Update on Unrelated Cord Blood Transplantation

Vanderson Rocha, MD, PhD
Professor of Haematology- Oxford University
BMT unit, Churchill Hospital
Oxford, UK

Scientific Director of Eurocord
Paris, France
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
- Survey on outcomes in children and adults
- New criteria for Cord Blood Unit Choice
- Conditioning regimen
- Complications (engraftment and infections)
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

293 EBMT
267 Non-EBMT

6958 cases (75%)
2379 cases (25%)

- Related n=708 (8%)
- Unrelated n=8618 (92%)

Children n=5071 (54%)
Adult n=4265 (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>
</tr>
<tr>
<td>1992</td>
<td>2</td>
</tr>
<tr>
<td>1993</td>
<td>1</td>
</tr>
<tr>
<td>1994</td>
<td>5</td>
</tr>
<tr>
<td>1995</td>
<td>15</td>
</tr>
<tr>
<td>1996</td>
<td>30</td>
</tr>
<tr>
<td>1997</td>
<td>58</td>
</tr>
<tr>
<td>1998</td>
<td>92</td>
</tr>
<tr>
<td>1999</td>
<td>123</td>
</tr>
<tr>
<td>2000</td>
<td>145</td>
</tr>
<tr>
<td>2001</td>
<td>192</td>
</tr>
<tr>
<td>2002</td>
<td>167</td>
</tr>
<tr>
<td>2003</td>
<td>187</td>
</tr>
<tr>
<td>2004</td>
<td>298</td>
</tr>
<tr>
<td>2005</td>
<td>440</td>
</tr>
<tr>
<td>2006</td>
<td>590</td>
</tr>
<tr>
<td>2007</td>
<td>695</td>
</tr>
<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>

N=7188

* 215 CBUs not infused are included in the bar chart
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
- 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
- Indications
  - 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**
  - ALL: 1150
  - AML: 604
  - MDS/MPD: 298
  - Non-Hodgkin Lymphoma: 77
  - Hodgkin Lymphoma: 62
  - Solid Tumor: 19
  - Immune Deficiency: 147
  - Metabolic Disorder: 388
  - Bone Marrow Failure Syndrome: 337
  - Histiocytosis: 147
  - Hemoglobinopathy: 37
  - Other diagnosis: 18

- **Non-Malignant**

---

Eurocord - International Registry on Cord Blood Transplantation
Indication for Unrelated UCBT in adults

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

- ALL: 21%, 17%
- AML: 39%, 37%
- MDS/MPD: 14%, 14%
- CML: 8%, 5%
- CLL: 1%, 4%
- Lymphoma: 12%, 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

Total: 1185
UCBT

- Registry update
- Indications
- Survey on outcomes in children and adults
- New criteria for Cord Blood Unit Choice
- Conditioning regimen and GVHD prophylaxis
- Complications (engraftment and infections)
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+: 29 ± 5%, n=74
MRD-: 54 ± 5%, n=96

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

Probability OS vs Months
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, %

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

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
  \[4.9 \times 10^7/\text{kg} \text{ (2.1-14.8)}\]

- 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

p<0.001

months

Probability

0.0  0.2  0.4  0.6  0.8  1.0

RIC

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

p<0.001

months

Probability

0.0  0.2  0.4  0.6  0.8  1.0

Eurocord - International Registry on Cord Blood Transplantation
UCBT

- Registry update
- Indications
- Survey on outcomes in children and adults in UK
- New criteria for Cord Blood Unit Choice
- Conditioning regimen and GVHD prophylaxis
- Complications (engraftment and infections)
From 1996 to 2011, 538 cord blood transplant were performed in UK and reported to Eurocord.

- 52 (9.7%) CBT from related donor
- 379 (70%) for children and 159(30%) for adult
- 65% for malignant disease

**Type of CBT**

- Single CB unmanipulated: 68%
- Single CB expanded: 1%
- CB + BM same donor: 2%
- Double CB: 26%
- Preliminary Cases: 3%
Unrelated CB Transplants in UK, results in children
5 year OS by type of disease

Non Malignant (n=165): 74±6%

Malignant (n=162): 44±4%
CB Transplants in UK, results in adults

OS by type of disease

- AML: 48±7%
- ALL: 41±8%
- MDS: 25±8%

OS by disease status

- Remission: 53±6%
- Advanced: 22±6%
CB Transplants in UK, results in adults

OS by type of
conditioning regimen

OS by type of graft

MAC, n=86: 43±7%

RIC, n=68: 37±6%

Single CBT, n=158: 44±7%

Double CBT, n=40: 41±8%
UCBT

- Registry update
- Indications
- Survey on outcomes in children and adults
- New criteria for Cord Blood Unit Choice
- Conditioning regimen and GVHD prophylaxis
- Complications (engraftment and infections)
Recomendations for CB unit choice 2012

Search for antibodies against HLA antigens of the cord blood unit

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></td>
<td>1%</td>
<td>8%</td>
<td>22%</td>
<td>44%</td>
<td>25%</td>
</tr>
<tr>
<td>6/6</td>
<td></td>
<td></td>
<td></td>
<td>4%</td>
<td>18%</td>
<td>24%</td>
</tr>
</tbody>
</table>

**Note:** The table shows the match percentages for different levels of HLA match. For example, 6/6 matches are at 54%.
Non-Relapse Mortality
- Allele-level Matched at A, B, C, DRB1 -

P<0.001
NRM at 1-year by pre-cryopreserved TNC and HLA-match

<table>
<thead>
<tr>
<th></th>
<th>HLA-match</th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>4/8</td>
<td>5/8</td>
<td>6/8</td>
<td>7/8</td>
<td></td>
</tr>
<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>
<td></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>
<td></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>
<td></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
- Indications
- Survey on outcomes in children and adults
- New criteria for Cord Blood Unit Choice

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

No Flu Based (n=1471) 86%

Fludarabine based MAC (n=384) 91%

$p<0.0001$
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 (10^7Kg)</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
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)
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?
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: *a registry a perspective*

- Registry update
- Indications
- Survey on outcomes in children and adults
- New criteria for Cord Blood Unit Choice
- Conditioning regimen
- Complications (engraftment and infections)
The **Probability Density** to engraft describes the probability to engraft at each time point from CBT, also considering competing events (ie early deaths).

- The engraftment probability peaks at +21, the median halves at +31 (20%) and drops to 5% at day 42.

The area under the curve beyond each time point represents the residual probability to engraft.
3 years Event-free survival after graft failure in UCBT recipients

- Second allogeneic transplants: 22±7% (n=54, deaths 39)
- No additional therapy: 13±7% (n=34, deaths 28)
- Autologous rescue: 12±7% (n=25, deaths 22)
Second Transplants Characteristics (n=54)

- Median time between first and second transplants = 56 days (33-116)
  - UBMT= 86 (64-98)
  - Haplo = 55 (36-105)
  - Cord Blood = 56 (33-116)

- Conditioning regimen
  - No conditioning n=5
  - Myeloablative n=5
    - BU + CY + ATG = 2
    - FLU + MELPH ± TBI = 2
    - FLU + CY + BU + MOAB = 1
  - Non-Myeloablative n=39
    - FLU + CY ± ATG ± TBI = 14
    - FLU ± ATG ± TBI = 8
    - ATG = 5
    - CY ± ATG ± TBI = 5
    - FLU + MELPH ±TBI ± ATG = 4
    - OTHERS = 3

- GVHD prophylaxis
  - CsA + steroids = 9
  - CsA + MMF = 7
  - CsA + MTX = 5
  - CsA = 6
  - MMF + steroids = 2
  - Others = 7

- T-cell depletion – 12 (24%)
  - Haplo (n=11)
  - UBMT (n=1)
Results

2 years event-free survival after second transplants according to the source of cells

Bone Marrow  60±22%  n=5  deaths 2
Double Cord Blood  42 ±17%  n=10  deaths 5
Haplo 25±14%  n=13  deaths 10
Single Cord Blood  9±6%  n=26  deaths 24

p=0.04
Risk factor associated with decreased cumulative hazard of severe **bacterial** infections

**Multivariate analysis**

Longer time to neutrophil recovery

<table>
<thead>
<tr>
<th>HR</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>4.54</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

*(time dependent)*
Risk factor associated with decreased cumulative hazard of severe **viral** infections

<table>
<thead>
<tr>
<th>Multivariate analysis</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>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: a registry a perspective

Summary

- Indications
- Survey on outcomes in children and adults
- New criteria for Cord Blood Unit Choice
- Conditioning regimen
- Complications (engraftment and infections)
Thanks also to

Eurocord Registry at Agence de Biomedecine
Cord Blood Banks
ALWP
EUROCORD TEAM 2012-2013

Annalisa Ruggeri, MD
Vanderson Rocha MD PhD
Scientific Director

Eliane Gluckman MD FRCP
Project Leader

Agnès Devergie MD

Chantal Kenzey Data Manager

Fernanda Volt, MT

Myriam Pruvost
Administrative Assistant

Luciana Tucunduva MD