Educational 2
Cord Blood Transplantation

Myeloablative versus Reduced Intensity Conditioning Regimen Cord Blood Transplants

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University of Rome “Tor Vergata”
Rome Transplant Network

4th April 2011, Paris
The preparative regimen for HSC transplantation of patients with malignant diseases should:

- Have sufficient immunosuppressive effect in order to avoid graft rejection
- Have tolerable morbidity without mortality
- Be capable of eradicating malignancy

No ideal preparative regimen currently exists

Finn B. Petersen and Scott I. Bearman: Preparative regimens and their toxicity. In Bone Marrow transplantation by SJ Forman, KG Blume and E Donnall Thomas, 1994
Conditioning Regimens by Chemo-Radiotherapy Intensity

**GENETIC DISPARITY**
- CLL / fcL
- CML
- LCL/AML
- MM

**Immunosuppression**
- Haplo / UCBT
- MUD
- Matched sibling

**Cytoreduction**
- TBI 2Gy
- Flag-Lda
- GMel100
- Bu8+F+ATG
- Mel200
- BEAM
- TBI+Cy
- TBI+F+TT
- Bu16+Cy

**AGGRESSIVENESS OF MALIGNANCY**
- Non-Ablative
- Reduced Intensity
- Ablative
What we want to know about Conditioning Regimens in Cord Blood Transplantation?

Which is the best?

Myeloablative Conditioning versus Reduced Intensity Conditioning

versus

other HSC Sources
Matched / MM Unrelated BM or PBSC Donor Haploidentical Transplant

versus

other HSC Sources
Matched / MM Unrelated BM or PBSC Donor Haploidentical Transplant
What we want to know about Conditioning Regimens in Cord Blood Transplantation?

Myeloablative Conditioning versus Reduced Intensity Conditioning
Myeloablative versus Reduced Intensity Conditioning Cord Blood Transplantation for Adults with Acute Leukemia

Preliminary analysis
Selection criteria

- First single cord blood transplants performed from 2000 to 2008
- Adults ≥ 18 years with AML or ALL
- Myeloablative or Reduced Intensity conditioning regimen
<table>
<thead>
<tr>
<th>Patient Characteristics</th>
<th>RIC</th>
<th>MAC</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>197</td>
<td>403</td>
<td></td>
</tr>
<tr>
<td>Age (y) Median</td>
<td>46</td>
<td>34</td>
<td>.001</td>
</tr>
<tr>
<td>Range</td>
<td>18-72</td>
<td>18-60</td>
<td></td>
</tr>
<tr>
<td>Weight (Kg) Median</td>
<td>60</td>
<td>63</td>
<td>ns</td>
</tr>
<tr>
<td>Female Gender</td>
<td>62%</td>
<td>49%</td>
<td>.003</td>
</tr>
<tr>
<td>CMV +</td>
<td>62%</td>
<td>70%</td>
<td>.01</td>
</tr>
</tbody>
</table>
## Transplant Characteristics

<table>
<thead>
<tr>
<th></th>
<th>RIC</th>
<th>MAC</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>N</strong></td>
<td>197</td>
<td>403</td>
<td></td>
</tr>
<tr>
<td><strong>Conditioning:</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fludarabine based</td>
<td>91%</td>
<td>41%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Serotherapy</td>
<td>29%</td>
<td>75%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td><strong>GVHD Prophylaxis:</strong></td>
<td></td>
<td></td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>MMF containing</td>
<td>72%</td>
<td>25%</td>
<td></td>
</tr>
<tr>
<td><strong>Median follow-up (mo)</strong></td>
<td>16 (1-64)</td>
<td>14 (1-112)</td>
<td></td>
</tr>
</tbody>
</table>
## Donor Characteristics

<table>
<thead>
<tr>
<th></th>
<th>RIC</th>
<th>MAC</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>197</td>
<td>403</td>
<td>ns</td>
</tr>
<tr>
<td>ABO major</td>
<td>32%</td>
<td>34%</td>
<td>ns</td>
</tr>
<tr>
<td>HLA match</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(HLA-A,-B by serology and DRB1 low resolution)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HLA Matched</td>
<td></td>
<td></td>
<td>ns</td>
</tr>
<tr>
<td>6/6 or 5/6</td>
<td>31%</td>
<td>34%</td>
<td></td>
</tr>
<tr>
<td>4/6 or 3/6</td>
<td>69%</td>
<td>76%</td>
<td></td>
</tr>
<tr>
<td>Nucleated cells infusedx10^7/kg</td>
<td>2.8</td>
<td>2.6</td>
<td>ns</td>
</tr>
</tbody>
</table>
MAC versus RIC after single CBT for Adults with AL

Non Relapse Mortality

MAC 47%
RIC 34%

months
MAC versus RIC after single CBT for Adults with AL

Relapse Incidence

RIC 49%
MAC 40%
MAC versus RIC after single CBT for Adults with AL

Disease Free Survival

In Remission

RIC 38%
MAC 37%

Not Remission

MAC 12%
RIC 10%
MAC versus RIC after single CBT for Adults with AL

Multivariate analysis

**Relapse**
- RIC: HR 2.02; p<0.001

**Transplant Related Mortality**
- RIC: HR 0.54; p=0.001

**Disease Free Survival**
- RIC: HR=1.04; p=0.74

RIC compared to MAC is associated to decreased TRM but higher RI in adults with AL.
What we want to know about Conditioning Regimens in Cord Blood Transplantation?

Which is the best?

Myeloablative Conditioning

Reduced Intensity Conditioning

Which is the best?
Analysis of risk factors for engraftment after single unit CBT

1946 Patients with Malignant Disorders after Myeloablative Regimen

Median age: 11 years (1-60)
Median Weight: 38 kg (5-100)

Diagnosis: 76% Acute Leukemia

Status of the disease: early 28%, intermediate: 39%, advanced: 33%

Median number of TNC infused: $3.4 \times 10^7$/kg (0.1 – 15)
Median number of CD34 infused: $1.5 \times 10^5$/kg (0.8-2.7)

HLA 6/6: 14%
5/6: 49%
4/6: 36%
3/6: 1%

Median follow-up: 22 months (2-169)
Multivariate analysis for neutrophil recovery

No Flu based (n=1471) 86%
Fludarabine based MAC (n=384) 91%
No  (n=267) 80%
Early GCSF (n=786) 90%
Early and Intermediate 88 %
Advanced 84 %
CD34 infused >1.5 x10^5/kg (n=607) 90%
CD34 infused < 1.5 x10^5/kg (n=557) 86%
HLA 6/6 (n=150) 90 %
HLA 5/6 (n=686) 88 %
HLA 4/6 (n=730) 86 %
HLA 3/6 (n=87) 74%
CD34 infused < 1.5 x10^5/kg (n=557) 86%

p<0.0001
p<0.0001
p<0.0001
p<0.0001
p= 0.015
p= 0.015
p<0.001
p<0.001
p<0.001
p<0.001

Overall Survival after single UCBT for patients with malignant disorders after MAC by use of Fludarabine

No Fludarabine Based (n=1471) 42%

Fludarabine based MAC (n=384) 39%

p=0.67
Impact of the use of Fludarabine or CY based Myeloablative Conditioning after CBT in adults with leukemias

H Bittencourt, S Nabhan et al. on behalf of Eurocord
### Impact of the use of Fludarabine or CY based MAC after CBT in adults with leukemias

<table>
<thead>
<tr>
<th>Number of Patients</th>
<th>231</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>33 (18-55)</td>
</tr>
<tr>
<td><strong>Disease</strong></td>
<td></td>
</tr>
<tr>
<td>Acute myeloid leukemia</td>
<td>87 (38%)</td>
</tr>
<tr>
<td>Acute lymphoblastic leukemia</td>
<td>85 (37%)</td>
</tr>
<tr>
<td>Myelodysplastic / Myeloproliferative syndrome</td>
<td>59 (25%)</td>
</tr>
<tr>
<td><strong>Disease status at transplantation</strong></td>
<td></td>
</tr>
<tr>
<td>Early and intermediate phase of the disease</td>
<td>149 (64%)</td>
</tr>
<tr>
<td>Advanced</td>
<td>82 (36%)</td>
</tr>
<tr>
<td><strong>Previous Autologous HSCT</strong></td>
<td></td>
</tr>
<tr>
<td>31 (13%)</td>
<td></td>
</tr>
<tr>
<td><strong>Donor-recipient HLA-disparities</strong></td>
<td></td>
</tr>
<tr>
<td>0-1 disparities</td>
<td>92 (40%)</td>
</tr>
<tr>
<td>2-3 disparities****</td>
<td>135 (60%)</td>
</tr>
<tr>
<td><strong>Nucleated Cell Dose at Infusion (x10^7/kg)</strong></td>
<td>2.5 (0.58-7.6)</td>
</tr>
</tbody>
</table>
Impact of the use of Fludarabine or CY based MAC after CBT in adults with leukemias

<table>
<thead>
<tr>
<th>Conditioning Groups:</th>
<th>Median Year of CBT</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>CY based MAC</strong></td>
<td>2004 (2000-2008)</td>
</tr>
<tr>
<td>CY + TBI (± Etoposide/Thiotepa)</td>
<td>160 (69%)</td>
</tr>
<tr>
<td>CY + BU (+ Thiotepa)</td>
<td>84</td>
</tr>
<tr>
<td><strong>Fludarabine based MAC</strong></td>
<td>71 (31%)</td>
</tr>
<tr>
<td>Fludarabine + BU (iv) + Thiotepa</td>
<td>76</td>
</tr>
<tr>
<td><strong>ATG/ALG</strong></td>
<td>209 (91%)</td>
</tr>
<tr>
<td><strong>Graft-versus-host disease prophylaxis</strong></td>
<td>180 (80%)</td>
</tr>
<tr>
<td>Cyclosporine + steroids</td>
<td></td>
</tr>
</tbody>
</table>
Impact of the use of Fludarabine or CY based MAC after CBT in adults with leukemias

Neutrophil Recovery (CI) after MAC CBT by type of Conditioning Regimen

early disease stage

FLU-MAC 96%

CY-MAC 82%
p=0.0006

advanced disease stage

FLU-MAC 88%

CY-MAC 69%
p=0.11
Impact of the use of Fludarabine or CY based MAC after CBT in adults with leukemias

Overall Survival

Early and intermediate disease

Flu-MAC 52%
CY-MAC 38%
p=0.04

Advanced disease

CY-MAC 28%
Flu-MAC 6%
p=0.70

Multivariate analysis for OS : Fludarabine (HR: 0.52; CI95%:0.27-0.97 – p=0.04)
GETH-RTN Protocol 2008
(TBF-MAC protocol)

EudraCT Code 2008-000927-24

GVH prophylaxis
ATG + CSA + MMF or Prednisone

Thiotepa 5 mg/kg/d iv in 4 hs

Busilvex 3.2 mg/kg iv in 3 hs

Fludarabine 50 mg/m²/d iv in 1 h

Thymoglobulin 2 mg/kg/d

Days
-7  -6  -5  -4  -3  -2  -1  0

CBT

TT TT BU BU BU

BU BU BU FLU FLU FLU

ATG ATG ATG

0
What we want to know about Conditioning Regimens in Cord Blood Transplantation?

- Myeloablative Conditioning CBT in AML
- versus
- Myeloablative Conditioning Haploidentical BM Transplant in AML
## UCBT for AML

### Transplant characteristics

<table>
<thead>
<tr>
<th>Conditioning regimen</th>
<th>n=573</th>
</tr>
</thead>
<tbody>
<tr>
<td>- Reduced Intensity</td>
<td></td>
</tr>
<tr>
<td>- Cy+Flu+TBI, n</td>
<td>282 (49%)</td>
</tr>
<tr>
<td>- Myeloablative</td>
<td>291 (51%)</td>
</tr>
<tr>
<td>- TT+Bu+Flu, n</td>
<td>98</td>
</tr>
<tr>
<td>- Cy+TBI, n</td>
<td>54</td>
</tr>
<tr>
<td>- Cy+Bu, n</td>
<td>34</td>
</tr>
<tr>
<td>- Cy+Flu+TBI, n</td>
<td>31</td>
</tr>
</tbody>
</table>

| Use of Anti-thymocyte globulin | 49% |

<table>
<thead>
<tr>
<th>GVHD prophylaxis</th>
<th>n=551</th>
</tr>
</thead>
<tbody>
<tr>
<td>- CsA + MMF ± steroids</td>
<td>58%</td>
</tr>
<tr>
<td>- CsA ± steroids</td>
<td>28%</td>
</tr>
<tr>
<td>- Other</td>
<td>14%</td>
</tr>
</tbody>
</table>
CBT in 98 AML
EUROCORD

2-year Overall Survival

CR1 + CR2 (n=77)
63±8%

Advanced (n=21)
8±7%

TBF-MAC

Haplo BMT in 45 AML
Rome Transplant Network
Pescara Transplant Unit

2-year Overall Survival

64±8% at 1 yr
59%±9

CR1 + CR2 n=34

ADVANCED n=11

18±12%
p= 0.019
**2-year Disease Free Survival**

**CBT in 98 AML**
EUROCORD

**TBF-MAC**

CR1+CR2 (n=77)

- 45±7%
- p=<0.001

**Advanced (n=21)**

- 8±7%
- p=0.007

**TBF-MAC**

**Haplo BMT in 45 AML**

Rome Transplant Network
Pescara Transplant Unit
What we want to know about Conditioning Regimens in Cord Blood Transplantation?

Myeloablative Conditioning CBT

versus

other HSC Sources
Matched / MM Unrelated BM or PBSC Donor Haploidentical Transplant
Impact of Stem Cell Source on Myeloablative Transplant Outcomes in Adults with Acute Leukemia

Mary Eapen MD MS
Center for International Blood and Marrow Transplant Research
Medical College of Wisconsin
Patient and Transplant Characteristics

- Patients $n=1525$
- Acute leukemia – N=880 AML; N=645 ALL
- Age > 16 years

- Donors of BM and PBPC were matched or 1-locus mismatched at HLA A, B, C and DRB1

- UCB units were matched or 1- or 2-loci mismatched at HLA A, B or DRB1 with a minimum cell dose of $2.5 \times 10^7$/kg

- Transplant years: 2002 – 2006
- Median follow up of surviving patients: 2 years

Eapen et al; Lancet Oncol 2010
## Donor-recipient HLA match

<table>
<thead>
<tr>
<th>Graft source</th>
<th>Matched</th>
<th>Mismatched</th>
</tr>
</thead>
<tbody>
<tr>
<td>BM (N=472)</td>
<td>70%</td>
<td>30%</td>
</tr>
<tr>
<td>PBPC (N=888)</td>
<td>71%</td>
<td>29%</td>
</tr>
<tr>
<td>CB (N=165)</td>
<td>6%</td>
<td>19% (1-locus) 75% (2-loci)</td>
</tr>
</tbody>
</table>

Eapen et al; Lancet Oncol 2010
Neutrophil Recovery

- 8/8 PBPC, 96%
- 8/8 BM, 92%
- 7/8 BM, 94%
- 4-6/6 UCB, 80%
- 7/8 PBPC, 96%

Eapen et al; Lancet Oncol 2010
Acute GVHD

Eapen et al; Lancet Oncol 2010

Days

Probability, %

0 10 20 30 40 50 60 70 80 90 100

0 20 40 60 80 100

4-6/6 UCB vs. 8/8 BM      RR 0.78, p=0.13
4-6/6 UCB vs. 8/8 PBPC  RR 0.57, p=0.002

4-6/6 UCB, 31%
8/8 PBPC, 47%
7/8 BM, 47%
8/8 BM, 38%
7/8 PBPC, 52%

7/8 BM, 47%
4-6/6 UCB, 31%
8/8 PBPC, 47%

Chronic GVHD

Months

Probability, %

0 4 8 12 16 20 24

0 10 20 30 40 50 60 70 80 90 100

4-6/6 UCB vs. 8/8 BM      RR 0.63, p=0.01
4-6/6 UCB vs. 8/8 PBPC  RR 0.38, p=0.001

4-6/6 UCB, 25%
8/8 PBPC, 47%
7/8 BM, 42%
8/8 BM, 42%
7/8 PBPC, 55%
7/8 BM, 40%
4-6/6 UCB, 25%
Transplant-related Mortality

- 4-6/6 UCB vs. 8/8 BM: RR 1.69, p=0.003
- 4-6/6 UCB vs. 8/8 PBPC: RR 1.62, p=0.003

Eapen et al; Lancet Oncol 2010
Leukemia-free Survival

Eapen et al; Lancet Oncol 2010

Probability, %

100
90
80
70
60
50
40
30
20
10
0

0 6 12 18 24

Months

Probability, %

100
90
80
70
60
50
40
30
20
10
0

0 6 12 18 24

Months

8/8 PBPC, 50%

7/8 BM, 52%

8/8 BM, 41%

PBPC 39%

4-6/6 UCB, 44%

7/8 BM, 14%

4-6/6 UCB, 15%

8/8 BM, 17%

PBPC, 17%

7/8 PBPC, 17%

7/8 BM, 41%

in Remission

NOT in Remission

Eapen et al; Lancet Oncol 2010
Summary

- Relative to 8/8 matched BM/PBPC from unrelated adult donor:

**Mismatched CB**
- Slower rate of hematopoietic recovery
- Lower rates of acute and chronic GVHD
- Higher rates of TRM
- No significant differences in LFS rates

Eapen et al; Lancet Oncol 2010
What we want to know about Conditioning Regimens in Cord Blood Transplantation?

Which is the best?

Myeloablative Conditioning

Reduced Intensity Conditioning

Which is the best?
**Reduced Intensity Conditioning**

**Eligibility:**
- < 70 yrs
- Heme malignancy
- High risk for TRM
  - age ≥ 45
  - extensive prior Rx
  - poor fitness

**Treatment Plan:**
- **Cytoxan**: 50 mg/kg
- **Fludarabine**: 200 mg/m²
- **sTBI**: 200 cGy
- **CSA**: 3 to + 100
- **Mycophenolate**: 3 to + 30
- **G-CSF**: until ANC > 2500/uL
- **Day +28**: BMBx

**UCBT Options:**
- Single UCB
- Double UCB

*University of Minnesota*
Reduced Intensity Conditioning
CB Transplant (n=110)

Median age: 51 years (17-69)

Reason for NMA

Age >45 yrs 46%
Co-morbidity 40%
Prior Auto 14%

Median follow up: 19 months (5-51)

Reduced Intensity Conditioning
CB Transplant (n=110)

Transplant Related Mortality

Reduced Intensity Conditioning CB Transplant (n=110)

Relapse

p=.07

single Unit CB 41%

double Unit CB 30%

Reduced Intensity Conditioning
CB Transplant (n=110)

Event Free Survival

Single CBT 24%
Double CBT 39%

p=.05

Reduced Intensity Conditionings in CBT

- Which are the outcomes using other conditioning regimens?
- Can we reproduce the results of the Minneapolis group?
- Which are the risk factors for outcomes?
Reduced Intensity Conditioning Regimen after single unrelated CBT for adults with hematological malignancies

An Eurocord-Netcord, SFGM-TC and Minnesota group analysis
Reduced Intensity Conditionings in CBT (n=176)

Patients and disease characteristics

Transplants performed from 1999-2006 with single units

Follow-up: 12 months (3-80)
Median age: 45 years (16-76)
Median weight: 61 kg (40-116)
CMV+: 61%

Previous autologous transplants: n=53 (30%)

allogeneic transplants: n=8 (5%)

Diagnosis

AML 45%
ALL 12%
MDS 8%
sec AML 10%
Chr L 7%
Lymph 17%
Myeloma 1%
### Reduced Intensity Conditionings in CBT

**TBI low dose (2 - 6 GY) no (n=45) yes (n=131)**

<table>
<thead>
<tr>
<th>Combination</th>
<th>No</th>
<th>Yes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cy</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Cy+Ara-C</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Cy+Melph+Thio</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Cy+Bu</td>
<td>3</td>
<td>0</td>
</tr>
<tr>
<td>Bu+Melph</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>Cy+Bu+Thio</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Fludarabine</td>
<td>3</td>
<td>3</td>
</tr>
<tr>
<td><strong>Cy+Fluda</strong></td>
<td>7</td>
<td>101</td>
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<tr>
<td>Fluda+Melph</td>
<td>5</td>
<td>5</td>
</tr>
<tr>
<td>Cy+Fluda+Melph</td>
<td>3</td>
<td>0</td>
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<tr>
<td>Fluda+Ara-C</td>
<td>0</td>
<td>4</td>
</tr>
<tr>
<td>Fluda+Thio</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Cy+Fluda+Thio</td>
<td>3</td>
<td>0</td>
</tr>
<tr>
<td>Bu+Fluda</td>
<td>3</td>
<td>18</td>
</tr>
<tr>
<td>Bu+Fluda+Melph</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>VP16+Melph+other</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Fluda+other</td>
<td>8</td>
<td>0</td>
</tr>
</tbody>
</table>

**Twenty-one different combinations!**
Reduced Intensity Conditionings in CBT (n=176)

Disease Free Survival according to Conditionings

- 51% CY+FLU+TBI 2GY
- 28% other conditionings

p = 0.0002
Multivariate analysis for DFS

- **Type of conditioning (CY+FLU+TBI 2 GY):**
  \[ HR = 0.53 \quad p < 0.001 \]

- **Early and intermediate phase of the disease:**
  \[ HR = 0.63 \quad p = 0.02 \]

Other variables included in the model (p<0.10)
status of the disease, diagnosis, age
What we want to know about Conditioning Regimens in Cord Blood Transplantation?

Reduced Intensity Conditioning
CBT

versus

other HSC Sources
Matched / MM Unrelated BM or PBSC Donor
Haploidentical Transplant
Impact of Stem Cell Source on RIC Transplant Outcomes in Adults with Acute Leukemia

Mary Eapen MD MS
Center for International Blood and Marrow Transplant Research
Medical College of Wisconsin
Patients & Donors

- Were included in this study patients:
  - Aged 21-69 yrs
  - With Acute Leukemia
  - Transplanted between 2000-2009
  - Unrelated donor recipients were included if they received a 7-8/8 allele level HLA-matched PB grafts
  - CB recipients were included if they received a 4-6/6 HLA-matched double CB grafts (class I at antigen level and class II allele level)
Methods

- We explored whether there were survival differences by conditioning regimen within each graft source:
  - ↑ survival after double CB with TBI200/Cy/Flu ± ATG vs. double CB with other regimens
  - No differences in the PB group
- Therefore 4 treatment groups were created:
  - MUD (8/8 allele matched unrelated donor)
  - MMUD (7/8 allele matched unrelated donor)
  - Double CB, TCF
  - Double CB, other regimens

<table>
<thead>
<tr>
<th>Variables</th>
<th>MUD</th>
<th>MMUD</th>
<th>dCB, TCF</th>
<th>dCB, other</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of patients</td>
<td>313</td>
<td>111</td>
<td>121</td>
<td>40</td>
<td>585</td>
</tr>
</tbody>
</table>
Neutrophil Recovery

- MUD: 96%
- MMUD: 95%
- dCB, TCF: 83%
- dCB, other: 83%
- p = 0.0007

Platelet Recovery

- MUD: 90%
- MMUD: 89%
- dCB, TCF: 66%
- dCB, other: 58%
- p < 0.0001
Grade 2 - 4 Acute GVHD

Cumulative Incidence, %

- MMUD: 38%
- MUD: 32%
- dCB, other regimen: 33%

p = 0.007

Grade 3 - 4 Acute GVHD

Cumulative Incidence, %

- CB, TCF: 50%
- MMUD: 22%
- MUD: 13%
- dCB, other: 18%

p = ns
Chronic Graft vs. Host Disease

Cumulative Incidence, %

Months

Cumulative Incidence, %

0 6 12 36 24 18

100

0 20 40 60 80 90 100

P<0.0001

MUD: 56%

MMUD: 54%

dCB, other: 36%

dCB, TCF: 34%

CIBMTR 

P910_50.ppt
Relapse

Cumulative Incidence, %

Months

0 6 12 36 24 18

0 20 40 60 80 90 100

MUD: 46%

MMUD: 45%
dCB, TCF: 52%
dCB, other: 39%

P=NS

P10_46.ppt
Leukemia-Free Survival

- MUD vs. dCB other: 0.68 (0.47 – 0.99) 0.046
- dCB, TCF: 26%
- MUD: 31%
- MMUD: 25%
- dCB, other: 9%
Summary

- Relative to 8/8 matched PBPC from adult unrelated donors
  - **Mismatched CB: co-infusion of 2 units**

- Lower Hematopoietic recovery

- Lower rates of TRM with TBI 200/Cy/FLU

- Higher rate of grade 2 acute GVHD but lower chronic GVHD

- No significant differences in rates of TRM, LFS and OS with TCF regimen

- Other regimens: higher rates of TRM and lower rates of LFS and OS
What we want to know about Conditioning Regimens in Cord Blood Transplantation?

Reduced Intensity Conditioning
Double CBT

versus

Reduced Intensity Conditioning
Haploidentical BM Transplant
Blood and Marrow Clinical Trials Network

- 2 parallel phase II trials of RIC SCT using:
  - HLA-haploidentical bone marrow (BMT CTN 0603)
  - Double unrelated cord blood (BMT CTN 0604)

- 27 Transplant Centers participated
  - 11 centers enrolled on 0603
  - 10 centers enrolled on 0604
  - 6 centers enrolled on both trials

by courtesy of Mary Eapen, CIBMTR
## Demographic and Disease Characteristics

<table>
<thead>
<tr>
<th></th>
<th>Cord (0604)</th>
<th></th>
<th>Haplo (0603)</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N=50</td>
<td></td>
<td>N=50</td>
<td></td>
</tr>
<tr>
<td><strong>Median age (range)</strong></td>
<td>58 (16-69)</td>
<td></td>
<td>45 (7-70)</td>
<td></td>
</tr>
<tr>
<td><strong>Performance status &gt; 90%</strong></td>
<td>40 (80%)</td>
<td></td>
<td>38 (76%)</td>
<td></td>
</tr>
<tr>
<td><strong>Disease</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>AML (CR1/CR&gt;1)</td>
<td>29 (18/11)</td>
<td></td>
<td>22 (10/12)</td>
<td></td>
</tr>
<tr>
<td>ALL (CR1/CR&gt;1)</td>
<td>6 (4/2)</td>
<td></td>
<td>6 (3/3)</td>
<td></td>
</tr>
<tr>
<td>Biphenotypic/undiff leukemia</td>
<td>1</td>
<td></td>
<td>3</td>
<td></td>
</tr>
<tr>
<td>Burkitt lymphoma</td>
<td>1</td>
<td></td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Hodgkin lymphoma (CR/PR)</td>
<td>5 (2/3)</td>
<td></td>
<td>7 (3/4)</td>
<td></td>
</tr>
<tr>
<td>Large cell lymphoma (CR/PR)</td>
<td>3 (2/1)</td>
<td></td>
<td>8 (3/5)</td>
<td></td>
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<tr>
<td>Mantle cell lymphoma (CR/PR)</td>
<td>0</td>
<td></td>
<td>3 (1/2)</td>
<td></td>
</tr>
<tr>
<td>Marginal zone or follicular NHL</td>
<td>5</td>
<td></td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Prior autologous Transplant</td>
<td>6 (12%)</td>
<td></td>
<td>11 (22%)</td>
<td></td>
</tr>
</tbody>
</table>

by courtesy of Mary Eapen, CIBMTR
Treatment Schemas

Cord Blood

- Cy 50 mg/kg
- BMT
- Day -6
- Fludarabine 40 mg/m²/day
- Double UCB Infusion
- TBI 200 cGy
- G-CSF
- MMF tid
- Cyclosporine

Haploidentical

- Cy 14.5 mg/kg/day
- BMT
- Day -6
- Fludarabine 30 mg/m²/day
- Cy 50 mg/kg/day
- Bone Marrow Infusion
- TBI 200 cGy
- G-CSF
- MMF tid
- Tacrolimus

by courtesy of Mary Eapen, CIBMTR
Relapse and Non-Relapse Mortality

Cord (0604)  Haplo (0603)

by courtesy of Mary Eapen, CIBMTR
Overall and Disease-free Survival

Cord (0604) vs Haplo (0603)

Survival (%)

Overall survival
Event-free survival

Months after transplantation

95% CI, 44%

95% CI, 38-67%

by courtesy of Mary Eapen, CIBMTR
Comparison of Outcomes After Unrelated Cord Blood Transplantation and Matched Unrelated Donor RIC Transplantation for Lymphoid Malignancies

Celso Arrais Rodrigues et al.

A Eurocord-Netcord Group/ Lymphoma Working Party and Chronic Leukaemia Working Party of the EBMT Study
Analysis of Risk Factors for Outcomes After Unrelated UCBT in Adults With Lymphoid Malignancies

n=104

PROGRESSION-FREE SURVIVAL

Low-dose TBI (n=48)
59%±7 at 18 months

Other regimens (n=56)
21%±6 at 18 months

p<0.0001

INCLUSION CRITERIA

- Hodgkin or non-Hodgkin Lymphoma excluding Burkitt and lymphoblastic
- Chronic lymphocytic leukemia
- Age ≥18
- Unrelated UCBT or MUD HSCT using mobilized PBSC
- RIC regimens
- Transplantation performed between 2000-2006

MUD: 284 vs. CBT: 75
Total: 359
NON-RELAPSE MORTALITY

**UCBT (n=75)**
- 28% at 3 years

**PBSC (n=284)**
- 31% at 3 years

\[ p = \text{ns} \]

**MULTIVARIATE ANALYSIS**

<table>
<thead>
<tr>
<th></th>
<th>HR</th>
<th>CI 95%</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Use of CB</td>
<td>1.23</td>
<td>0.65-2.33</td>
<td>0.53</td>
</tr>
<tr>
<td>Age&gt;50 years</td>
<td>1.93</td>
<td>1.27-2.94</td>
<td>0.002</td>
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<tr>
<td>Chemoresistant disease</td>
<td>1.83</td>
<td>1.20-2.77</td>
<td>0.005</td>
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</tbody>
</table>
RIC-UCBT vs. RIC-MUD Transplantation for Lymphoid Malignancies

RELAPSE

UCBT (n=75)
37.8% at 3 years

PBSC (n=284)
35.4% at 3 years

p = ns

MULTIVARIATE ANALYSIS

<table>
<thead>
<tr>
<th></th>
<th>HR</th>
<th>CI 95%</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Use of CB</td>
<td>1.19</td>
<td>0.68-2.10</td>
<td>0.54</td>
</tr>
<tr>
<td>Aggressive vs. indolent</td>
<td>2.27</td>
<td>1.29-3.99</td>
<td>0.005</td>
</tr>
<tr>
<td>HL vs. indolent</td>
<td>1.95</td>
<td>1.03-3.71</td>
<td>0.04</td>
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<tr>
<td>Refractory disease</td>
<td>2.25</td>
<td>1.53-3.31</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>
**RIC-UCBT vs. RIC-MUD Transplantation for Lymphoid Malignancies**

**PROGRESSION-FREE SURVIVAL**

- **UCBT (n=75)**: 38% ± 6 at 2y, \( p = ns \)
- **PBSC MUD (n=284)**: 41% ± 2 at 2y

**MULTIVARIATE ANALYSIS**

<table>
<thead>
<tr>
<th></th>
<th>HR</th>
<th>CI 95%</th>
<th>( p )</th>
</tr>
</thead>
<tbody>
<tr>
<td>Use of CB</td>
<td>1.33</td>
<td>0.88-1.99</td>
<td>0.18</td>
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<tr>
<td>Non-indolent vs. indolent</td>
<td>1.69</td>
<td>1.21-2.35</td>
<td>0.002</td>
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<tr>
<td>Refractory disease</td>
<td>2.02</td>
<td>1.53-2.67</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>
SUMMARY

MULTIVARIATE ANALYSES

After adjustment for the differences in the 2 groups

CBT vs. MUD-PBSCT

No differences in:

• Non-relapse related mortality
• Relapse or progression
• Progression-free survival
• Overall survival
CONCLUSION

Umbilical Cord Blood:

Valuable alternative for patients with advanced Lymphoma or CLL who lack an HLA-matched donor in the RIC setting
CONCLUSIONS

From all retrospective analyses, results of MAC and RIC Cord Blood Transplants are respectively well comparable with those obtained using different hematopoietic stem cell sources (BM-MUD; PBSC-MUD; Haploidential Donor).

Prospective, randomized studies are warranted

Myeloablative Conditioning Regimens should be compared with TBF-mac regimen (TT-i.v.BU-Flu)

Reduced Intensity Conditioning Regimens should be compared with TCF-ric regimen (TBI200/Cy/Flu)
Acknowledgements