NiCord Single Unit Expanded Umbilical Cord Blood Transplantation: Final Results of a Multicenter Phase I/II Trial

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Jerusalem, Israel
Umbilical Cord Blood Stem Cell Grafts

• Advantages
  – Readily available stem cells source
  – Tolerance across HLA barriers
  – Nearly 30 year of experience
  – Less chronic GvHD vs. Matched Unrelated donor
    • Eapen M et al Lancet 2010
  – Potent anti-tumor activity
    • Milano F et al NEJM 2016

• Disadvantages
  – Low stem cell dose
    • Delayed hematopoietic recovery
    • Delayed immunologic recovery
  – Increased resource utilization

Potential Solution

Ex-vivo Expansion Cord Blood Stem Cells
NiCord Stem Cell Expansion Technology

- An ex vivo expanded cell product derived from a umbilical cord blood
- Developed in the laboratories of Gamida Cell Ltd.
- Culture system: Nicotinamide + TPO, IL-6, FLT-3 ligand and SCF

**Affect on CD34+ Stem Cells**
- Preserves gene expression profile similar to non-cultured cells
- Modulates cellular metabolism and transport related genes
- Increase in stress resistance
- Increase in stem cell engraftment efficiency
Pilot Trial: NiCord + Unmanipulated Double Cord Blood Transplantation

- 11 patients, myeloablative conditioning (2010-2012)
- NiCord expanded graft + Unmanipulated cord blood graft
- NiCord engraftment dominant in 8 of 11 recipients
- Shortened time to hematopoietic recovery (compared to historical controls)
  - Neutrophils >500 (mean days): 25 → 11
  - Platelets > 20K (mean days): 41 → 31
  - 3 year overall survival: 67%
  - 3 year progression-free survival: 67%
- NiCord derived hematopoiesis stable and robust
  - Median f/u 6yrs (range 5-7 years)

Patrick Stiff, MD Loyola University, Chicago
Horwitz et al. JCI 2014
Can NiCord be used as a single, stand-alone graft?
Phase I/II Multicenter Study of NiCord as a Stand-alone Graft

Primary Objective
1. To assess the cumulative incidence neutrophil engraftment at 42

Design
- 12-65 years old
- AML, ALL, MDS, CML, Lymphoma
- Myeloablative Conditioning regimen;
  - Regimen A: TBI 1350cGy, Fludarabine and Cyclophosphamide/Thiotepa
  - Regimen B: Thiotepa, Busulfan, Fludarabine
  - Regimen C: Clofarabine, Fludarabine, Busulfan
- GvHD prophylaxis
  - Mycophenolate mofetil, Tacrolimus or cyclosporine
- 13 sites: US, EU, Asia
**Protocol Schema**

**NiCord Unit**
- Shipped to Centralized Manufacturing facility

**CD 133+ Cell Selection**
- CD133 Negative Fraction
- CD133+ Fraction

**Non-cultured fraction (NF)**
- Lymphocyte Containing Cryopreserved

**Cultured fraction (CF)**
- Cultured 21±2d in cytokines + Nicotinamide
- Transported Frozen to Site

**NiCord Graft**
- Myeloablative Conditioning
- MMF
- Tacrolimus

**Day 0**
- +60
- +180

**American Society of Hematology**
# Demographic and Baseline Characteristics

<table>
<thead>
<tr>
<th></th>
<th>NiCord N (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of evaluable patients</td>
<td>36 (100)</td>
</tr>
<tr>
<td>Age (years)</td>
<td></td>
</tr>
<tr>
<td>13-18</td>
<td>4 (11)</td>
</tr>
<tr>
<td>19-39</td>
<td>11 (31)</td>
</tr>
<tr>
<td>40 +</td>
<td>21 (58)</td>
</tr>
<tr>
<td><strong>Median (range)</strong></td>
<td>44 (13-63)</td>
</tr>
<tr>
<td>HLA Match Score</td>
<td></td>
</tr>
<tr>
<td>4/6</td>
<td>26 (72)</td>
</tr>
<tr>
<td>5/6</td>
<td>8 (22)</td>
</tr>
<tr>
<td>6/6</td>
<td>2 (6)</td>
</tr>
<tr>
<td>Conditioning Regimen</td>
<td></td>
</tr>
<tr>
<td>Regimen A (TBI, Fludarabine +/- Cy or Thiotepa)</td>
<td>15 (42)</td>
</tr>
<tr>
<td>Regimen B (Thiotepa, Busulfan, Fludarabine)</td>
<td>19 (53)</td>
</tr>
<tr>
<td>Regimen C (Clofarabine, Fludarabine, Busulfan)</td>
<td>2 (6)</td>
</tr>
<tr>
<td>Weight (Kg)</td>
<td></td>
</tr>
<tr>
<td><strong>Median (range)</strong></td>
<td>75 (41-125)</td>
</tr>
</tbody>
</table>
## 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></td>
</tr>
<tr>
<td>High risk first complete morphologic remission (CR1)</td>
<td>9 (25)</td>
</tr>
<tr>
<td>Second Remission</td>
<td>5</td>
</tr>
<tr>
<td><strong>Acute Myelogenous Leukemia</strong></td>
<td>17 (47)</td>
</tr>
<tr>
<td>First complete morphologic remission (CR1)</td>
<td></td>
</tr>
<tr>
<td>Second Remission</td>
<td>13</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>Low</td>
<td>8 (22)</td>
</tr>
<tr>
<td>Intermediate</td>
<td>15 (42)</td>
</tr>
<tr>
<td>High</td>
<td>13 (36)</td>
</tr>
</tbody>
</table>
Graft Characteristics

<table>
<thead>
<tr>
<th></th>
<th>Median Cell Dose (Range)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>TNC (x 10e7/kg)</strong></td>
<td>2.4 (1.8-3.6)</td>
</tr>
<tr>
<td><strong>CD34+ (x 10e8)</strong></td>
<td>3.7 (2.3-7.8)</td>
</tr>
<tr>
<td><strong>CD34+ (x 10e6/kg)</strong></td>
<td>0.13 (0.08-0.25)</td>
</tr>
<tr>
<td><strong>Post-NiCord Expansion</strong></td>
<td>4.4 (1.5-13.1)</td>
</tr>
<tr>
<td><strong>33-Fold Expansion</strong></td>
<td></td>
</tr>
<tr>
<td><strong>4.4 (1.5-13.1)</strong></td>
<td></td>
</tr>
<tr>
<td><strong>0.2 (0.1-0.4)</strong></td>
<td></td>
</tr>
</tbody>
</table>

*As reported by cord blood bank

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# Standard Myeloablative Umbilical Cord Blood Transplantation CIBMTR Matched Control Cohort

<table>
<thead>
<tr>
<th>Selection Criteria Applied Sequentially</th>
<th>Number of Matching Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>CBU transplants from 2010 to 2013*</td>
<td>1037</td>
</tr>
<tr>
<td>Age 13-63</td>
<td>820</td>
</tr>
<tr>
<td>Myeloablative conditioning</td>
<td>519</td>
</tr>
<tr>
<td>Disease status similar to NiCord patients</td>
<td>371</td>
</tr>
<tr>
<td>Cell count criteria</td>
<td>184</td>
</tr>
<tr>
<td>HLA match criteria</td>
<td>153</td>
</tr>
<tr>
<td>Performance score criteria</td>
<td>146</td>
</tr>
<tr>
<td>Final sample size</td>
<td>146</td>
</tr>
</tbody>
</table>

*Double Cord-80%  Single Cord-20%
The data presented here include data obtained from the Center for International Blood and Marrow Transplant Research.
NiCord Phase I/II Outcome

Non-relapse Mortality

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

Relapse

Year 2 Estimate: 33.2%
(95% CI 15.9, 51.6)
NiCord Phase I/II Outcome: Disease-free and Overall Survival

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%)

Median Follow-up (survivors); 14 month (5-37 months)
NiCord Phase I/II; Acute Graft vs. Host Disease

Grade II/IV

Cumulative Incidence of Grade II-IV Acute GvHD

Day 100 Estimate: 44.4% (95% CI: 27.7%, 59.9%)

Grade III/IV

Cumulative Incidence of Grade III-IV Acute GvHD

Day 100 Estimate: 11.1% (95% CI: 3.4%, 23.8%)
NiCord Phase I/II: Chronic Graft vs. Host Disease

Mild/Moderate/Severe

Month 12 Estimate 40.5%
(95% CI: 23.7%, 56.7%)

Cumulative Incidence

Year 1 Estimate 9.8%
(95% CI: 2.4%, 23.7%)

Year 2 Estimate 9.8%
(95% CI: 2.4%, 23.7%)

Month 24 Estimate 9.8%
(95% CI: 2.4%, 23.7%)

Moderate/Severe

N at Risk
36
14
4
0
0

N at Risk
36
22
11
6
4

Months Post Transplant
Immune Reconstitution: NiCord vs. Unmanipulated Dual Cord

*Barker et al: Results of a prospective multicenter, myeloablative adult double-unit cord blood transplantation trial N=56 Brit J Haem 2015
## NiCord Single Cord Phase I/II Study Results Summary; n=36

<table>
<thead>
<tr>
<th>Endpoint</th>
<th>Details</th>
</tr>
</thead>
<tbody>
<tr>
<td>Time to neutrophil engraftment (median)</td>
<td>11 days (range 6-26)</td>
</tr>
<tr>
<td>Time to platelet engraftment (median)</td>
<td>34 days (range 25-96)</td>
</tr>
<tr>
<td>aGvHD grade II-IV and III-IV at 100 days</td>
<td>44% and 11%</td>
</tr>
<tr>
<td>cGvHD Moderate-Severe at 1 year</td>
<td>10%</td>
</tr>
<tr>
<td>Graft Failure</td>
<td>Primary-1, Secondary-2 (HHV6-1, Adenovirus-1)</td>
</tr>
<tr>
<td>Chimerism (engrafted patients n=34)</td>
<td>Full donor (&gt;95%); 97% Mixed chimerism; 3%</td>
</tr>
<tr>
<td>Transplant Related Mortality at 1 year</td>
<td>20%</td>
</tr>
<tr>
<td>Disease-free/Overall Survival at 1yr</td>
<td>49%/51%</td>
</tr>
</tbody>
</table>

**Median follow-up of survivors: 14 months (range 5-37)**
Conclusions

• NiCord
  – Median 10 day reduction in time to neutrophil engraftment
  – Median 12 day reduction in time to platelet engraftment
    • Compared to standard myeloablative umbilical cord blood transplantation (CIBMTR)
  – Robust and durable engraftment > 7 years
  – Elimination of need for dual umbilical cord blood grafts
  – Reduced risk of bacterial infections
  – Fewer days in hospital during first 100 days post transplantation
    • Compared to single center matched historical control cohort
      – Anand/Horwitz et al. BBMT 2017
NiCord vs. Standard Umbilical Cord Blood Transplantation Phase III Registration Trial (FDA and EMA)

- NiCord vs. Standard (single or double) UCBT
- Myeloablative conditioning
- Sponsor: Gamida Cell
- USA, Europe, Asia
- Open for accrual

Adult patients with high-risk hematological malignancies

Primary endpoint
Time to engraftment
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P. Stiff- Chicago
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Sheba Medical Center
Laurence Friedman

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