Cord Blood Transplant Past and Future

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Eurocord
ISCT Paris 24/04/2014
Background

• Since 1988, umbilical cord blood (CB) has been successfully used to treat children and adults needing stem cell transplantation

• CB is easily collected (non-invasive), provides a rapidly available source of stem cells

• No risk for the donor and few ethical problems

• CB stem cells are immature cells that allow for a higher number of HLA mismatches than other standard cell sources

• Clinical outcomes after CB HSCT are similar to outcomes to HSCT using bone marrow or PBSC
Background

• In the past, CB was routinely discarded with the placenta as medical waste after a baby’s birth and it was considered property of the hospital

• Once the therapeutics characteristics of the CB were identified, informed consent for the collection and storage of CB became necessary
<table>
<thead>
<tr>
<th>Year</th>
<th>Event</th>
</tr>
</thead>
<tbody>
<tr>
<td>1988</td>
<td>First Cord Blood Transplant</td>
</tr>
<tr>
<td>1995</td>
<td>Establishment of Eurocord group</td>
</tr>
<tr>
<td>1998</td>
<td>Large series of UCBT= cell dose and HLA</td>
</tr>
<tr>
<td>2002</td>
<td>Use of cord blood cells in adults with promising results</td>
</tr>
<tr>
<td>2006</td>
<td>More adults than children transplanted with cord blood cells</td>
</tr>
<tr>
<td>2008</td>
<td>Allele matched UBMT compared to UCBT</td>
</tr>
<tr>
<td>2010</td>
<td>HLA C typing and outcomes</td>
</tr>
<tr>
<td>2013</td>
<td>HLA allele level typing</td>
</tr>
</tbody>
</table>
The ideal stem cell source

- Immediate availability
- Few HLA restriction
- Absence of risk for the donor
- Applicable to all diseases and all ages
- Associated with rapid lympho hematopoietic recovery, potent graft versus malignancy effect, little risk of acute and chronic GVH and high disease free survival
Cord Blood Transplantation
Advantages

• More than 25 years experience
• Immediate availability, absence of donor risk, HLA mismatches accepted
• General applicability for children and adults with malignant and non-malignant disorders
• Genetically diverse populations are more likely to benefit from cord blood
• Survival outcomes comparable to other sources of stem cells
• Use extended in older populations with reduced intensity conditioning and double cord blood transplant
• New results for improving engraftment and immune reconstitution
Safety

• When done by trained professionals, the collection of CB presents no risk to either the mother or the baby
Ethical and Legal Issues

• When considered for CB donation, pregnant women receive a large amount of information about the donation process and the consequences of the different types of banking. It is crucial to disclose:

  – Who has access to the CB
  – Where it is stored
  – How is it stored
  – Donor’s privacy protection

ENABLES THE PREGNANT WOMEN TO MAKE AN INFORMED DECISION
Problems unique to Cord Blood Transplantation

- Delayed hematopoietic recovery

- In part attributed to relatively low TNC delivered and donor-recipient HLA-mismatch

- Likely to result in longer length of stay

- But GVHD risks are lower which may offer an advantage in terms of costs as well as quality of life
Number of cord blood units worldwide

Total number of cord blood units

610,950 CBUs

Data from BMDW - Bone Marrow Donors Worldwide
<table>
<thead>
<tr>
<th>Eurocord registry database*</th>
<th>2013</th>
<th>1988-2013</th>
</tr>
</thead>
<tbody>
<tr>
<td>Countries / Centres / EBMT centres (N)</td>
<td>36 / 225 / 150</td>
<td>51 / 590 / 306</td>
</tr>
<tr>
<td>Cord blood units (N)</td>
<td>1048</td>
<td>13 522**</td>
</tr>
<tr>
<td>European CBUs (%)</td>
<td>78%</td>
<td>58%</td>
</tr>
<tr>
<td>CBT cases (N)</td>
<td>809</td>
<td>10 911</td>
</tr>
<tr>
<td>Unrelated (%)</td>
<td>97%</td>
<td>93%</td>
</tr>
<tr>
<td>European (%)</td>
<td>65%</td>
<td>64%</td>
</tr>
<tr>
<td>Single / Double (%)*</td>
<td>45% / 27%</td>
<td>61% / 23%</td>
</tr>
<tr>
<td>Children (%)</td>
<td>36%</td>
<td>53%</td>
</tr>
</tbody>
</table>

**Eurocord Registry status as off December, 31st, 2013. Still collecting 2013 data

**324 CBUs (2%) released but not infused are not included in the table
Eurocord Registry at ABM
European CBUs shipped by year

N=8081

<table>
<thead>
<tr>
<th>Year of shipment</th>
<th>Nº of CBUs</th>
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<tbody>
<tr>
<td>1990</td>
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<td>2010</td>
<td>881</td>
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<td>2011</td>
<td>823</td>
</tr>
<tr>
<td>2012</td>
<td>860</td>
</tr>
<tr>
<td>2013</td>
<td>835</td>
</tr>
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</table>
Eurocord Registry at ABM
Unrelated European CBT by year and recipient’s age
Why UCBT in adults has been increasing over the years and is now a plateau?

- Use of double cord to increase the TNC dose and facilitate engraftment
- Increased confidence in the procedure
  Several published reports showed similar outcomes of UCBT with HLA matched bone marrow or peripheral blood stem cell donors
- The use of reduced intensity conditioning (RIC) regimen that decreases the mortality related to transplantation
- **Decreased use in recent years**:
  - Competition with related haplo identical HSCT
  - Cost of graft acquisition especially for dUCBT
Eurocord Registry at ABM
Unrelated European CBT by recipient’s age and diagnosis

Children
median age 5.2 years (0.1-18)

Adults
median age 43.5 years (18.1-76.2)
Eurocord Registry at ABM
Unrelated European CBT by recipient’s age and graft type

In children: 89% single CBT
In adults: 60% double CBT

* Still collecting 2013 data
Single and double UCBT: distribution of age for adult patients

- >60 y: Eurocord 433, CIBMTR 477
- 50-59 y: Eurocord 752, CIBMTR 805
- 40-49 y: Eurocord 719, CIBMTR 790
- 30-39 y: Eurocord 736, CIBMTR 780
- 16-30 y: Eurocord 1103, CIBMTR 1171

35% adults >50 years
Transplants by diagnosis

**Children**
- Acute leukemia: 11%
- MDS / MPD: 7%
- Lymphomas / Solid tumors: 3%
- Bone Marrow Failure Sd: 2%
- Hemoglobinopathy: 9%
- Immune Deficiency: 10%
- Metabolic Disorder: 11%
- Histiocytosis / Others: 47%

**Adults**
- Acute leukemia: 14%
- MDS / MPD: 3%
- Lymphomas: 3%
- Plasma cell disorders / Solid tumors: 1%
- Bone Marrow Failure Sd: 20%
- Hemoglobinopathy: 47%
- Immune Deficiency: 59%
Single and Double UCBT in EBMT centers, n=3237
Children: 2-y OS according to disease

- **Malignant**: 50± 1%; n=1159
- **Non-malignant**: 63 ± 2%; n=1113

P<0.001
Single and Double UCBT in EBMT centers, n=2768
Adult, 2-y OS according to disease:

- MDS/MPS: 25±3%; n=380
- Plasma cell disorder: 44±6%; n=94
- Lymphoma: 44±3%; n=329
- Acute leukemia: 38±2%; n=1685
- Chronic leukemia: 40±3%; n=268

p=0.017
How to improve results

• Choice of the cord blood unit
  – Increase cell dose:
    • double cord
    • Ex vivo expansion
    • Improve homing
  – HLA matching
• Conditioning
• Improve immune reconstitution
Impact of allele-level HLA matching on outcomes after myeloablative single unit umbilical cord blood transplantation for hematologic malignancy

Non-relapse Mortality

Eapen M et al, Blood 2014
Neutrophil Recovery

P=0.005

8/8 (71%)
7/8 (62%)
6/8 (66%)
5/8 (58%)
4/8 (56%)
3/8 (53%)
2/8 (40%)
1/8 (12.5%)
Non-relapse Mortality
- Total Nucleated Cell Dose -

7/8 HLA-matched, TNC < 3 x 10^7/kg (N=33; 45%)
7/8 HLA-matched, TNC > 5 x 10^7/kg (N=138; 21%)
7/8 HLA-matched, TNC ≥ 3 – 5 x 10^7/kg (N=52; 24%)

Eapen M et al, Blood 2014
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
Double Cord blood

- Facilitates engraftment by increasing total cell dose
- Lowers risk of relapse
- Higher GVHD incidence
- Reduced TRM when compared to single-unit historic controls, however some reports showed similar outcomes with the use of sUCBT and dUCBT
- Cost of acquisition of two cord blood and cost-effectiveness of the procedure
Conditioning regimen in UCBT

**MAC** (single or double units)

**TBI 12 GY + CY**

**BU + CY + Fludarabine (120-150mg/m2) + ATG**

**TBF:** Thiotepa + BU + Fludarabine + ATG

**RIC** (single or double units)

**TCF:** TBI 2 Gy + CY + Fludarabine ± ATG
Comparison of outcomes after single or double cord blood transplantation in adults with acute leukemia using different types of myeloablative conditioning regimen in remission - a retrospective study

Annalisa Ruggeri,, Guillermo Sanz, Henrique Bittencourt Alessandro Rambaldi, Ibrahim Yakoub-Agha, Jose Ribeira, William Arcese, Lionel Mannone, Jorge Sierra, Carlos Solano, Samir Nabhan, Luciana Tucunduva, Fernanda Volt, Chantal Kenzey, Eliane Gluckman, Myriam Labopin, Vanderson Rocha

on behalf of Eurocord and the Acute Leukemia Working Party of EBMT.

Leukemia 2013

No conflict of interest to disclose
Relapse at 2-year-MAC sUCBT and dUCBT in adults with AL in CR1

CI of relapse: 19±3%

Group 1: sUCBT-CyTBI12/BU: 25±4%, n=68
Group 2: sUCBT-TBF+ATG: 18±3%, n=88
Group 3: dUCBT-CyFluTBI12: 16±3%, n=83

No factors associated with RI in the multivariate analysis
LFS at 2-year-MAC sUCBT and dUCBT in adults with AL in CR1

Group 1: sUCBT-CyTBI12: 30±7%, n=68

Group 2: sUCBT-TBF+ATG: 46±6%, n=88

Group 3: dUCBT-CyFluTBI12/BU: 48±6%, n=83

p=0.03
Results - 2y LFS after UCBT for adults with ALL

Tucunduva L et al, BMT in press
MAC setting in malignant diseases

- **In children with AL**, single CBT with TBI (or Bu)+CY+FLU without ATG are associated with very good outcomes.

- **In Adults with AL**

  TBI+CY+Flu without ATG using double cord blood transplants and TBF+ATG using single units have similar results.
Which is the “best” RIC for UCBT?
Treatment-Related Mortality

Cumulative Incidence, %

<table>
<thead>
<tr>
<th>Group</th>
<th>Hazard Ratio</th>
<th>95% CI</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>dCB other vs. dCB TCF ± ATG</td>
<td>2.96</td>
<td>(1.61 – 5.45)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>MMUD vs. dCB TCF ± ATG</td>
<td>1.77</td>
<td>(1.04 – 2.99)</td>
<td>0.035</td>
</tr>
<tr>
<td>MUD vs. dCB other</td>
<td>0.37</td>
<td>(0.18 – 0.62)</td>
<td>0.0001</td>
</tr>
</tbody>
</table>

- dCB, other: 52%
- MMUD: 30%
- MUD: 23%
- dCB, TCF: 22%
Leukemia-Free Survival

<table>
<thead>
<tr>
<th>Months</th>
<th>MUD vs. dCB other</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>0.68 (0.47 – 0.99)</td>
</tr>
<tr>
<td></td>
<td>0.046</td>
</tr>
</tbody>
</table>

- MUD: 31%
- MMUD: 25%
- dCB, TCF: 26%
- dCB, other: 9%
Early Release Paper

Alternative donor hematopoietic stem cell transplantation for mature lymphoid malignancies after reduced-intensity conditioning regimen: similar outcomes with umbilical cord blood and unrelated donor peripheral blood

Rodrigues C et al, 2013

UCBT = 104

PB = 541

75% TCF

29%

28%

56%

49%
Cost-effectiveness

• When comparing different transplant approaches such as the use of sUCBT and dUCBT it is important to consider the cost-effectiveness of the procedures

• One limitation of using dUCBT is the cost of the 2 units

• Studies comparing of the total cost of the 2 procedures have not been previously published

• With that objective, we designed a study to evaluate outcomes and cost-effectiveness of double compared to single UCBT with RIC or MAC regimens, in France, in adults with acute leukemia in CR1

Labopin, Haematologica 2013
## Cost-effectiveness analysis

### MAC

<table>
<thead>
<tr>
<th></th>
<th>sUBCT</th>
<th>dUBCT</th>
<th>Difference</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Total cost</strong></td>
<td>199,314 €</td>
<td>220,616 €</td>
<td>21,302 €</td>
</tr>
<tr>
<td><strong>QALY</strong></td>
<td>1.369</td>
<td>1.985</td>
<td>0.616</td>
</tr>
<tr>
<td><strong>ICER</strong></td>
<td>34,581 €</td>
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</tbody>
</table>

### RIC

<table>
<thead>
<tr>
<th></th>
<th>Total cost</th>
<th>sUBCT</th>
<th>dUBCT</th>
<th>Difference</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Total cost</strong></td>
<td>171,868 €</td>
<td>204,288 €</td>
<td>32,420 €</td>
<td></td>
</tr>
<tr>
<td><strong>QALY</strong></td>
<td>1.491</td>
<td>1.975</td>
<td>0.484</td>
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<tr>
<td><strong>ICER</strong></td>
<td>66,983 €</td>
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</table>

Labopin, Haematologica 2013
Conclusion - Summary

- Results of single and double UCBT are similar for patients with acute leukemia, supporting the use of dUCBT when a single UCB unit (TNC dose (>2.5x10^7/Kg)) is not available

- In the MAC setting, a single UCBT with adequate TNC using TBF gives same results as double UCBT

- As for cost-effectiveness between single and double UCBT, date from France suggests that, in both MAC and RIC settings, dUCBT is associated with better outcomes and is more cost-effective strategy for adult pts with acute leukemia

- However, costs vary according to countries and the cost-effectiveness of the procedures needs to be evaluated in the specific context where the UCBT is performed
Criteria of CB unit choice- EUROCORD

- Look at the number of cells in MAC, RIC:
  - >2.5x10^7 NC/kg and or >1x10^5 CD34+/kg

- 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, avoiding C mismatches
  - Allele typing of HLA -A and –B (++ in case of 4/6 CBU)

- 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 (>4.0x10^7 NC/kg) and find the best HLA match
  - If the minimum number of cells for a single UCBT is not achieved, a double UCBT should be considered

- Other considerations, if several CBU are available consider:
  - Cord Blood Bank accreditation status and location
  - ABO compatibility
  - NIMA and KIR status

- Patients screening for antibodies against HLA antigens of the cord blood unit
Next steps

• Role of HLA matching in single and double cord blood transplant based on high resolution HLA typing, HLA-C, KIR, NIMA, SNPs and other polymorphic genetic factors
• Interaction between cell dose and HLA
• Improve immune reconstitution with T regs, NK, CTL infusion
• Perform prospective randomized studies on conditioning and GVH prevention
• Role of ex-vivo expansion and homing molecules
Cord blood non-hematopoietic subpopulations

- Umbilical arteries
- Umbilical cord
- Umbilical vein
- Wharton’s Jelly

- Cord blood
- Umbilical Cord Mesenchymal Stromal Cells (UC-MSC)
- Unrestricted Somatic Stromal Cells (USSC)
- Cord Blood Mesenchymal Stromal Cells (CB-MSC)
- Endothelial Colony-Forming Cells (E-CFC; M.Yoder.)
- Very Small Embryonic-Like cells (VSEL)

- Identification of a novel hierarchy of endothelial progenitor cells using human peripheral and umbilical cord blood
  David A. Ingram, Laura E. Mead, Hiroshi Tanaka, Virginia Meade, Amy Fenoglio, Kelly Mortell, Karen Pollak, Michael J. Kurzrok, David Giley, and Mervin C. Yoder