Haploidentical Donor Transplants: Outcomes and Comparison to Other Donor Types

Paul V. O’Donnell
BSBMT Education Day
London
12 October 2011
Clinical Problem: Identification of a Donor for Allogeneic Transplantation

Preferred donor: HLA-matched sibling (≈30%)

Initiate Search for Unrelated Donor (≈70%)

Find MURD (≈35%)

Transplanted (≈23%)

Search for Alternative Donor (≈35%)
- Mismatched related “haploidentical”
- Unrelated Cord blood
- Mismatched unrelated
Obstacles in Haploidentical Transplants
Ablative or Nonablatative

• T-replete BMT
  - GvHD: High frequency of donor alloreactive T-cells in unmanipulated grafts
  - Rejection: Residual recipient alloreactive T-cells which survive conditioning

• T-depleted BMT
  - High failure rates due to ≥ 30% NRM at 1 yr
    - GvHD
    - Opportunistic infections
## Haploidentical Transplants: Ablative Conditioning

<table>
<thead>
<tr>
<th>Allograft</th>
<th>Center</th>
<th>Reference</th>
<th>% Rejection</th>
<th>% III/IV GvHD</th>
<th>NRM (1 yr)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>T-replete</strong></td>
<td>Royal Marsden</td>
<td>Powles, 1983</td>
<td>29</td>
<td>80</td>
<td>54</td>
</tr>
<tr>
<td></td>
<td>Seattle</td>
<td>Beatty, 1985</td>
<td>21</td>
<td>63</td>
<td></td>
</tr>
<tr>
<td><strong>T-depleted</strong></td>
<td>Perugia</td>
<td>Aversa, 2005</td>
<td>9</td>
<td>2</td>
<td>37</td>
</tr>
<tr>
<td><em>Ex vivo</em></td>
<td>Tubingen</td>
<td>Lang, 2004</td>
<td>17</td>
<td>2</td>
<td>29</td>
</tr>
</tbody>
</table>
# Haploidentical Transplants: Nonablative Conditioning

<table>
<thead>
<tr>
<th>Allograft</th>
<th>Center</th>
<th>Reference</th>
<th>% Rejection</th>
<th>% III/IV GvHD</th>
<th>NRM (1 yr)</th>
</tr>
</thead>
<tbody>
<tr>
<td>T-depleted (anti-CD2)</td>
<td>MGH</td>
<td>Spitzer, 2005</td>
<td>43</td>
<td>31</td>
<td>23</td>
</tr>
<tr>
<td><em>In vivo</em></td>
<td></td>
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<tr>
<td>Duke</td>
<td>Rizzieri, 2005</td>
<td>8</td>
<td>13</td>
<td>31</td>
<td></td>
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</table>
Cyclophosphamide-induced Tolerance Following Bone Marrow Transplantation From Haploidentical Donors

Key Background
Drug-induced Tolerance

Anti-mitotic drug (Cyclophosphamide)

Antigen → Response

2-5 days

• Soluble Ag
  Schwartz & Dameschek, 1958
  Berenbaum & Brown, 1964

• Skin graft survival
  Berenbaum, 1963
  Santos & Owen, 1965
Nomoto Model: “Cells Followed by Cy”

Spleen Cells → Cy

Recipient → MHC^B

Donor → MHC^A

Skin, solid organ transplant tolerance

Direct evidence for clonal destruction of allo-reactive T cells in the mice treated with cyclophosphamide after allo-priming

T. MAEDA, M. ETO, Y. NISHIMURA, K. NOMOTO, Y.-Y. KONG & K. NOMOTO Department of Immunology, Medical Institute of Bioregulation, Kyushu University, Fukuoka, Japan

Alloreactive T-cells: Direct recognition of foreign MHC of haploidentical recipient

Clonal Deletion Of anti-donor T-cells
Apply “Cells followed by Cy” to Haploidentical BMT

Goal: To establish donor $\leftarrow$ recipient T-cell tolerance
Basic Nonablative BMT Platform

- TBI 200 cGy
- Allograft Infusion
- Conditioning: Induce host tolerance
- Add: Post-transplant Cy
- Induce donor and host tolerance

Flu 30 mg/m²/day

Mouse Model of Haploidentical BMT

Donor BMT (spleen + marrow cells) → MHC^A → Cy day +2*

Recipient (S/P Flu/TBI Conditioning) → MHC^B

No BMT (Nonablative) at 6 wk

*S'ntem cells resistant to Cy – high levels of aldehyde dehydrogenase

Jones et al. Blood 1995

Luznik, Fuchs et al. Blood 2001
Bone Marrow Infusion

TBI 200 cGy

Cy?

BMT Day

-6 -5 -4 -3 -2 -1 0 1 2 3 4 5 10 20 30 40 50 180

Flu 30 mg/m²/day

Cy 50 mg/kg

Johns Hopkins Phase I Trial
(Cy Dose-finding Pre-transplant)

O’Donnell, et al. 2002
BMT

Cy 14.5 mg/kg/day

TBI
200 cGy

Bone Marrow Infusion

MMF tid

G-CSF

Tacrolimus

Flu 30 mg/m²/day

Cy 50 mg/kg

BMT Day

-6 -1 0 3 4 5 10 20 30 40 50 180

Johns Hopkins and Seattle Phase II Trials

Luznik, O’Donnell et al. 2008
## Patient & Donor Characteristics

<p>| | |</p>
<table>
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</thead>
<tbody>
<tr>
<td>N</td>
<td>68</td>
</tr>
<tr>
<td>Median age, yr (range)</td>
<td>46 (1-71)</td>
</tr>
<tr>
<td>Ethnicity minorities (%)</td>
<td>22</td>
</tr>
<tr>
<td>High-risk malignancies (%)</td>
<td></td>
</tr>
<tr>
<td>Myeloid (40% AML)</td>
<td>50</td>
</tr>
<tr>
<td>Lymphoid (40% HL)</td>
<td>50</td>
</tr>
<tr>
<td>Donors</td>
<td></td>
</tr>
<tr>
<td>Parents:Siblings:Children</td>
<td>1:2:1</td>
</tr>
<tr>
<td>HLA-mismatches ≥ 3/10</td>
<td>&gt;90%</td>
</tr>
</tbody>
</table>
Hematopoietic Recovery/Engraftment

Recovery [median (range)]

- Days to ANC $\geq 500/$mcL 15 (11-42)
- Days to PLT $> 20,000$ 28 (0-395)
- Transfusions (Seattle)
  - RBC 04 (0-25)
  - PLT 03 (0-50)

Failure to Engraft 9/66 evaluable (13%)

- Autologous recovery 8/9

% Full Donor CD3 Chimerism (>95%)

- D28 96
# Hospitalizations/Infections

**Admissions** (45/51 patients [88%])
- Median No. (range) 1 (0-5)
- Median LOS, d (range) 5 (1-59)
- % Fever, infection as reason for adm 63

**Opportunistic Infections**
- Bacterial 58 (GPC)
- Invasive fungal (Aspergillus) 3/51 (6%)
- Viral (CMV)
  - Reactivation in high-risk patients (D±R+) 26/33 (79%)
  - CMV pneumonitis None
Graft-versus-Host Disease

A: Acute GVHD

- Grades II-IV: 33%
- Grades III-IV: 5%

B: Extensive chronic GVHD

- Cy d 3 (Seattle; n=28): 25%
- Cy d 3.4 (Baltimore; n=40): 5%
Relapse and Survival

A

Cumulative incidence (%)

Days after transplantation

58%

15%

Non-relapse mortality

B

Survival (%)

Days after transplantation

36%

Overall survival

Event-free survival

26%

C

Event-free survival (%)

Days after transplantation

HR 0.5, p=0.02

Lymphoid (n=36)

Myeloid (n=31)
Survival: HL versus other diagnoses (Seattle Cohort)

- Overall Survival, Other Dx (n=32)
- Overall Survival, Hodgkin (n=23)
- Event-Free Survival, Other Dx (n=32)
- Event-Free Survival, Hodgkin (n=23)

Probability vs. Years after Transplant:
- 61% at 3 yr
- 41% (Hodgkin)
- 21% at 3 yr
- 18% (Hodgkin)

P = .04

O'Donnell, Hematologics 2010
## NM-HCT for Hodgkin’s lymphoma

### Comparison of donor type

<table>
<thead>
<tr>
<th></th>
<th>Matched Related (N=34)</th>
<th>Matched Unrelated (N=24)</th>
<th>Haploidentical Related (N=21)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median follow-up Mo (range)</td>
<td>15 (4-91)</td>
<td>26 (8-58)</td>
<td>15 (4-49)</td>
</tr>
<tr>
<td>% Refractory</td>
<td>21</td>
<td>38</td>
<td>43</td>
</tr>
<tr>
<td>GvHD (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Acute Grades III/IV</td>
<td>16</td>
<td>8</td>
<td>11</td>
</tr>
<tr>
<td>Extensive chronic</td>
<td>50</td>
<td>63</td>
<td>35 (p=0.14)</td>
</tr>
<tr>
<td>NRM at 2 yr (%)</td>
<td>21</td>
<td>8</td>
<td>9</td>
</tr>
<tr>
<td>Survival at 2 yr (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>OS</td>
<td>53</td>
<td>58</td>
<td>58</td>
</tr>
<tr>
<td>PFS</td>
<td>23</td>
<td>29</td>
<td>51 (p=0.03)</td>
</tr>
</tbody>
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Burroughs et al., BBMT 2008
BMT CTN Parallel Phase II Trials: Haplo-BM and Double Umbilical Cord Blood

**Eligibility**
- Adult patients (N=50) with high-risk leukemias and lymphomas
  - CR or PR (lymphomas)
- No suitably matched sibling donor
  - HLA mismatches
    - ≥2/10 for haplo; ≥2/6 for dUCB
- Cytotoxic chemotherapy within 3 mo of transplant

**Hypothesis**
- Survival at 180 days is ≥60%, similar to CIBMTR results of unrelated donor transplantation after RIC
  *(Giralt et. al. BBMT, 2007)*

*Brunstein, et al. Blood 2011*
# Patient Characteristics

<table>
<thead>
<tr>
<th></th>
<th>dUCB</th>
<th>Haploidentical</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>50</td>
<td>50</td>
</tr>
<tr>
<td>Median age (range), yr</td>
<td>58 (15-69)</td>
<td>48 (7-70)</td>
</tr>
<tr>
<td>High-risk Malignancies (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Myeloid (AML)</td>
<td>29</td>
<td>22</td>
</tr>
<tr>
<td>Lymphoid</td>
<td>21</td>
<td>28</td>
</tr>
</tbody>
</table>
Treatment Regimens

A

- Cy 50 mg/kg
- Fludarabine 40 mg/m²/day

B

- Cy 14.5 mg/kg/day
- Fludarabine 30 mg/m²/day

Minneapolis Protocol

Hopkins Protocol
Hematopoietic Recovery

A. Double UCB – Neutrophil Recovery

B. Double UCB – Platelet Recovery

C. Haplo-marrow – Neutrophil Recovery

D. Haplo-marrow – Platelet Recovery

- Neutrophils ≥500/μl (cumulative incidence)
- Platelet recovery (cumulative incidence)

Days after transplantation

- 15 d
- 16 d
- 38 d
- 24 d
Graft-versus-Host Disease

A. Double UCB – Acute GVHD

- grades II-IV
- grades III-IV

40% 21%

B. Double UCB – Chronic GVHD

25%

C. Haplo-marrow – Acute GVHD

32%

D. Haplo-marrow – Chronic GVHD

13%
Survival

A. Double UCB

B. Double UCB

C. Haplo-marrow

D. Haplo-marrow

Cumulative incidence (%)}

Days after transplantation

Survival (%)}

Months after transplantation

Relapse
Non-relapse mortality

Overall survival
Event-free survival

31%
24%
45%
7%
74%
54%
84%
62%
46%
48%
BMT CTN 1101: Multi-center, Phase III, Randomized Trial of Haplo-BM vs. dUCB

• Eligibility
  • Same criteria as Phase II trials except children allowed
  • Both donor sources must be suitable and available

• Null Hypothesis (ITT)
  • Pointwise PFS at 2 yr (nonproportional hazards)
  • N=410; 80% power to detect 15% difference

• Secondary endpoints
  • Will also include QOL, immune reconstitution and cost effectiveness analysis

• Expected activation: January 2012
Cy 14.5 mg/kg/day

TBI 200 cGy

HCT Day

Cy 50 mg/kg

Flu 30 mg/m²/day

PBSC Infusion

G-CSF

MMF tid

Tacrolimus

Guy’s/St. Thomas’ - Seattle
### Haploidentical PBSCT

<table>
<thead>
<tr>
<th><strong>N</strong></th>
<th>18</th>
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<tbody>
<tr>
<td><strong>Diagnoses</strong></td>
<td></td>
</tr>
<tr>
<td>Myeloid</td>
<td>4</td>
</tr>
<tr>
<td>Lymphoid</td>
<td>14</td>
</tr>
<tr>
<td><strong>Median Age</strong></td>
<td>51</td>
</tr>
<tr>
<td><strong>Median No. Mismatches</strong></td>
<td></td>
</tr>
<tr>
<td>HvG</td>
<td>5 (2-5)</td>
</tr>
<tr>
<td>GvH</td>
<td>4 (2-5)</td>
</tr>
<tr>
<td><strong>Median graft composition</strong></td>
<td></td>
</tr>
<tr>
<td>CD34 (x 10^{-6}/kg)</td>
<td>6 (3.6-8) [6]*</td>
</tr>
<tr>
<td>CD3 (x 10^{-7}/kg)</td>
<td>18 (12-30) [5]*</td>
</tr>
<tr>
<td><strong>Median time to hematopoietic recovery (d, range)</strong></td>
<td></td>
</tr>
<tr>
<td>Neutrophils</td>
<td>16 (13-23)</td>
</tr>
<tr>
<td>Platelets</td>
<td>17 (0-25)</td>
</tr>
<tr>
<td><strong>Full donor CD3 Chimera at D28</strong></td>
<td>17/18 (1 autologous recovery)</td>
</tr>
<tr>
<td><strong>Acute GvHD</strong></td>
<td></td>
</tr>
<tr>
<td>Grade II</td>
<td>11/16 (69% [5/16 Ila])</td>
</tr>
<tr>
<td>Grade III</td>
<td>1/16 (6%)</td>
</tr>
<tr>
<td><strong>NIH Chronic GvHD</strong></td>
<td></td>
</tr>
<tr>
<td></td>
<td>0/10</td>
</tr>
<tr>
<td><strong>NRM</strong></td>
<td>1/18 (6%)</td>
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*BM

*BM* Raj & O’Donnell, unpublished 2011
## Alternative Donors: Comparative Studies

### RIC Transplants

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<thead>
<tr>
<th></th>
<th>N</th>
<th>Med Age</th>
<th>%My</th>
<th>%Ly</th>
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<tr>
<td><strong>MRD</strong></td>
<td></td>
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<tr>
<td>Ho, et al. BBMT 17:1196 (2011)</td>
<td>187</td>
<td>56</td>
<td>52</td>
<td>48</td>
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<tr>
<td><strong>URD</strong></td>
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<tr>
<td>Ho, et al. BBMT 17:1196 (2011)</td>
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<td>57</td>
<td>52</td>
<td>48</td>
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<tr>
<td><strong>dUCB</strong></td>
<td></td>
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<tr>
<td><strong>Haplo</strong></td>
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</table>
RIC Transplants: Comparative Outcomes

**Graft Rejection**

**Grades III/IV GvHD**

**Chronic GvHD**

**1 Year NRM**

MRD | URD | dUCB | Haplo
RIC Transplants: Comparative Outcomes

1 Year PFS

3 Year PFS

1 Year OS

3 Year OS

MRD  URD  dUCB  Haplo
RIC Transplants: Comparative Outcomes

2 Year Relapse Rate

Study

Per Cent

Ho 2011
Giralt 2007
Mielcarek 2007
Brunstein 2007
Brunstein 2011
Luznik 2008
ODonnell 2010
Brunstein 2011

MRD
URD
dUCB
Haplo
Summary

“Low tech” approach of post-transplant Cy is a safe and effective means of inducing donor-host tolerance after haploidentical transplantation

- Inexpensive ($300)
- Low incidences of:
  - Graft failure
  - Severe acute and chronic GvHD (BM and PBSC)
  - Non-relapse mortality
  - Serious opportunistic infections
- Non-myeloablative: autologous hematopoietic recovery after graft failure
Summary (cont’d)

• HLA-mismatched UCB or related (haploidential) marrow are sources of alternative donor allografts with outcomes comparable to those of HLA-matched donors

• Relapse remains the major cause of treatment failure
  • Potential improvements
    • Increased intensity of conditioning
    • Donor lymphocyte infusions (haplo only)
    • Post-transplant maintenance therapy with novel agents (demethylation, HDAC inhibition, proteosome inhibition, tyrosine kinase inhibition)
And, especially the nurses, the patients and their families