Rapid and Robust CD4+ and CD8+ T-, NK-, B- and Monocyte Cell Reconstitution after Nicotinamide-Expanded Cord Blood Transplantation

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Disclosures

• DMC member / chair (consulting):
  – Magenta, Chimerix, Bluebird Bio

• Consulting:
  – Avrobio, Takeda

• Grants: Sanofi (unrestricted)
Today messages

• CD4+ reconstitution after Nicotinamide-expanded CBT is at least as fast as unmanipulated CBT and BMT in adolescents and young adults.

• Immune reconstitution after NiCord transplantation was associated with recovery of a broad spectrum of T-, B- and NK-cell subsets.
Cord blood as Hematopoietic (Stem) Cell Source (HCS)

**Advantages**

- Readily available HSC
- Some mismatch is allowed (donor available for many patients)
- Less chronic GvHD vs. Matched Unrelated donor
  - *Eapen M et al Lancet 2010*
  - *Langenhorst, Blood Advances 2019*
- Potent anti-tumor activity
  - *Milano F et al NEJM 2016*

![Graph showing probability of relapse](image)

- P=0.07 for comparison of HLA-matched vs cord blood
- P=0.02 for comparison of HLA-mismatched vs cord blood

<table>
<thead>
<tr>
<th></th>
<th>Number at risk</th>
<th>Years after Transplantation</th>
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<tbody>
<tr>
<td>Cord blood</td>
<td>45</td>
<td>23  11  2  1</td>
</tr>
<tr>
<td>HLA-matched</td>
<td>104</td>
<td>31  23 11 4</td>
</tr>
<tr>
<td>HLA-mismatched</td>
<td>35</td>
<td>7   6   3  1</td>
</tr>
</tbody>
</table>

*Milano F et al. NEJM 2016*
Cord blood as HCS

Disadvantages

Low cell dose leads to delayed hematopoietic recovery

Increased resource utilization

Low Cell Dose

- Slow Engraftment & Graft Failure
- Higher Resource Utilization
- Higher Morbidity and Non-relapse Mortality
- Higher Rate of Infections
- Delayed Immune Recovery

Higher Morbidity and Non-relapse Mortality
Solution: Nicotinamide expansion of uCB-unit

• *Ex-vivo* expansion from entire uCB unit
  ▫ CD133+ cultured fraction
  ▫ CD133- non-cultured
    ▪ T-cell containing fraction is cryopreserved until transplantation

• Culture system:
  • Culture media + **Nicotinamide** + cytokines:
    • TPO, IL-6, FLT-3 ligand and SCF

• Culture length: 21 +/- 2 days
Phase I/II Study of Stem-Cell Transplantation Using a Single Cord Blood Unit Expanded Ex Vivo With Nicotinamide

N=36, med.age 44 (13-63)yrs

Phase I/II median CD34+ cells infused: 6.4 x 10^6/kg
Phase I/II median CD3+ cells infused: 2.3 x 10^6/kg
Challenges in HCT for upcoming years

Unmet needs

1. Reducing the Toxicity of HCT:
   1. Short term toxicity: viral reactivation, TRM, GvHD
   2. Long term toxicity

2. Better disease control

Balanced & Predictable T-cell (CD4+) Reconstitution essential
(e.g. Lancet H 2015, 2017, Blood 2016, JACI 2017)
IR definition:
>50/uL, twice within 100 days

**OS according to Adeno and AML-relapse and CD4+ reconstitution**

IR reactivation:
- No AdV vs AdV with IR: p=0.57
- No AdV vs AdV without IR: p<0.0001
- AdV with IR vs AdV without IR: p=0.0030

P=0.033
Immune Reconstitution “add on” Study at Central Laboratory

Primary endpoint:
Comparison of probability of CD4 immune reconstitution

Secondary endpoint:
Reconstitution over time of CD4+, CD8+, monocytes, natural killer (NK)- and B-cells, including subsets, TRECks, recent thymic emigrents

Controls:
UMCU CBT (n=27); median age = 16 (12-28); 100% CloFluBu, malignancy
UMCU BMT (n=20); median age = 14 (12-20); 100% CloFluBu, malignancy
CD4 immune reconstitution According to Cell Source

According to Cell Source

Days after HCT

Ni-exp CB (n=27)
CB (n=27)
BM (n=20)

>90% IR

IR = >50x10^6/L within 100 days

P=0.99
Ni-exp CB: CD4 and CD8 T cell Reconstitution

**CD4**
- Group: NiCord, CB, BM
- Cells (x10^6/L)
- Time after HCT
- NS

**CD8**
- Group: NiCord, CB, BM
- Cells (x10^6/L)
- Time after HCT
- NS
B- and NK-cell Reconstitution according to Cell Source

B cells

NK cells

Cells (x10^6/L)

Group
NiCord
CB
BM

Time after HCT

p=0.026

p<0.001
Monocyte immune reconstitution according to Cell source

Monocyte reconstitution (x10^6/L) vs. Time after HCT

- Group
  - NiCord
  - CB
  - BM
**NK cell Reconstitution**

Week: 2 3 6 10 14 26

**Group**
- NiCord
- CB
- BM

NK−cell recovery (x10^6 CD56+CD16+CD3− cells/L blood)

<0.001

- **NiCord**
  - Week 2: 10% effector NK cells, 90% Naive NK cells
  - Week 3: 15% effector NK cells, 85% Naive NK cells
  - Week 6: 20% effector NK cells, 80% Naive NK cells
  - Week 10: 25% effector NK cells, 75% Naive NK cells
  - Week 14: 30% effector NK cells, 70% Naive NK cells
  - Week 26: 35% effector NK cells, 65% Naive NK cells

- **unCBT/BMT**
  - Week 2: 5% effector NK cells, 95% Naive NK cells
  - Week 3: 10% effector NK cells, 90% Naive NK cells
  - Week 6: 15% effector NK cells, 85% Naive NK cells
  - Week 10: 20% effector NK cells, 80% Naive NK cells
  - Week 14: 25% effector NK cells, 75% Naive NK cells
  - Week 26: 30% effector NK cells, 70% Naive NK cells
B cell Reconstitution

Week: 2 3 6 10 14 26

NiCord

unCBT/BMT

P=0.02

Week: 2 3 6 10 14 26

NiCord

unCBT/BMT

P=0.02

Week: 2 3 6 10 14 26

NiCord

unCBT/BMT

P=0.02
CD4+ cell Reconstitution

<table>
<thead>
<tr>
<th>Week:</th>
<th>2</th>
<th>3</th>
<th>6</th>
<th>10</th>
<th>14</th>
<th>26</th>
</tr>
</thead>
<tbody>
<tr>
<td>NiCord</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>unCBT/BMT</td>
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</tbody>
</table>

Week: 2 3 6 10 14 26

- Th1
- Th2
- Th17
- Th22
- Treg

NiCord day 365 - CD4+ T cells

Naive CD4+
EM CD4+
CM CD4+
EMRA...
Phase III Study of Nicotinamide-Expanded Cord Blood for Allogeneic Transplantation in Patients with Hematologic Malignancies

Patients with High-Risk Hematologic Malignancies
AML, MDS, ALL, CML, lymphoma
Age 12-65
Eligible for Allogeneic Bone Marrow Transplantation
No Suitable Donor

RANDOMIZE
N=120

NiCord
Primary Endpoint
Time to neutrophil engraftment
Immune Reconstitution
-DFS
-Viral
-GvHD

Standard Cord Blood
Today messages

• CD4+ reconstitution after Nicotinamide-expanded CBT is at least as fast as unmanipulated CBT and BMT in adolescents and young adults

• Immune reconstitution after Nicotinamide-expanded CBT was associated with recovery of a broad spectrum of T-, B- and NK-cell subsets

• Optimal comparison of IR in a randomized controlled Phase III trial is underway
Lab Boelens/Nierkens

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Colin de Haar
Lotte Spel
Rick Admiraal
Celina Szanto
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Brigitte van den Broek

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Moniek de Witte
Eefke Petersen

Duke Cancer Institute
Mitchel Horwitz

Pediatric BMT program Utrecht
Marc Bierings
Birgitta Versluys
Caroline Lindemans
Corinne Gerhardt
Arienne de Wildt

Pharmacy UMC Utrecht
Erik van Maarseveen
Alwin Huijtema

Participating transplant centers
M Horwitz- Duke University
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Pau Montesinos- Valencia
P. Stiff- Chicago
D. Valcarcel- Barcelona
M. Jagasia- Nashville
D. Cilloni- Turin
J. Boelens, J. Kuball- Utrecht
R. Hanna- Cleveland
L. Piu, W. Hwang- Singapore
J. Wagner, C. Brunstein- Minnesota
# Characteristics UMCU CBT and BMT patients

<table>
<thead>
<tr>
<th></th>
<th>CB (n=27)</th>
<th>BM (n=20)</th>
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<tbody>
<tr>
<td><strong>Age</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>13-18</td>
<td>27</td>
<td></td>
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<tr>
<td>19-39</td>
<td>0</td>
<td></td>
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<tr>
<td>40+</td>
<td>0</td>
<td></td>
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<tr>
<td>Median (range)</td>
<td>15 (12-18)</td>
<td>14 (12-20)</td>
</tr>
<tr>
<td><strong>HLA Match score</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>4/6</td>
<td>8</td>
<td>0</td>
</tr>
<tr>
<td>5/6</td>
<td>9</td>
<td>0</td>
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<tr>
<td>6/6</td>
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<td>8/8</td>
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<td>8/10</td>
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<tr>
<td>9/10</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>10/10</td>
<td>1</td>
<td>19</td>
</tr>
<tr>
<td><strong>Conditioning regimen</strong></td>
<td>(Clo)BuFlu</td>
<td></td>
</tr>
<tr>
<td></td>
<td>27</td>
<td>20</td>
</tr>
<tr>
<td><strong>Weight (kg)</strong></td>
<td>Median (range)</td>
<td>21-74</td>
</tr>
</tbody>
</table>
2 Phases of T cell Immune Reconstitution
“homeostatic peripheral expansion” and “thymic recovery”

Depends primarily on nr of T cells infused and “in vivo” depleting agents
## What Immune Marker is Best Predictor for Outcome?

**Cohort of 273 HCTs: pediatric/young adult**

<table>
<thead>
<tr>
<th></th>
<th>CD3 &gt; 100</th>
<th>CD4 &gt; 50</th>
<th>CD8 &gt; 50</th>
<th>B-cell</th>
<th>NK-cell</th>
</tr>
</thead>
<tbody>
<tr>
<td>CMV</td>
<td>0.56</td>
<td>0.31</td>
<td>0.74</td>
<td>0.13</td>
<td>0.18</td>
</tr>
<tr>
<td>HHV6</td>
<td>0.51</td>
<td>0.02*</td>
<td>0.33</td>
<td>0.37</td>
<td>0.66</td>
</tr>
<tr>
<td>BK-virus</td>
<td>0.82</td>
<td>0.27</td>
<td>0.93</td>
<td>0.87</td>
<td>0.23</td>
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<tr>
<td>Adenovirus</td>
<td>0.26</td>
<td>0.02*</td>
<td>0.66</td>
<td>0.54</td>
<td>0.24</td>
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<tr>
<td>EBV</td>
<td>0.45</td>
<td>0.03*</td>
<td>0.8</td>
<td>0.16</td>
<td>0.35</td>
</tr>
<tr>
<td>AML</td>
<td>0.53</td>
<td>0.012</td>
<td>0.7</td>
<td>0.8</td>
<td>0.42</td>
</tr>
</tbody>
</table>

*MV P-values: Twice above cutt-off <100 days after HCT*
NiCord Phase I/II Outcome

Relapse

Year 2 Estimate: 33.2% (95% CI 15.9, 51.6)

NRM: Year 2 Estimate: 23.8%; (95% CI 10.9, 39.5)

Estimated Disease-Free Survival
1yr: 49.1% (95% CI 32.2%, 64.8%)
2yr: 43.0% (95% CI 24.2%, 60.5%)

Estimated Overall Survival
1yr: 51.2% (95% CI 32.9%, 66.8%)
2yr: 51.2% (95% CI 32.9%, 66.8%)

aGvHD grade II-IV: 44.0% (95% CI: 27.7%, 59.9%)
aGvHD grade III-IV: 11.1% (95% CI: 3.4%, 23.8%)

cGvHD (mild/moderate/severe): Month 12 Estimate 40.5%
(95% CI: 23.7%, 56.7%)
cGvHD (moderate/severe) Month 24 Estimate 9.8%
(95% CI: 2.4%, 23.7%)

With courtesy of M. Horwitz
### Demographic and Other Baseline Characteristics

<table>
<thead>
<tr>
<th>Primary Diagnosis</th>
<th>NiCord N (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Acute Lymphoblastic Leukemia</strong></td>
<td>9 (25)</td>
</tr>
<tr>
<td>High risk first complete morphologic remission (CR1)</td>
<td>5</td>
</tr>
<tr>
<td>Second Remission</td>
<td>4</td>
</tr>
<tr>
<td><strong>Acute Myelogenous Leukemia</strong></td>
<td>17 (47)</td>
</tr>
<tr>
<td>First complete morphologic remission (CR1)</td>
<td>13</td>
</tr>
<tr>
<td>Second Remission</td>
<td>4</td>
</tr>
<tr>
<td><strong>Myelodysplastic Syndrome</strong></td>
<td>7 (19)</td>
</tr>
<tr>
<td><strong>Chronic Myelogenous Leukemia</strong></td>
<td>2 (6)</td>
</tr>
<tr>
<td><strong>Hodgkin’s Disease</strong></td>
<td>1 (3)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Disease Risk</th>
<th>NiCord N (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Low</strong></td>
<td>8 (22)</td>
</tr>
<tr>
<td><strong>Intermediate</strong></td>
<td>15 (42)</td>
</tr>
<tr>
<td><strong>High</strong></td>
<td>13 (36)</td>
</tr>
</tbody>
</table>