HAPLO-CORD HEMATOPOIETIC STEM CELL TRANSPLANTATION

Frequency, Risk Factors and Outcomes of Cord Graft Failure (CGF) After Haplo-Cord Transplantation

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Senior Transplant Fellow
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Allogeneic Stem Cell Transplantation

- Only curative treatment in high-risk or recurrent hematologic malignancies and certain non-malignant hematologic disorders

- Matched related donor (MRD) is preferred (8/8 match at HLA-A, -B, -C, and -DR)
  - Only ~30% have a MRD

- Matched unrelated donor (MUD) is next preferred
  - Only 60% of white patients have a MUD
  - Only 20% of black patients have a MUD
  - Only 20-45% of other minorities have a MUD

- Approximately 5,000 per year require an alternative donor

Source: National Marrow Donor Program

Ballen et al; Bone Marrow Transplant 2007
Umbilical Cord Blood (UCB)

- Blood remaining in the placenta and in the umbilical cord after childbirth
- Minimal numbers of T-cells
- Maternal-Fetal tolerance
  - Treg (CD4+, CD25+, FoxP3+)
  - Hyporeactive dendritic cells ➔ Less CD4 Th1 ➔ Less GVHD
  - NK cells less function
- Higher concentration of more proliferative stem cells (outcompetes adult stem cells)
  - Longer telomeres
  - Faster exit from Go/G1
  - Increased cytokine/paracrine sensitivity

Combined Cord and CD34+ Selected Haploidentical Grafts: **Haplo-Cord HCT**

- Rapid early T-cell depleted haplo engraftment
- Safely allows delayed engraftment of UCB cells

% Donor Chimerism

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**Cord Blood Graft**

**Haploidentical Graft**

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0 10 40

Time
Graft Failure (GF)

- **Function:** Inability to achieve neutrophils $\geq 0.5 \times 10^9/L$ by Day X
- **Engraftment:** Donor chimerism $< X\%$ at Day X

<table>
<thead>
<tr>
<th>Donor Type</th>
<th>Graft Failure $%$ - MA</th>
<th>Graft Failure $%$ - RIC</th>
</tr>
</thead>
<tbody>
<tr>
<td>Matched Related</td>
<td>&lt;5%</td>
<td>&lt;5%</td>
</tr>
<tr>
<td>Matched Unrelated</td>
<td>&lt;5%</td>
<td>&lt;5%</td>
</tr>
<tr>
<td>Mismatched Unrelated</td>
<td>2-14</td>
<td>3-4</td>
</tr>
<tr>
<td>Haploidentical</td>
<td>0-10</td>
<td>2-13</td>
</tr>
<tr>
<td>Umbilical Cord Blood</td>
<td>4-20</td>
<td>6-12</td>
</tr>
</tbody>
</table>

Mechanisms/Causes of Graft Failure

• Infections in the recipient (CMV, HHV6, parvo)
• Drug toxicity
• Recipient immune-mediated, involving:
  • Lymphocytes (especially T-cells)
  • Natural killer (NK) cells
  • Possibly antibodies

Risk Factors Associated with GF

- Degree of HLA-mismatch (particularly HLA Class 1)
- Use of unrelated grafts
- T-cell depletion
- Cell dose
- Use of reduced-intensity conditioning (RIC)
- Patient alloimmunization (transfusions, pregnancy)
- Donor specific antibodies (DSA)
- Major ABO mismatch

Cord Graft Failure (CGF)

- Function: Inability to achieve neutrophils ≥0.5x 10^9/L by day 28
- Engraftment: Cord chimerism <5% at Day 60 in the unfractionated and CD3 compartments

<table>
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</table>

## Cord Graft Failure (CGF) After Haplo-Cord HCT with RIC: Patient and Graft Characteristics

<table>
<thead>
<tr>
<th></th>
<th>No Graft Failure</th>
<th>Graft Failure</th>
<th>All Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>N (%)</strong></td>
<td>80 (85%)</td>
<td>14 (15%)</td>
<td>94</td>
</tr>
<tr>
<td><strong>Age, Median</strong></td>
<td>52 (range 20-73)</td>
<td>43 (range 18-69)</td>
<td>50 (range 18-73)</td>
</tr>
<tr>
<td><strong>Active Disease at Transplant, %</strong></td>
<td>49</td>
<td>29</td>
<td>47</td>
</tr>
<tr>
<td><strong>UCB &gt;4/6 HLA-match, %</strong></td>
<td>77</td>
<td>64</td>
<td>73</td>
</tr>
<tr>
<td><strong>UCB Collected TNC Dose x 10^7</strong></td>
<td>2.1 (+/- 1.1)</td>
<td>1.9 (+/- 0.63)</td>
<td></td>
</tr>
<tr>
<td><strong>Haplo &gt;5/10 HLA-match, %</strong></td>
<td>23</td>
<td>14</td>
<td>21</td>
</tr>
<tr>
<td><strong>Haplo TNC Dose x 10^6</strong></td>
<td>3.8 (+/-1.6)</td>
<td>5.0 (+/- 2.2)</td>
<td></td>
</tr>
<tr>
<td><strong>Major ABO Mismatch, %</strong></td>
<td>32</td>
<td>14</td>
<td>28</td>
</tr>
<tr>
<td><strong>DSA, %</strong></td>
<td>4</td>
<td>0</td>
<td>4</td>
</tr>
</tbody>
</table>
Cord Graft Failure (CGF) After Haplo-Cord HCT with Reduced Intensity Conditioning: Frequency and Risk Factors

- Frequency of CGF: 14/94 (15%)
- Factors NOT associated with CGF:
  - UCB Cell doses
  - UCB Cell viabilities
  - Degree of UCB or Haplo HLA match
  - Major ABO mismatch
- Factors associated with CGF:
  - Haploidentical TNC cell dose
  - Haploidentical CD34 cell dose
Cord Graft Failure (CGF) After Haplo-Cord HCT with Reduced Intensity Conditioning: Neutrophil Engraftment

- Median Time to ANC Engraftment: 11 days
- 11 without ANC Engraftment by Day +28
- Cumulative Incidence of ANC Engraftment
  - At Day +28: 90%
  - At Day +48: 99%

Tsai et al. ASH 2014
Cord Graft Failure (CGF) After Haplo-Cord HCT with Reduced Intensity Conditioning: Outcomes After Cord Graft Failure

Median Survival after CGF: 12.7 months

- Died N=7
  - Graft Failure N=2
  - Infection N=2
  - Progressive Disease N=3

- Alive N=7
  - In Remission, N=5
    - 1 Alive at 5.5 yrs
    - 1 Alive at 1.5 yr
    - 2 Alive at 1+ yr
  - Relapsed, N=2
    - 1 Alive at 8 mo
    - 2 Alive at 4+ yrs

All with predominantly haplo or mixed haplo-auto

Median survival after GF with UCBT with RIC = 3.8 months.
[Narimatsu et al. BJH 2005]

Tsai et al. ASH 2014
Cord Graft Failure (CGF) After Haplo-Cord HCT with Reduced Intensity Conditioning: Conclusions

- Higher haplo cell doses should be avoided
- Factors not found to be associated: UCB cell doses, UCB cell viability, degree of UCB and haplo HLA-match, ABO mismatch
- Relatively long-term survival possible due to sustained mixed to predominantly haploidentical chimerism
- Haploidentical graft is a “safety net” in the event of CGF
- Unknown: How the rate of UCB engraftment or the ultimate achievement of full UCB chimerism relative to haploidentical chimerism affects outcomes

Tsai et al. ASH 2014
Acknowledgements

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Non-Inherited Maternal Antigen (NIMA)

- Fetal exposure to NIMA generates regulatory T-cells
- T-regs suppress alloreactive cells

Examples of NIMA Match versus NIMA Mismatch

<table>
<thead>
<tr>
<th>Recipient</th>
<th>A1</th>
<th>A24</th>
<th>B7</th>
<th>B65</th>
<th>DR0102</th>
<th>DR1501</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>NIMA match</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CB unit 1</td>
<td>A2</td>
<td>A24</td>
<td>B7</td>
<td>B65</td>
<td>DR0102</td>
<td>DR1501</td>
</tr>
<tr>
<td>Mother of unit 1</td>
<td>A1</td>
<td>A24</td>
<td>B57</td>
<td>B65</td>
<td>DR0102</td>
<td>DR1305</td>
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<tr>
<td><strong>NIMA mismatch</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CB unit 2</td>
<td>A2</td>
<td>A24</td>
<td>B7</td>
<td>B65</td>
<td>DR0102</td>
<td>DR1501</td>
</tr>
<tr>
<td>Mother of unit 2</td>
<td>A3</td>
<td>A24</td>
<td>B7</td>
<td>B65</td>
<td>DR0102</td>
<td>DR1501</td>
</tr>
</tbody>
</table>

van Rood et al. PNAS 2009
Non-Inherited Maternal Antigen (NIMA)

- 1,121 UCBT in the NY Blood Center National Cord Cord Program
  - 62 HLA matched (6%)
  - 79 mismatched unit with a NIMA match (NMT) (7%)
  - 980 mismatched grafts w/o NIMA match (no-NMT) (87%)

- Improved:
  - TRM (p=0.012)
  - OS (p=0.022)
  - Treatment failure (p=0.020)
  - ANC recovery (p=0.031)
  - Decreased relapse (p=0.0740)
  - Platelet recovery and GVHD not different

van Rood et al. PNAS 2009
Inherited Paternal Antigen (IPA)

- Fetal cells with IPA (HLA or mHA) enter maternal circulation
- Maternal lymphocytes sensitized
- Maternal microchimerism $\rightarrow$ GVT

Example of IPA Targeting versus No IPA Targeting by Maternal Microchimerism

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<th>B7</th>
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<th>DR1501</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>IPA targeted</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CB unit 1</td>
<td>A2</td>
<td>A24</td>
<td>B7</td>
<td>B65</td>
<td>DR0102</td>
<td>DR1501</td>
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<td>A1</td>
<td>A24</td>
<td>B57</td>
<td>B65</td>
<td>DR0102</td>
<td>DR1305</td>
</tr>
<tr>
<td><strong>Not IPA targeted</strong></td>
<td>A2</td>
<td>A24</td>
<td>B7</td>
<td>B65</td>
<td>DR0102</td>
<td>DR1501</td>
</tr>
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<td>DR1501</td>
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</table>

van Rood et al. PNAS 2011
Inherited Paternal Antigen (IPA)

- **94% shared 1 or more IPA by chance**
- Decreased relapse (HR = 0.15; p<0.001)
- III-IV aGVHD not significantly increased (HR = 1.43; p=0.73)
- Higher birth order of donor independently associated with reduced relapse
- Shared IPA may contribute to decreased relapse

van Rood et al. PNAS 2011
NIMA and “Virtual 6/6 or 5/6” UCB units

- 6/6 UCB = 5/6 + NIMA match (TRM and relapse)
- 5/6 UCB = 4/6 + 2 NIMA match

- 6/6 or 5/6-inherited UCB unit in 850 of 2,020 patients (42%)

- 6/6 or 5/6-inherited or virtual-matched UCB unit for 1,617 of 2,020 patients (80%)

Van der Zanden et al. BBMT 2014; van Rood et al. Proc Natl Acad Sci 2009; Rocha et al. BMT 2012
UCB Stem Cell Transplantation

The full potential of cord blood remains to be seen:
- Cord selection may be improved
- Better matched cord units may be available, AND to more people than initially thought

We may yet achieve better outcomes:
- Increased graft-versus-tumor (decreased relapse)
- Decreased graft-versus-host-disease
<table>
<thead>
<tr>
<th></th>
<th>Haploidentical</th>
<th>Umbilical Cord Blood</th>
</tr>
</thead>
<tbody>
<tr>
<td>Availability</td>
<td>Available</td>
<td>Available</td>
</tr>
<tr>
<td>HLA Match</td>
<td>Less stringent</td>
<td>Less stringent</td>
</tr>
<tr>
<td>TRM</td>
<td>Variable</td>
<td>Increased</td>
</tr>
<tr>
<td>Graft Versus Tumor</td>
<td>Good</td>
<td>Good</td>
</tr>
<tr>
<td>Graft Versus Host</td>
<td>May be increased</td>
<td>May be decreased</td>
</tr>
<tr>
<td>Graft Rejection</td>
<td>May be increased</td>
<td>May be increased</td>
</tr>
<tr>
<td>Immune Reconstitution</td>
<td>May be delayed/suboptimal</td>
<td>May be delayed/suboptimal</td>
</tr>
<tr>
<td>Donor Available Later</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Expense</td>
<td>Less</td>
<td>More</td>
</tr>
<tr>
<td>Time</td>
<td>Typically quick to procure</td>
<td>Typically quick to procure</td>
</tr>
</tbody>
</table>
UCMC Haplo-Cord Results (updated)

Total of 66 patients from 01/2007 to 05/2013

**Overall Survival**

**Disease Free Survival**
Haplo-Cord
Results (updated)
Risk Factors Associated with CGF

- Cell Dose (TNC and CD34)
- Quality of preserved cells
- Limited numbers of accessory cells (e.g., lymphocytes, mesenchymal cells)
- HLA disparity
- CB stem cell homing capacity
- Presence of donor-specific antibodies (DSA)

<table>
<thead>
<tr>
<th></th>
<th>Matched unrelated donor</th>
<th>Haplo cord</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Time to ANC &gt;500</td>
<td>10</td>
<td>11</td>
<td>0.1</td>
</tr>
<tr>
<td>Time to Plt&gt;20,000</td>
<td>18</td>
<td>23</td>
<td>0.05</td>
</tr>
<tr>
<td>PFS at 1 year (95%CI)</td>
<td>46 (34-58)</td>
<td>41 (26-56)</td>
<td>0.6</td>
</tr>
<tr>
<td>OS at 1 year (95%CI)</td>
<td>57 (44-70)</td>
<td>64 (49-79)</td>
<td>0.8</td>
</tr>
<tr>
<td>Cum Inc TRM at 100 day (95%CI)</td>
<td>9% (2-16)</td>
<td>9% (0-18)</td>
<td>0.2</td>
</tr>
<tr>
<td>Cum Inc TRM at 1 year (95%CI)</td>
<td>25% (14-36)</td>
<td>29% (15-44)</td>
<td>0.2</td>
</tr>
<tr>
<td>Cum Inc Relapse at 1 year (95%CI)</td>
<td>30% (18-42)</td>
<td>26% (12-40)</td>
<td>0.5</td>
</tr>
<tr>
<td>Cum Inc aGVHD at 100 day (95%CI)</td>
<td>25% (14-36)</td>
<td>29% (13-43)</td>
<td>0.7</td>
</tr>
<tr>
<td>Cum Inc cGVHD at 1 year</td>
<td>6% (0-12)</td>
<td>7% (0-15)</td>
<td>0.9</td>
</tr>
</tbody>
</table>
14/94 (15%) Developed CGF

- CGF N=14 (15%)
  - Died <1 year, N=7
  - Alive >1 year, N=7
- Graft Failure N=2
- Infection N=2
- Progressive Disease N=3
- In Remission N=5
- Relapsed, N=2

All with CGF engrafted neutrophils by Day +28

Median Survival after CGF: 12.7 months