
<tbody>
<tr>
<td>1990</td>
<td>3</td>
</tr>
<tr>
<td>1991</td>
<td>1</td>
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<tr>
<td>1992</td>
<td>2</td>
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<td>1993</td>
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<td>1997</td>
<td>58</td>
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<td>1998</td>
<td>92</td>
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<td>1999</td>
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<td>2000</td>
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<td>2001</td>
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<td>2002</td>
<td>167</td>
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<td>2003</td>
<td>187</td>
</tr>
<tr>
<td>2004</td>
<td>298</td>
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<tr>
<td>2005</td>
<td>440</td>
</tr>
<tr>
<td>2006</td>
<td>590</td>
</tr>
<tr>
<td>2007</td>
<td>695</td>
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<tr>
<td>2008</td>
<td>823</td>
</tr>
<tr>
<td>2009</td>
<td>813</td>
</tr>
<tr>
<td>2010</td>
<td>878</td>
</tr>
<tr>
<td>2011</td>
<td>817</td>
</tr>
<tr>
<td>2012</td>
<td>813</td>
</tr>
</tbody>
</table>

* 215 CBUs not infused are included in the bar chart

N=7188
Eurocord Registry - European CBT

Unrelated Cord Blood Transplantations performed in Europe until December, 31st, 2012, data from Eurocord registry

Number of unrelated CBT per million population

- 30
- 16
- 10
- 5
- 1
- 0.1
- No data

Eurocord Registry
Unrelated European CBT by recipient’s age and graft type

In children: 92% single CBT

In adults: 47% double CBT

* Still collecting 2012 data
UCBT

- Registry update

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  - Survey on outcomes in children and adults
  - New criteria for Cord Blood Unit Choice
  - Conditioning regimen and GVHD prophylaxis
  - Complications (engraftment and infections)
Indications of Unrelated UCBT in Children

### Malignant

<table>
<thead>
<tr>
<th>Condition</th>
<th>Cases</th>
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<tbody>
<tr>
<td>ALL</td>
<td>1150</td>
</tr>
<tr>
<td>AML</td>
<td>604</td>
</tr>
<tr>
<td>MDS/MPD</td>
<td>298</td>
</tr>
<tr>
<td>Non-Hodgkin Lymphoma</td>
<td>77</td>
</tr>
<tr>
<td>Hodgkin Lymphoma</td>
<td>62</td>
</tr>
<tr>
<td>Solid Tumor</td>
<td>19</td>
</tr>
<tr>
<td>Immune Deficiency</td>
<td>6</td>
</tr>
<tr>
<td>Metabolic Disorder</td>
<td>480</td>
</tr>
<tr>
<td>Bone Marrow Failure Sd</td>
<td>388</td>
</tr>
<tr>
<td>Histiocytosis</td>
<td>337</td>
</tr>
<tr>
<td>Hemoglobinopathy</td>
<td>147</td>
</tr>
<tr>
<td>Other diagnosis</td>
<td>37</td>
</tr>
<tr>
<td>Total</td>
<td>1150</td>
</tr>
</tbody>
</table>

### Non-Malignant

<table>
<thead>
<tr>
<th>Condition</th>
<th>Cases</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total</td>
<td>1150</td>
</tr>
</tbody>
</table>

This chart illustrates the distribution of unrelated umbilical cord blood transplantation (UCBT) indications among malignant and non-malignant conditions in children.
Indication for Unrelated UCBT in adults

- Single, n= 1735
- Double, n= 1752

- ALL: 21%
- AML: 39% 37%
- MDS/MPD: 14% 14%
- CML: 8% 5%
- CLL: 1% 4%
- Lymphoma: 15%
- Other: 2% 4%
- Non malignant diseases: 3% 4%
Age distribution for adult patients

- >60 y: 433
- 50-59 y: 752
- 40-49 y: 790
- 30-39 y: 736
- 16-30 y: 1103

N=1185
UCBT

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Survival after UCBT for children with malignant (n=1055) and in Children with ALL (n=170)

CR1 (n=546) 65%

>CR1 (n=844) 46%

Non remission (n=209) 21%

MRD⁻: 54 ± 5%, n=96

MRD⁺: 29 ± 5%, n=74

p=0.006
Survival after UCBT for children with non-malignant disorders (n=681)

0-1 HLA MM: 72±4%
≥2 HLA MM: 52±4%
Children with Hurler disease
Disease Free Survival by type of donor and HLA

HLA identical sibling 81±6% or HLA 6/6 unrelated CB 81±8%
HLA matched unrelated donor 10/10 66±7% or CB 5/6 68±6%
Unrelated CB 4/6 57±9% (if high CD34 cell dose EFS=73±13%)
HLA matched low resolution or mismatched (antigen or allelic level) (incl. T cell depleted) 41±7%

P=0.004

Boelens J on behalf of Eurocord-EBMT, Minneapolis and Duke University, Blood 2013
2 Years Survival in Adults (single and double unrelated CBT)

- Myelodysplastic Syndrome 33±3%; n=440
- Myeloma 41±6%; n=104
- Lymphoma 42±3%; n=435
- Acute leukemia 37±1%; n=1845
- Chronic Leukemia 40±3%; n=290
2 Years Survival in Adults (single and double unrelated CBT) with Acute Leukemia (n=1552) by disease status

CR1 (n= 636) - 48%

CR2 (n= 557) - 41%

More advanced (n= 359) - 12%
Overall Survival
AML by disease status and conditioning adults >50 years- (n=257)

CR and MAC, n=29
CR and RIC, n=176
Rel and MAC, n=17
Rel and RIC, n=35

46 ± 4%
33 ± 10%
30 ± 12%
6 ± 4%

Ruggeri A et al
Leukemia-free Survival after Single UCBT – MAC in adults with leukemias

- Transplantation in Remission -

Probability, %

Months 0 6 12 18 24
8/8 matched BM 246 177 139 99 82
7/8 matched BM 106 69 46 35 31
8/8 matched PBPC 452 316 220 143 112
7/8 matched PBPC 166 89 66 45 36
4/6-6/6 matched UCB 123 77 47 30 24

Eapen et al; Lancet Oncol 2010
Survey on Double UCBT for adults
Double UCBT in adults (n=1055)

- Median age at transplant: 45 years (18-76)
- Median weight: 71 kg (40-151)
- Median follow-up: 14 months (1-85)
- Median number of collected nucleated cells
  \[4.9 \times 10^7/kg\] (2.1-14.8)

- HLA compatibility (n=855)
  - 6/6: 1% (n=12)
  - 5/6: 26% (n=222)
  - 4/6: 73% (n=598)
Double UCBT in adults with AL (n=578)

Neutrophil recovery

MAC (n=221): 93% ± 2
RIC (n=334): 85% ± 2

p=NS
Double UCBT in adult with AL (n=578)

Survival by disease status at dUCBT

MAC

CR1 (n=90): OS 58%±6
CR2 (n=75): OS 42%±6
Advanced (n=54): OS 21%±6

RIC

CR1 (n=136): OS 66%±4
CR2 (n=102): OS 54%±5
Advanced (n=72): OS 33%±6

p<0.001
UCBT

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Recomendations for CB unit choice 2012

Search for antibodies against HLA antigens of the cord blood unit (Cord Blood Bank accreditation and location)

1. Look at the number of TNC and/or CD34+ cells in MAC, RIC:
   \[ \geq 2.5-3.0 \times 10^7 \text{ NC/kg and/or } \geq 1 \times 10^5 \text{ CD34+/kg} \]

2. Second look at HLA matches:
   - 0-1 mm better than 2 avoid 3-4 mm
   - Prefer class I mismatches than class II
   - Include HLA C typing low resolution, avoiding mismatches C +DRB1

3. Then adapt to graft indication:
   - Malignant diseases: cell dose is the best prognostic factor because HLA differences reduce relapse (GVL)
   - Non malignant diseases: increase cell dose (\[ \geq 4.0 \times 10^7 \text{ NC/kg } \]) and find the best HLA match ( avoid CB 4/6 )
   - If the criterion for the minimum number of cells for a single CBU transplantation is not achieved, a double CBT should be considered

4. Other considerations, if several CBU are available consider:
   - Cord Blood Bank accreditation and location
   - ABO compatibility
   - NIMA status
Is Allele-Level HLA-Matching Relevant for Single Umbilical Cord Blood Transplants?

Eurocord and Center for International Blood and Marrow Transplant Research

## Lesser vs. Allele-level HLA-match (n=1500)

<table>
<thead>
<tr>
<th></th>
<th>3/8</th>
<th>4/8</th>
<th>5/8</th>
<th>6/8</th>
<th>7/8</th>
<th>8/8</th>
</tr>
</thead>
<tbody>
<tr>
<td>4/6</td>
<td></td>
<td>11%</td>
<td>31%</td>
<td>49%</td>
<td>10%</td>
<td>___</td>
</tr>
<tr>
<td>5/6</td>
<td>1%</td>
<td>8%</td>
<td>22%</td>
<td>44%</td>
<td>25%</td>
<td>___</td>
</tr>
<tr>
<td>6/6</td>
<td>___</td>
<td>___</td>
<td>4%</td>
<td>18%</td>
<td>24%</td>
<td>54%</td>
</tr>
</tbody>
</table>
Non-Relapse Mortality
- Allele-level Matched at A, B, C, DRB1 -

Years

Incidence, %

P < 0.001

- 8/8 (9%)
- 7/8 (26%)
- 6/8 (26%)
- 5/8 (34%)
- 4/8 (37%)
- 3/8 (41%)
NRM at 1-year by pre-cryopreserved TNC and HLA-match

<table>
<thead>
<tr>
<th>HLA-match</th>
<th>4/8</th>
<th>5/8</th>
<th>6/8</th>
<th>7/8</th>
</tr>
</thead>
<tbody>
<tr>
<td>TNC ≤ 3.0</td>
<td>43% (28-58)</td>
<td>44% (33-57)</td>
<td>36% (24-49)</td>
<td>45% (29-62)</td>
</tr>
<tr>
<td>TNC &gt; 3.0–5.0</td>
<td>*39% (30-49)</td>
<td>31% (24-38)</td>
<td>21% (14-30)</td>
<td>15% (7-26)</td>
</tr>
<tr>
<td>TNC &gt; 5.0</td>
<td>*25% (17-33)</td>
<td>25% (20-31)</td>
<td>20% (15-25)</td>
<td>19% (13-26)</td>
</tr>
</tbody>
</table>

*Significant difference: p=0.02 testing TNC >3.0 – 5.0 vs. >5.0.
Other groups testing TNC >3.0 – 5.0 vs. >5.0: p-value=NS
The multivariate model tested TNC ≤ 3.0 vs. >3.0 (optimal cut point determined statistically in the model for mortality). In the univariate analysis there is a significant difference between TNC ≤ 3.0 vs. >3.0.
Select units with TNC ≥ 3 x 10^7/kg

Best HLA-match
Allele-level match at HLA-A, -B, -C and -DRB1

Avoid 3/8 HLA-matched transplants
Absence of HLA-C typing match at HLA-B
HLA-C at confirmatory typing

7/8 and 6/8 are better tolerated than 5/8 or 4/8 HLA-matched transplants

TNC in excess of minimum required does not lower NRM
UCBT

• Registry update

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• Complications (engraftment and infections)
Neutrophil recovery after single UCBT for patients with malignant disorders after myeloablative conditioning regimen (n=1946)

Fludarabine based MAC (n=384)  91%
No Flu Based (n=1471)  86%

p< 0.0001
Conditioning regimen
Myeloablative

Analyze the impact of TT, iv BU, F+ATG (TBF-ATG) on long term outcomes after single unit UCBT compared to other MAC regimens in adults with leukemias in remission

H Bittencourt et al. # 377, Oral session EBMT
Thiotepa-Busulfan-Fludarabine versus Cyclophosphamide-based Myeloablative Conditioning Regimen In Remission
### Early Stage (n=147)

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Group 1, sUCBT Cy-based n=93</th>
<th>Group 2, sUCBT Bu+Flu+TT n=54</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>33 (18-54)</td>
<td>32 (19-51)</td>
</tr>
<tr>
<td>HLA match – 4/6</td>
<td>51 (56%)</td>
<td>28 (53%)</td>
</tr>
<tr>
<td>Acute Leukemia*</td>
<td>79 (85%)</td>
<td>52 (96%)</td>
</tr>
<tr>
<td>Median TNC after thawing (10^7 Kg)</td>
<td>2.5 (0.6-7.6)</td>
<td>2.3 (1.4-4.9)</td>
</tr>
<tr>
<td>GVHD Prophylaxis:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CSA+Steroids</td>
<td>78 (84%)</td>
<td>38 (70%)</td>
</tr>
<tr>
<td>ATG</td>
<td>83 (89%)</td>
<td>48 (89%)</td>
</tr>
</tbody>
</table>

* P<0.05

Besides ABO major incompatibility (P=0.02), there was no other differences among the 2 groups for patients disease and UCBT characteristics (gender, weight, CMV status, previous autologous HSCT, CD34+ infused cells).
EFS at 5 years
Early Stage

DFS: 32%

Group 1: sUCBT-Cy-based: 28%
Group 2: sUCBT-BuFluTT: 41%

BuFluTT associated with better event-free survival in multivariate analysis
HR 0.64 (CI95%:0.41-0.99 – P=0.04)

P=0.07
TBF Single UCBT
vs
other MAC single UCBT
vs
TBI+CY+Flu double UCBT

What are the results?
Are outcomes after myeloablative conditioning regimen in double cord blood transplantation (UCBT) better than single UCBT for adults with acute leukemia in remission? Eurocord-EBMT analysis

Annalisa Ruggeri et al

No conflict of interest to disclose
LFS at 2 years
MAC sUCBT and dUCBT in adults with AL in CR1

Group 1: sUCBT-CyTBI12: 30±7%, n=68 (Cell dose 2.9)

Group 2: sUCBT-BuFluTT+ATG: 46±6%, n=88 (Cell dose 3.1)

Group 3: dUCBT-CyFluTBI12: 48±6%, n=83 (Cell dose 3.7)

p=0.03
Which is the “best” RIC for UCBT?
Disease Free Survival according to conditioning after single and double UCBT for malignancies in adults (n=155)

- CY+TBI 2GY+FLU (n=101)
  - 51%
- Others
  - 28%

P = 0.0002
Phase II trial in France on the use of TCF–RIC in UCBT for AML (n=79)

Cumulative Incidence of Relapse

2 year estimate: 46%

Should we include Thiotepa or increase TBI in the RIC?

Rio B et al
Should we include ATG in the conditioning regimen in MAC and RIC?
Results - 2y LFS after UCBT for adults with ALL

MAC

- no ATG 39±6% (n=72)
- ATG 23±3% (n=212)

p=0.02

RIC

- no ATG 47±6% (n=62)
- ATG 33±10% (n=25)

p=0.04

Tucunduva L et al
UCBT

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Risk factor associated with decreased cumulative hazard of severe bacterial infections

Multivariate analysis

Longer time to neutrophil recovery  
(● time dependent)  

HR 4.54  p <0.0001
Risk factor associated with decreased cumulative hazard of severe viral infections

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>HR</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Positive CMV serology</td>
<td>3.54</td>
<td>0.0005</td>
</tr>
<tr>
<td>Number of HLA disparities &gt; 2</td>
<td>4.76</td>
<td>0.02</td>
</tr>
<tr>
<td>Longer time to engraftment (time dependent)</td>
<td>2.5</td>
<td>0.0007</td>
</tr>
<tr>
<td>Infections before transplant</td>
<td>2.18</td>
<td>0.05</td>
</tr>
</tbody>
</table>
Risk factor associated with decreased cumulative hazard of severe **fungal** infections

**Multivariable analysis**

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>HR</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Recipient’s age &gt; 15 years</td>
<td>9.65</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Diagnosis of Inborn and BMF</td>
<td>7.69</td>
<td>0.04</td>
</tr>
<tr>
<td>Longer time to engraftment (time dependent)</td>
<td>5.88</td>
<td>0.02</td>
</tr>
<tr>
<td>Acute GVHD III-IV (time dependent)</td>
<td>4.24</td>
<td>0.03</td>
</tr>
</tbody>
</table>
UCBT

Summary

• Indications

• Survey on outcomes in children and adults

• New criteria for Cord Blood Unit Choice

• Conditioning regimen

• Complications (engraftment and infections)
The Eurocord Office, Hôpital Saint-Louis, Paris

Eurocord - International Registry on Cord Blood Transplantation