Donor Selection in Paediatric allo-HSCT:

Unrelated Cord Blood Transplantation

for Malignant and Non-Malignant Diseases

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Hopital Saint Louis, Paris, France
First cord blood transplant
<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>1989-92</td>
<td>Clinical observation that GVHD was reduced in HLA incompatible CBT</td>
</tr>
<tr>
<td>1993-95</td>
<td>Feasibility of HLA incompatible unrelated cord blood transplants</td>
</tr>
<tr>
<td>1995</td>
<td>Establishment of Eurocord group</td>
</tr>
<tr>
<td>1997</td>
<td>Nucleated cell dose more important factor for engraftment and survival, influence of HLA on engraftment</td>
</tr>
<tr>
<td>1998</td>
<td>Large series of UCBT = confirmation of cell dose and HLA</td>
</tr>
<tr>
<td>&gt;2000</td>
<td>Retrospective comparisons between UBMT and UCBT</td>
</tr>
<tr>
<td>2002</td>
<td>Use of cord blood cells in adults with promising results</td>
</tr>
<tr>
<td>2003</td>
<td>Criteria of cord blood choice and indications</td>
</tr>
<tr>
<td>2004</td>
<td>Use of double cord and RIC regimen in adults</td>
</tr>
<tr>
<td>2004</td>
<td>Isolation of USSC from umbilical cord blood</td>
</tr>
<tr>
<td>2004</td>
<td>Comparable results between unrelated CBT and UBMT in adults</td>
</tr>
<tr>
<td>2006</td>
<td>More adults than children transplanted with cord blood cells</td>
</tr>
<tr>
<td>2007-09</td>
<td>Allele matched UBMT compared to UCBT in children and adults</td>
</tr>
</tbody>
</table>
Estimate number of patients with an indication of an allogeneic hematopoietic stem cell transplants

- Conditional probability of finding an 8 of 8 allele level matched unrelated adult donor is
  - 51% for Caucasians
  - 30% for Hispanics
  - 20% for Asians
  - 17% for African Americans
Survival

9-10% lower overall survival with each additional mismatch

<table>
<thead>
<tr>
<th>Match</th>
<th>n</th>
<th>Survival % (95%CI)</th>
<th>RR (CI)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>8/8</td>
<td>1840</td>
<td>52 (50-54)</td>
<td>1.00</td>
<td></td>
</tr>
<tr>
<td>7/8</td>
<td>988</td>
<td>43 (40-46)</td>
<td>1.25 (1.13-1.37)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>6/8</td>
<td>633</td>
<td>33 (30-37)</td>
<td>1.65 (1.48-1.84)</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

Lee SJ, Blood 2007
### Searching and identifying an alternative stem cell donor

#### Main criteria to be considered

<table>
<thead>
<tr>
<th></th>
<th>UBMT</th>
<th>UCBT</th>
<th>Haplo-HSCT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Information on A + B + DRB1 typing (%)</td>
<td>16 – 56</td>
<td>~ 80</td>
<td>100</td>
</tr>
<tr>
<td>Median search time (months)</td>
<td>3 – 6</td>
<td>&lt; 1</td>
<td>immediate</td>
</tr>
<tr>
<td>Donors identified but not available (%)</td>
<td>20 – 30</td>
<td>~ 1</td>
<td>None</td>
</tr>
<tr>
<td>Rare haplotypes represented (%)</td>
<td>2 – 10</td>
<td>20</td>
<td>Not applicable</td>
</tr>
<tr>
<td>Main limiting factor to graft acquisition</td>
<td>HLA identity</td>
<td>Cell dose</td>
<td>Poor mobilization</td>
</tr>
<tr>
<td>Ease of rearranging date of cell infusion</td>
<td>Difficult</td>
<td>Easy</td>
<td>Easy</td>
</tr>
<tr>
<td>Potential for immunotherapy</td>
<td>Yes</td>
<td>No</td>
<td>Yes (limited)</td>
</tr>
<tr>
<td>Potential for viral transmission to recipient</td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>Potential for congenital disease transmission</td>
<td>No</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Risk for the donor</td>
<td>Low</td>
<td>No</td>
<td>Low</td>
</tr>
<tr>
<td>Main problems to be overcome</td>
<td>GvHD</td>
<td>Graft failure, delayed immune recovery</td>
<td>Delayed immune recovery, lack of T-cell-mediated GVL effect</td>
</tr>
</tbody>
</table>


$n \approx 14,000$ (estimated number based on CIBMTR, Eurocord and Japanese CB registries)
5223 cord blood transplantations performed from 1988 to March 2009 in 47 countries and 437 transplant centres

- 238 EBMT 3590 (68%) cases
- 199 Non-EBMT 1513 (29%) cases

Related  n= 499 (10%)  
Children  n=3046 (59%)  
Unrelated n=4655 (90%)  
Adults  n=2157 (41%)  

Eurocord - International Registry on Cord Blood Transplantation
Unrelated CBT according to recipient age by year reported to Eurocord

- Children: n=2522
- Adults: n=2041

*Still collecting data

Eurocord - International Registry on Cord Blood Transplantation
Clinical Results in Children with Malignant Diseases
Unrelated single cord blood for children (n=1944) by diagnosis

- 68% (n=1324)
Single UCBT in children with malignancies

Transplant related mortality according to the period of CBT

1994-1999: 32% +/- 3
2000-2002: 24% +/- 2
2003-2006: 17% +/- 2

p = 0.04
Clinical Results in Children with
Acute Lymphoblastic Leukemia
## Patient and disease characteristics

<table>
<thead>
<tr>
<th></th>
<th>CR1</th>
<th>CR2</th>
<th>Advanced</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>N</strong></td>
<td>87</td>
<td>152</td>
<td>122</td>
</tr>
<tr>
<td>Median age at UCBT</td>
<td>4.7 (0.4-16)</td>
<td>6.7 (0.7-16)</td>
<td>8.0 (0.5-16)</td>
</tr>
<tr>
<td>&lt;1 year</td>
<td>18%</td>
<td>&lt;1%</td>
<td>&lt;1%</td>
</tr>
<tr>
<td></td>
<td>43%</td>
<td>44%</td>
<td>58%</td>
</tr>
<tr>
<td></td>
<td>0</td>
<td>2%</td>
<td>10%</td>
</tr>
<tr>
<td></td>
<td>-</td>
<td>21 mo</td>
<td>23 mo</td>
</tr>
</tbody>
</table>
### Disease Characteristics

<table>
<thead>
<tr>
<th></th>
<th>CR1 (n= 87)</th>
<th>CR2 (n=152)</th>
<th>Advanced (n=122)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pre-B</td>
<td>47%</td>
<td>56%</td>
<td>66%</td>
</tr>
<tr>
<td>B</td>
<td>21%</td>
<td>19%</td>
<td>12%</td>
</tr>
<tr>
<td>T</td>
<td>17%</td>
<td>16%</td>
<td>14%</td>
</tr>
<tr>
<td>Null</td>
<td>7%</td>
<td>3%</td>
<td>6%</td>
</tr>
<tr>
<td>Biphenotypic</td>
<td>8%</td>
<td>6%</td>
<td>2%</td>
</tr>
<tr>
<td>Poor risk</td>
<td>89%</td>
<td>38%</td>
<td>39%</td>
</tr>
<tr>
<td>Cytogenetics</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>t (9;22), t (4;11)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
UCBT for Children with ALL

Cumulative incidence of relapse at 3 years according to disease status (n=361)

- CR1: 32 ± 6%
- Adv: 30 ± 4%
- CR2: 27 ± 4%
Leukemia Free Survival according to disease status (n=361)

**UCBT for Children with ALL**

CR1 33 ± 7%
CR2 35 ± 4%
Adv 21 ± 4%
Leukemia free survival according to first relapse on or off chemotherapy for Children with ALL in CR2 (n=152).

- On therapy: n=73, 26 ± 6%
- Off therapy: n=65, 45 ± 7%

(months)
Outcome after Unrelated Umbilical Cord blood and Unrelated Bone Marrow Transplants for Children with Acute Leukemia

Eurocord (EBMT) - Cord Blood Transplant group - Netcord - Unrelated Bone Marrow Registries study

Bone Marrow Transplant Unit and Biostatistics Department
Hôpital Saint-Louis, Paris

V Rocha, J Cornish et al, Blood, 2001
UCBT vs UBMT for Children with AL

Multivariate analysis of early outcomes

Adjusted Relative Risk

- Neutrophil recovery: NS
- Platelets recovery: p<0.001
- Acute GVHD: p<0.001
- 100 day TRM: p=0.01
- Early Relapse: p=0.02

UBMT n=262
T-UBMT n=180
UCBT n=99
UCBT vs UBMT for Children with AL

Multivariate analysis of long term outcomes (patients surviving after day 100)

- **Chronic GVHD**: $p<0.001$
- **Relapse**: NS
- **Death**: $p=0.07$, NS
A Meta-Analysis of Unrelated Donor Umbilical CBT versus UD Bone Marrow Transplantation in Pediatric Patients

- 161 children UCBT (mostly 1 or 2 antigen-mismatched), compared with 316 children undergoing UBMT (almost entirely fully matched with the recipient)
- T-cell-depleted UBMT was excluded; where data were available, Only fully matched UBMT was used in the analysis.

RESULTS

- Incidence of chronic GVHD was lower with UCBT (relative risk [RR] = 0.26; 95% confidence interval [CI] = 0.12-0.57; P = .16), but the incidence of grade III-IV acute GVHD did not differ (RR = 1.46; 95% CI = 0.42-5.03; P = .55).

- There was no difference in 2-year OS in children (RR = 0.76; 95% CI = 0.31-1.87; P = .55).

Unrelated Cord Blood versus allele typing Unrelated Bone Marrow Transplants in Children with Acute Leukemia

M Eapen et al on behalf of CIBMTR and NYBC
## UCBT versus allele typing UBMT

### Disease Characteristics

<table>
<thead>
<tr>
<th>Disease</th>
<th>BM (n=282)</th>
<th>CB (n=503)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ALL</td>
<td>69%</td>
<td>61%</td>
</tr>
<tr>
<td>AML</td>
<td>31%</td>
<td>39%</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Disease status*</th>
<th>BM (n=282)</th>
<th>CB (n=503)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1st CR</td>
<td>17%</td>
<td>21%</td>
</tr>
<tr>
<td>≥ 2nd CR</td>
<td>67%</td>
<td>50%</td>
</tr>
<tr>
<td>Relapse/PIF</td>
<td>16%</td>
<td>29%</td>
</tr>
</tbody>
</table>

* P < 0.05

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Neutrophil Recovery

- BM (n=116), 97%
- CB matched (n=35), 85%
- CB MM high dose >3x10e7/kg (n=362), 79%
- CB MM low dose ≤3x10e7/kg (n=97), 64%
Leukemia-free Survival

Adjusted Probability, %

- CB matched (n=35) 60%
- CB 1-Ag MM >3x10^7/kg (n=157) 45%
- BM matched (n=116) 38%
- CB 2-Ag MM (n=267) 33%
- CB 1-Ag MM >3x10^7/kg (n=44) 35%


<table>
<thead>
<tr>
<th></th>
<th>Cord blood</th>
<th>vs</th>
<th>Bone Marrow</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>ENGRAFTMENT</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>ACUTE GVHD</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>CHRONIC GVHD</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>EARLY TRM</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>RELAPSE</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>SURVIVAL</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Outcomes of Fully Haploidentical Hematopoietic Stem Cell Transplantation compared to Unrelated Cord Blood Transplantation in Children with Acute Lymphoblastic Leukaemia.

A retrospective analysis on behalf of Eurocord, Pediatric disease and Acute Leukemia Working Party of EBMT.

# DISEASE CHARACTERISTICS

<table>
<thead>
<tr>
<th>Variable</th>
<th>Haplo (n=127)</th>
<th>UCB (n=341)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Presenting WBC</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>24.2 (1.2-700)</td>
<td>36.7 (0.5-187)</td>
<td>0.34</td>
</tr>
<tr>
<td>Phenotype</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>T cell</td>
<td>15%</td>
<td>18%</td>
<td>0.57</td>
</tr>
<tr>
<td>Cytogenetics</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>t(9;22) or t(4;11)</td>
<td>21%</td>
<td>20%</td>
<td>0.7</td>
</tr>
<tr>
<td>Status at Tx</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CR1</td>
<td>17%</td>
<td>23%</td>
<td>0.26</td>
</tr>
<tr>
<td>CR2</td>
<td>38%</td>
<td>41%</td>
<td></td>
</tr>
<tr>
<td>CR3</td>
<td>25%</td>
<td>19%</td>
<td></td>
</tr>
<tr>
<td>Advanced</td>
<td>20%</td>
<td>16%</td>
<td></td>
</tr>
<tr>
<td>Interval diag to Tx (days)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CR1</td>
<td>185</td>
<td>203</td>
<td>0.91</td>
</tr>
<tr>
<td>CR2</td>
<td>956</td>
<td>871</td>
<td>0.51</td>
</tr>
<tr>
<td>CR3</td>
<td>1720</td>
<td>1647</td>
<td>0.48</td>
</tr>
<tr>
<td>Advanced</td>
<td>524</td>
<td>615</td>
<td>0.95</td>
</tr>
</tbody>
</table>
LEUKAEMIA FREE SURVIVAL

P = 0.39

CB (n=341) 29 ± 3%

Haplo (n=127) 23 ± 4%
Multivariate analysis
TRM, Relapse and LFS

* Reference Group

P=0.26
P=0.01
P=0.46
Haploidentical HSCT in children with very high risk ALL in remission Leukemia Free Survival

≥ 9 haplo in the study period n=34; 49 ± 9%

Less than 9 haplo in the study period n=59; 17 ± 5%

P=0.002
UCBT in children with ALL

DFS according to the number of patients by center

- Events
- \(<10\) pts: 113, 64
- \(\geq 10\) pts: 82, 54

\(p=0.009\)
Clinical Results in Children with Non-Malignant Disorders
Unrelated single cord blood for children (n=1944) by diagnosis

- 32% (n=620)
Diagnosis in the group of non-malignant disorders

- PID: 35%
- Metabolic: 32%
- BMFS: 30%
- Hbpathies: 2%
- Others: 1%
- Others: 1%
Overall survival after UCBT for children with non malignant disorders

- BMFS (n=156) 43%
- PID (n=177) 68%
- Metabolic (n=172) 66%
Unrelated Transplants for Immunodeficiency Disease, Age <16, 1996-2006 - by Graft Type -

<table>
<thead>
<tr>
<th></th>
<th>BM n=310</th>
<th>UCB n=258</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Year of transplant</td>
<td>2000</td>
<td>2003</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Median age</td>
<td>1.9 y</td>
<td>1.0</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Interval from dx-Tx</td>
<td>10 mo</td>
<td>6 mo</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>SCID</td>
<td>28%</td>
<td>38%</td>
<td>0.04</td>
</tr>
<tr>
<td>WAS</td>
<td>29%</td>
<td>27%</td>
<td></td>
</tr>
<tr>
<td>Other</td>
<td>43%</td>
<td>35%</td>
<td></td>
</tr>
<tr>
<td>Median FUP</td>
<td>24 mo</td>
<td>24 mo</td>
<td></td>
</tr>
</tbody>
</table>
Neutrophil Recovery after Unrelated Transplants for Immunodeficiency Disease, Age ≤16, 1996-2006 - by Graft Type -

Cumulative Incidence, %

- Bone marrow (N = 286, 93% @ day-42)
- Cord blood (N = 258), 83% @ day-42

P = 0.0009 @ day-42
Probability of Survival after Unrelated Transplants for Immunodeficiency Disease, Age ≤16, 1996-2006 - by Graft Type -

- Bone marrow (N = 286, 68% @ 2-yrs) - Cord blood (N = 258, 66% @ 2-yrs)

P = 0.7283 @ 2-years
Unrelated Transplants for Immunodeficiency Disease, Age <16, 1996-2006
- by Graft Type -

Survival at 2 years (non adjusted)

<table>
<thead>
<tr>
<th></th>
<th>BM n=310</th>
<th>UCB n=258</th>
</tr>
</thead>
<tbody>
<tr>
<td>SCID</td>
<td>65±11%</td>
<td>68±10%</td>
</tr>
<tr>
<td>WAS</td>
<td>72±11%</td>
<td>76±11%</td>
</tr>
<tr>
<td>Other</td>
<td>62±11%</td>
<td>57±11%</td>
</tr>
</tbody>
</table>
Diagnosis in the group of non-malignant disorders

- PID: 35%
- Metabolic: 30%
- BMFS: 2%
- Hbopathies: 1%
- Others: 32%
**UCBT for Hurler disease**

**EFS according to number of HLA disparities**

- **0 HLA Disparity**: 100%
- **1 HLA Disparity**: 65±7%
- **2 and 3 HLA Disparities**: 64±10%

P=0.06
Neutrophil Recovery after Unrelated Transplants for Metabolic Disease, Age ≤16, 1996-2006 - by Graft Type -

- Bone marrow (N = 196, 87% @ day-42)
- Cord blood (N = 330, 84% @ day-42)

Cumulative Incidence, %

Days

P = 0.3546 @ day-42
Overall Survival after Unrelated Transplants for Metabolic Disease, Age ≤16, 1996-2006 - by Graft Type -

Bone marrow (N = 196, 64% @ 2-yrs)

Cord blood (N = 330, 61% @ 2-yrs)

P = 0.5862 @ 2-years
Diagnosis in the group of non-malignant disorders

- PID: 35%
- Metabolic: 32%
- BMFS: 30%
- Hbpathies: 2%
- Others: 1%

Graph shows the distribution of diagnoses among non-malignant disorders.
Overall survival after UCBT for children with BMFS by type of disease

- **Inherited BMFS (n=19)**: 68%
- **Fanconi (n=108)**: 41%
- **SAA (n=25)**: 36%
Survival according to number of HLA disparities

- 6/6 (n=12) 78%
- 5/6 (n=35) 45%
- 3/6 (n=5) 25%
- 4/6 (n=40) 21%

p=0.005
Survival according to number of nucleated cells infused /kg

≥ 4.9 x 10^7 (n=44)  50 %

< 4.9 x 10^7 (n=43)  26 %

p=0.005
Neutrophil Recovery after Unrelated Transplants for Aplastic Anemia and other Inherited Bone Marrow Failure disease, Age ≤16, 1996-2006 - by Graft Type -

Bone marrow (N = 410, 92% @ day-42)

Cord blood (N = 222), 62% @ day-42

P < 0.0001 @ day-42
Overall Survival after Unrelated Transplants for aplastic anemia and Other Inherited Bone Marrow Failure Disease, Age ≤16, 1996-2006 - by Graft Type -

- Bone marrow (N = 410, 62% @ 2-years)
- Cord blood (N = 222, 45% @ 2-years)

P = 0.0001 @ 2-years
Unrelated Transplants for BMFS, Age <16, 1996-2006 - by Graft Type -

**Survival at 2 years (non adjusted results)**

<table>
<thead>
<tr>
<th></th>
<th>BM</th>
<th>UCB</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n=400</td>
<td>n=200</td>
</tr>
<tr>
<td>Inherited BMFS</td>
<td>55±8%</td>
<td>39±8%</td>
</tr>
<tr>
<td>(including Fanconi)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>SAA</td>
<td>66±6%</td>
<td>42±12%</td>
</tr>
</tbody>
</table>
Impact of number and type of HLA incompatibilities and cell dose on outcomes of unrelated cord blood transplants for patients with malignant and non-malignant disorders
UCBT malignant disorders (n=929)

TRM according to number of HLA and cell dose

Cumulative incidence

P < 0.0001
UCBT malignant disorders (n=929)

Relapse according to number of HLA

Cumulative incidence

HLA identical
1 diff
2 diff
3 diff
4 diff

P = 0.01

P = 0.002
UCBT malignant disorders (n=929)

Overall survival according to number of HLA and cell dose

P=0.168

Overall survival

0-1 HLA and cell dose >= 2
2 HLA diff and cell dose >= 2
0-1 HLA and cell dose < 2
2 HLA diff and cell dose < 2
3-4 HLA diff and cell dose >= 2
3-4 HLA diff and cell dose < 2

Months
UCBT in non-malignant disorders (n=268)

TRM according to number of HLA

Cumulative incidence

Days

P = 0.00287
UCBT in non-malignant disorders (n=268)

TRM according to number of HLA and cell dose

\[ P = 0.00065 \]

0 and 1 HLA diff and cell dose < 3.5 (n=28)

0 and 1 HLA diff and cell dose >= 3.5 (n=117)

2 and 3 HLA diff and cell dose < 3.5 (n=30)

2 and 3 HLA diff and cell dose >= 3.5 (n=62)
Overall survival according to HLA and cell dose

UCBT in non-malignant disorders (n=268)

- 0 and 1 HLA diff and cell dose >= 3.5 (n=117)
- 2 and 3 HLA diff and cell dose >= 3.5 (n=62)
- 0 and 1 HLA diff and cell dose < 3.5 (n=28)
- 2 and 3 HLA diff and cell dose < 3.5 (n=30)

P < 0.0001
Criteria of CB unit choice

- Which is the best cell count marker: NC? CD34? CFU-GM?
- Is viability of NC or CD34 associated with engraftment?
- Is HLA-C important in the selection of the cord blood unit?
- Is HLA allele typing important in CBT?
- Double and RIC: Cell dose and HLA? Other?
- Are there other factors related to the CB unit that can improve outcomes?
  - KIR?
  - NIMA?
- Years of Cord Blood Unit storage?
- ABO compatibility?
- Donor gender?
- Bank effect? and standards?
- Antibodies against HLA?
Criteria of CB unit choice

- Which is the best cell count marker: NC? CD34? CFU-GM?
<table>
<thead>
<tr>
<th>Graft characteristics n=155</th>
<th>All patients n=155</th>
<th>Single CBT n=96</th>
<th>Double CBT n=59</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median nucleated cells collected (10^7/Kg), range</td>
<td>4.1 (2.1-12.2) n=151</td>
<td>3.8 (2.1-6.4) n=96</td>
<td>4.6 (3.2-12.2) n=55</td>
</tr>
<tr>
<td>Median nucleated cells infused (10^7/Kg), range</td>
<td>3.1 (0.6-7.9) n=151</td>
<td>2.8 (0.6-6.4) n=96</td>
<td>3.6 (1.1-7.9) n=55</td>
</tr>
<tr>
<td>Median CD34 cells collected (10^6/Kg), range</td>
<td>1.5 (0.1-5.3) n=147</td>
<td>1.4 (0.1-3.9) n=95</td>
<td>1.6 (0.6-5.3) n=52</td>
</tr>
<tr>
<td>Median CD34 cells infused (10^5/Kg), range</td>
<td>1.1 (0.1-5.3) n=141</td>
<td>1.1 (0.1-3.9) n=87</td>
<td>1.2 (0.2-5.3) n=52</td>
</tr>
<tr>
<td>Median cell loss after thawing</td>
<td>25%</td>
<td>25%</td>
<td>27%</td>
</tr>
</tbody>
</table>

Eurocord - International Registry on Cord Blood Transplantation
Criteria of CB unit choice

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  - Antibodies against HLA?
Criteria of CB unit choice

- Is HLA-C important in the selection of the cord blood unit?

Eurocord-CIBMTR collaborative study
Donor-Recipient HLA matching

<table>
<thead>
<tr>
<th>HLA-A,-B,-DRB1</th>
<th>HLA-C</th>
</tr>
</thead>
<tbody>
<tr>
<td>Matched N=104</td>
<td>Matched</td>
</tr>
<tr>
<td></td>
<td>81 (78%)</td>
</tr>
<tr>
<td>1-locus mismatch N=304</td>
<td>114 (37%)</td>
</tr>
<tr>
<td>2-loci mismatch N=294</td>
<td>54 (18%)</td>
</tr>
</tbody>
</table>
Neutrophil Recovery

Cumulative Incidence, %

Days

0 10 20 30 40 50 60

100 90 80 70 60 50 40 30 20 10 0

5/6 C match (N=114; 86%)
5/6 C MM (N=190; 81%)
6/6 C MM (N=23; 83%)
6/6 C match (N=81; 91%)
4/6 C match (N=54; 75%)
4/6 C MM (N=240; 75%)

P=0.151

Not in remission at HCT
RR 0.63, p=0.001
Year >2004
RR 1.37, p=0.004

RR 0.63, p=0.001
Year >2004
RR 1.37, p=0.004
Overall Survival

Overall Survival

Probability, %

Months

6/6 C MM (N=23; 55%)
6/6 C match (N=81; 60%)

5/6 C match (N=114; 59%)
5/6 C MM (N=190; 57%)

4/6 C match (N=54; 53%)
4/6 C mismatch (N=240; 53%)

Not in remission at HCT
RR 2.06, p<0.001

P=0.993
Criteria of CB unit choice

- Which is the best cell count marker: NC? CD34? CFU-GM?
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  - Donor gender?
  - Bank effect? and standards?
Overall survival of AML patients

With KIR-ligand incompatibility (n=26)
70%±11 at 2 yrs

Without KIR-ligand incompatibility (n=68)
36%±8 at 2 yrs

p=0.016

Eurocord group *Leukemia* 2009
Donor age in unrelated cord blood transplants (n=363, Eurocord data)

Survival of UCBT recipients according to median number of years between collection and transplantation.
Neutrophil recovery after UCBT according to ABO compatibility (n=409)

Compatible or minor (n=274) 76%

Major (n=135) 69%

P = 0.035
Criteria of donor choice
Recommendations 2009

1. First look at the number of cells in MAC, RIC, single and double CBT:
   >2.5x10^7 NC/kg et/ou >1.5x10^5 CD34+/kg
   Infused >2.0x10^7 NC/kg

2. Second look at HLA matches
   - 0-1 mm better than 2 avoid 3-4 mm
   - Prefer class I mismatches than class II (does not matter in advanced phase of disease?)
   - If no choice increase the number of cells

3. Other
   - It seems that in double CBT number of HLA disparities and ABO compatibility is also important
   - If acute leukemia in remission KIR ligand mismatch
   - Search for antibodies against HLA

4. 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.
Single CBT - children

- TNC dose infused (median) $10^7$/kg
- TNC dose collect. (median) $10^7$/kg
- >2 HLA disparity (%)
- Adv. dis. Status (%)

<table>
<thead>
<tr>
<th>Period</th>
<th>TNC dose infused (median) $10^7$/kg</th>
<th>TNC dose collect. (median) $10^7$/kg</th>
<th>&gt;2 HLA disparity (%)</th>
<th>Adv. dis. Status (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;2000</td>
<td>4.2</td>
<td>4.9</td>
<td>5.6</td>
<td>5%</td>
</tr>
<tr>
<td>2000-2004</td>
<td>6.8</td>
<td>5%</td>
<td>6.8</td>
<td>5%</td>
</tr>
<tr>
<td>2005-2008</td>
<td>7.8</td>
<td>1.5%</td>
<td>7.8</td>
<td>1.5%</td>
</tr>
</tbody>
</table>
Overall survival (children with malignant disease)

- 1994-1998  n= 276  2y OS 42±3%
- 1999-2000  n= 234  2y OS 43±3%
- 2001-2003  n= 347  2y OS 43±3%
- 2004-2008  n= 459  2y OS 47±3%

Progress in cord blood transplantation
Algorithm for Alternative Allogeneic Donor in children with Hematological malignancies without HLA identical Siblings

HLA high resolution typing

MMRD or Haplo (Center experience)

Simultaneous Search

Cord Blood Banks

Unrelated donors

<table>
<thead>
<tr>
<th>HLA: 0-1/6</th>
<th>HLA: 2/6</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt;2.5x10^7/kg CN</td>
<td>&gt; 3.5x10^7/kg CN</td>
</tr>
<tr>
<td>&gt;1.5x10^5/kg CD34+</td>
<td>&gt;2x10^5/kg CD34+</td>
</tr>
</tbody>
</table>

<8/10 or urgent

HLA 9 ou 10/10

Cord blood

BM

Eurocord - International Registry on Cord Blood Transplantation
Algorithm for Alternative Allogeneic Donor in children with non malignancies without HLA identical Siblings

HLA high resolution typing

Simultaneous Search

Cord Blood Banks

Unrelated donors

HLA: 0-1/6
>3x10^7/kg CN
>2x10^5/kg CD34+

HLA: 2/6
> 4 x10^7/kg CN
>2.5x10^5/kg CD34+

<8/10 or urgent

HLA 9 (?) ou 10/10

Cord blood

BM
Eurocord team 2008-2009