Center for International Blood and Marrow Transplant Research – Trends in Use of Haploidentical Transplantation
Number of First Allogeneic HCTs in the US By Year

CIBMTR, unpublished data
Numbers of Allogeneic HCTs in the US
By Year and Donor Type

Excludes twins, related CB, 0-1 mism relatives
Numbers of Allogeneic HCTs in the US By Year and Donor Type

Excludes twins, related CB, 0-1 mism relatives
Distribution of Graft Sources

2010
- HLA-id sib: 37%
- Matched unrelated: 11%
- Mism unrelated: 6%
- Haploident: 6%
- Single Cord: 4%
- Double Cord: 5%

2013
- HLA-id sib: 33%
- Matched unrelated: 41%
- Mism unrelated: 11%
- Haploident: 6%
- Single Cord: 3%
- Double Cord: 6%
“Alternative Donor” Transplants in the US by Year and Graft Type
Distribution of Alternative Graft Sources

2010
N=1646

2013
N=1825

- 41% Mism unrelated
- 25% Haploident
- 20% Single Cord
- 20% Double Cord

N=1825

- 43% Mism unrelated
- 22% Haploident
- 22% Single Cord
- 13% Double Cord
Numbers of Allogeneic HCTs in US Caucasians By Year and Donor type
Numbers of Alternative Donor HCTs in US Caucasians By Year and Donor type

- Mism unrelated
- Haploidentical
- Single Cord
- Double Cord
- Total Cord


Numbers range from 0 to 700.
Numbers of Allogeneic HCTs in African-Americans By Year and Donor type

- HLA-id sib
- Matched unrelated
- Mism unrelated
- Haploidentical
- Single Cord
- Double Cord
- Total Cord
Numbers of Alternative Donor HCTs in African-Americans By Year & Donor type

- Mism unrelated
- Haploidentical
- Single Cord
- Double Cord
- Total Cord
Distribution of Graft Sources – 2013

Caucasians
N=5866
- 46%
- 32%
- 5%
- 4%
- 3%
- 10%

African Americans
N=596
- 32%
- 19%
- 12%
- 10%
- 9%
- 8%
- 4%
- 3%

HLA-id sib
Matched unrelated
Mism unrelated
Haploident
Single Cord
Double Cord

CIBMTR
CENTER FOR INTERNATIONAL BLOOD & MARROW TRANSPLANT RESEARCH
Numbers of Allogeneic HCTs by Age, Year and Donor type

- <16 Sib
- <16 Mism unrelated
- <16 Cord
- 16+ Sib
- 16+ Mism unrelated
- 16+ Cord
- <16 Matched unrelated
- <16 Haplo
- 16+ Haplo

Year:
- 2010
- 2011
- 2012
- 2013
Numbers of Allogeneic HCTs in Children by Year and Donor type

- <16 Total
- <16 Sib
- <16 Matched unrelated
- <16 Mism unrelated
- <16 Haplo
- <16 Cord

Year:
- 2010
- 2011
- 2012
- 2013

Donor types: Total, Sib, Matched unrelated, Mism unrelated, Haplo, Cord
Numbers of Allogeneic HCTs in Children by Year and Donor type
Numbers of Allogeneic HCTs in Adults by Year and Donor type

- 16+ Sib
- 16+ Matched unrelated
- 16+ Mism unrelated
- 16+ Haplo
- 16+ Cord
HLA Inheritance

Mother

A 1 2
B 3 4
C 5 6
DR 7 8

Father

A 9 10
B 11 12
C 13 14
DR 15 16

Patient

A 1 9
B 3 11
C 5 13
DR 7 15

Child 1

A 1 31
B 3 32
C 5 33
DR 7 34

Sibling 2

A 1 10
B 3 12
C 5 14
DR 7 16

Sibling 3

A 2 9
B 4 11
C 6 13
DR 8 15

Child 2

A 2 21
B 4 22
C 6 23
DR 8 24
HLA-haploidentical BMT circa 1990

Ablative conditioning
T cell-replete bone marrow
CsA + MTX prophylaxis

C Anasetti et al., Hum Immunol 29:79, 1990
Probability of event-free survival in 66 patients who received transplantation in remission and 38 patients who received transplantation in relapse.

Aversa F et al. JCO 2005;23:3447-3454
Cumulative incidence of leukemia relapse at 2 years for patients with acute lymphoblastic leukemia (ALL; A) or acute myeloid leukemia (AML; B) who were in either hematologic remission (CR; solid lines) or relapse (REL; dotted lines).

Aversa F et al. JCO 2005;23:3447-3454
Cumulative incidence of transplant-related deaths at 2 years for patients with acute lymphoblastic leukemia (ALL; A) or acute myeloid leukemia (AML; B) who were in either hematologic remission (solid lines) or relapse (dotted lines) at transplantation.

Aversa F et al. JCO 2005;23:3447-3454
Cyclophosphamide-induced tolerance

T-cell activation

- Alloreactive T cells
  - Peptide-MHC
  - CD80/CD86
  - CD28
  - CD40
  - CD40L
  - T cell

- Dendritic cell

T-cell proliferation

- Activated effector T cell
  - IL-2

Cy day +3

- Proliferating ALLOREACTIVE cells are killed
- Non-proliferating non-alloreactive cells are spared

- Anti-CMV
- Anti-HSV
PT/Cy decreases GVHD after haploidentical HCT

Only recipients of haplo grafts got PT/Cy

Haploidentical versus double cord HCT after reduced intensity conditioning
BMT CTN 0603 (haplo) and BMT CTN 0604 (double cord)

- Parallel phase II trials (n=50/trial) of alternative donor stem cell transplantation after fludarabine/200 cGy TBI-based conditioning
- Acute leukemia in CR, lymphoma
- Hypothesis: Survival at six months is >60% (CIBMTR benchmark for unrelated HCT)
- Trials conducted at 16 or 17 centers each, completed within 18 months
## Patient Characteristics

<table>
<thead>
<tr>
<th></th>
<th>CTN 0604</th>
<th>CTN 0603</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>dUCB (N=50)</td>
<td>HaploBM (N=50)</td>
</tr>
<tr>
<td><strong>Median age</strong> (range)</td>
<td>58 (16-69)</td>
<td>48 (17-70)</td>
</tr>
<tr>
<td><strong>Primary disease</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ALL</td>
<td>12%</td>
<td>12%</td>
</tr>
<tr>
<td>AML</td>
<td>58%</td>
<td>44%</td>
</tr>
<tr>
<td>Other leukemia</td>
<td>2%</td>
<td>6%</td>
</tr>
<tr>
<td>Lymphoma</td>
<td>28%</td>
<td>38%</td>
</tr>
</tbody>
</table>
Treatment Regimens

0604

- Day -6: Cy 50 mg/kg
- Day -4: Fludarabine 40 mg/m²/day
- Day -3: Double UCB Infusion
- Day -2: TBI 200 cGy
- Day -1: G-CSF
- Day 0: MMF tid
- Days 20-180: Cyclosporine

0603

- Day -6: Cy 14.5 mg/kg/day
- Day -4: Fludarabine 30 mg/m²/day
- Day -3: Bone Marrow Infusion
- Day -2: TBI 200 cGy
- Day -1: G-CSF
- Day 0: MMF tid
- Days 5-180: Tacrolimus
Graft-versus-host disease

Cumulative incidence (%)

Cord (0604)

Acute GVHD

Chronic GVHD

Haplo (0603)

Days after transplantation

Months after transplantation

28%

26%

40%

21%

32%

28%

26%
BMT CTN 0603/0604

Non-relapse mortality and relapse

Non-relapse mortality

Relapse

Cumulative Incidence, %

Months Post Transplant

Non-relapse mortality

cord 28%
haplo 8%

Relapse

50% 52% 58%
haplo

36% 34% 32%
cord
BMT CTN 0603/0604: Survival

Overall survival

- **haplo**: 35%
- **cord**: 36%

Progression-free survival

- **haplo**: 40%
- **cord**: 36%
The results of BMT CTN 0603 and 0604 establish which of the following?

A. Non-relapse mortality is higher after cord blood than after haplo HCT
B. Relapse is higher after haplo than after cord blood HCT
C. Progression-free survival after cord blood or haploHCT is not significantly different
D. All of the above
E. None of the above

Answer: “E” (none of the above). Results from parallel phase II trials cannot be compared statistically.
The results of BMT CTN 0603 and 0604 provide equipoise for a randomized phase III clinical trial with progression-free survival as the primary endpoint.

BMT CTN 1101 Hypothesis: Two year PFS is similar after related haplo-BM donor transplantation or after dUCB transplantation.
BMT CTN 1101: Study Endpoints

**Primary**
- Progression-free survival at 2 yrs

**Secondary**
- Engraftment
- GVHD
- Relapse
- TRM
- Quality of Life
- Cost Effectiveness
- Immune reconstitution (planned)

Sample size: n=410 patients over 4 years (approximately 8/month)
Patient ≥ 18 and ≤70 yrs.
Acute leukemia or lymphoma
Available both
1) 4-6/6 HLA-matched
   UCB units
2) 4-6/8 HLA matched
   related donor

Randomization
Stratified by Transplant Center

Adequate organ function
Performance score ≥70

Double UCB

Haplo-BM
BMT CTN 1101
Ancillary and co-acccruing studies

- Cost-effectiveness analysis (R01-HL116291, PI: Scott Ramsey)
- Easy to read informed consent (ETRIC; BMT CTN 1205)
- PBMCs collected (pre-BMT, d28, d56, d180, d365) and stored for analysis of immune reconstitution
BMT CTN 1101

Eligibility

- Age 18-70
- Diagnoses:
  - Acute leukemia, not good risk, in CR
  - Relapsed, chemosensitive Hodgkin, large cell, or mantle cell lymphoma (not eligible for autoSCT)
  - Follicular or marginal zone lymphoma, relapsed after at least two prior regimens
- No matched sibs and BOTH GRAFT SOURCES AVAILABLE
BMT CTN 1101: Accrual (as of 9/14/14)

- Trial opened June 19, 2012
- 35 centers activated
- 5 centers pending activation
- German cooperative group DKMS joining in early 2015
- 114 patients accrued; total target is 410
1101 Will Not Answer All Questions

- Restricted to reduced intensity conditioning in adults
- Diverse diseases with little power to discern disease-specific efficacy differences
- Comparison only to double cord transplants
GS14-01 Comparison of Haplo and HLA-Matched Unrelated Donor HCT in AML

- 1982 MUDs; 192 haplos
- AML, all stages
- Age 21-70 years
- 2008-2012, US and a single Italian center
- Post-tx Cy for GVHD prophylaxis in haplos
- Variety of GVHD prophylaxis regimens in unrelated donor HCTs
- Primary outcome: 2 year survival (all surviving patients censored at 2 years)
## Patient Characteristics - Myeloablative

<table>
<thead>
<tr>
<th></th>
<th>Haplo (N=104)</th>
<th>Unrelated (N=1245)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Centers</strong></td>
<td>7</td>
<td>101</td>
</tr>
<tr>
<td><strong>Median age</strong></td>
<td>47 y</td>
<td>47 y</td>
</tr>
<tr>
<td><strong>Sorror Index</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>33%</td>
<td>32%</td>
</tr>
<tr>
<td>1</td>
<td>24%</td>
<td>23%</td>
</tr>
<tr>
<td>2</td>
<td>11%</td>
<td>23%</td>
</tr>
<tr>
<td>3</td>
<td>4%</td>
<td>22%</td>
</tr>
<tr>
<td>Unknown</td>
<td>29%</td>
<td>&lt;1%</td>
</tr>
<tr>
<td><strong>Disease status</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CR1</td>
<td>46%</td>
<td>55%</td>
</tr>
<tr>
<td>CR2+</td>
<td>20%</td>
<td>20%</td>
</tr>
<tr>
<td>Not in CR</td>
<td>34%</td>
<td>25%</td>
</tr>
<tr>
<td><strong>Year of HCT</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2009</td>
<td>11%</td>
<td>23%</td>
</tr>
<tr>
<td>2010</td>
<td>13%</td>
<td>24%</td>
</tr>
<tr>
<td>2011</td>
<td>35%</td>
<td>29%</td>
</tr>
<tr>
<td>2012</td>
<td>41%</td>
<td>25%</td>
</tr>
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NS = Not significant, <.001 = Significant at p < .001
## Patient Characteristics – Reduced Intensity

<table>
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<th>Haplo (N=104)</th>
<th>Unrelated (N=1245)</th>
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</thead>
<tbody>
<tr>
<td><strong>Centers</strong></td>
<td>17</td>
<td>82</td>
</tr>
<tr>
<td><strong>Median age</strong></td>
<td>55 y</td>
<td>62 y &lt;.001</td>
</tr>
<tr>
<td><strong>Sorror Index</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>27%</td>
<td>30% &lt;NS</td>
</tr>
<tr>
<td>1</td>
<td>25%</td>
<td>23%</td>
</tr>
<tr>
<td>2</td>
<td>17%</td>
<td>21%</td>
</tr>
<tr>
<td>3</td>
<td>31%</td>
<td>27%</td>
</tr>
<tr>
<td><strong>Disease status</strong></td>
<td></td>
<td>NS</td>
</tr>
<tr>
<td>CR1</td>
<td>49%</td>
<td>61%</td>
</tr>
<tr>
<td>CR2+</td>
<td>35%</td>
<td>17%</td>
</tr>
<tr>
<td>Not in CR</td>
<td>16%</td>
<td>22%</td>
</tr>
<tr>
<td><strong>Year of HCT</strong></td>
<td></td>
<td>NS</td>
</tr>
<tr>
<td>2008</td>
<td>13%</td>
<td>16%</td>
</tr>
<tr>
<td>2009</td>
<td>20%</td>
<td>18%</td>
</tr>
<tr>
<td>2010</td>
<td>22%</td>
<td>21%</td>
</tr>
<tr>
<td>2011</td>
<td>20%</td>
<td>23%</td>
</tr>
<tr>
<td>2012</td>
<td>25%</td>
<td>22%</td>
</tr>
</tbody>
</table>
Myeloablative Conditioning

Treatment-related Mortality

Relapse

Disease-free Survival

Survival

Adjusted Cumulative Incidence, %

Adjusted Probability, %

Years

0 1 2

0 20 40 60 80 100

0 2

0 1 2

0 20 40 60 80 100

PT-CY (n=104)
MUD (n=1245)
PT-CY (n=104)
MUD (n=1245)
PT-CY (n=104)
MUD (n=1245)
PT-CY (n=104)
MUD (n=1245)
What Do We Know?

• Haploidentical HCT can be performed with low GVHD and low early TRM and acceptable 2-3 year overall mortality

• Haploidentical HCT is increasingly used, predominantly for patients who do not have an HLA-matched adult donor
What Don’t We Know?

• The long-term outcome of haploidentical HCT, particularly long-term disease control
• Differences in efficacy by specific blood cancer
• Outcomes in children or non-malignant disease
• Optimal graft type (PB or BM) or preparative regimen
• Relative efficacy compared to other donor sources (all studies to date underpowered to detect 10-15% differences in outcome)
Conclusions

• Haploidentical HCT is a valid option in patients without an HLA-identical adult donors but there are insufficient data to recommend it over umbilical cord blood or HLA-mismatched unrelated donor HCTs.

• Given the level of uncertainty regarding the optimal “alternative donor”, participation in clinical trials in should be encouraged.
What’s Missing? Other Types of Donors

- Twin
- 0-1 Mism Rel
- Related Cord

![Graph showing the trend of different types of donors from 2010 to 2013.](chart.png)