3rd Annual ASBMT Regional Conference for NPs, PAs and Fellows

Haplo vs Cord vs URD Debate

Claudio G. Brunstein
Associate Professor
University of Minnesota Medical School
Take home message

“Finding a donor should rarely be a barrier to a patient to proceed to a potentially curative hematopoietic cell transplant.”
Definitions

• Donor types are:
  – Matched and mismatched siblings
  – Matched and mismatched unrelated
  – Umbilical cord blood, related and unrelated
  – Partially matched related (Haploidentical)

• Cell sources are
  – Bone marrow
  – Peripheral blood
  – Umbilical cord blood
Prospective randomized phase 3 data demonstrate similar survival for peripheral blood and bone marrow transplantation.
What is the ideal donor type for allogeneic HCT?

• Always engrafts
• Causes no GVHD
• Provides immune reconstitution
• Potent GVL
• Minimally affects survival

Human Leukocyte Antigen System
Chromosome 6
Immunogenetics

HLA Complex

Chromosome 6

Long arm

Short arm

HLA region

Class II

DP

DQ

DR

Class I

B

C

A
Kelsey Besse 1, Martin Maiers 1,2, Dennis Confer 1,2, Mark Albrecht 1,*

1 Bioinformatics Research, National Marrow Donor Program, Minneapolis, Minnesota
2 Center for International Blood and Marrow Transplant Research, Minneapolis, Minnesota
Age-Related Clonal Hematopoiesis Associated with Adverse Outcomes

Siddhartha Jaiswal, M.D., Ph.D., Pierre Fontanillas, Ph.D., Jason Flannick, Ph.D.,
Alisa Manning, Ph.D., Peter V. Grauman, B.A., Brenton G. Mar, M.D., Ph.D.,
R. Coleman Lindsay, M.D., Ph.D., Craig H. Merrel, M.D., Ph.D., Noel Burtt, B.S.,
Alejandro Chavez, M.D., Ph.D., John M. Higgins, M.D., Vladislav Molchanov, Ph.D.,
Frank C. Kuo, M.D., Ph.D., Michael J. Kluk, M.D., Ph.D., Brian Henderson, M.D.,
Leena Kinnunen M.Sc., Heikki A. Koistinen, M.D., Ph.D., Claes Ladenvall, Ph.D.,
Gud Getz, Ph.D., Adolfo Correa, M.D., Ph.D., Benjamin F. Banahan, Ph.D.,
Stacey Gabrieli, Ph.D., Sekar Kathiresan, M.D., Heather M. Stringham, Ph.D.,
Mark I. McCarthy, M.D.,* Michael Boehrke, Ph.D.,* Jaakko Tuomilehto, M.D., Ph.D.,
Christopher Haiman, Sc.D., Leif Groop, M.D., Ph.D., Gil Atzmon, Ph.D.,
James G. Wilson, M.D., Donna Neuberg, Sc.D., David Altshuler, M.D., Ph.D.,* and
Benjamin L. Ebert, M.D., Ph.D.†

<table>
<thead>
<tr>
<th>Age (yr)</th>
<th>Frequency</th>
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</table>

No. with Mutation | Total
-----------------|------
0                | 240  
1                | 855  
50               | 2894 
138              | 5441 
282              | 5002 
219              | 2300 
37               | 317  
14               | 86   
5                | 17   

*Department of Medicine, Massachusetts General Hospital, Boston, Massachusetts
†Department of Medicine, Massachusetts General Hospital, Boston, Massachusetts
# HLA Match Likelihoods for Hematopoietic Stem-Cell Grafts in the U.S. Registry

Loren Gragert, B.S., B.A., Mary Eapen, M.B., B.S., Eric Williams, Ph.D., John Freeman, B.S., Stephen Spellman, M.B.S., Robert Baitty, M.P.P., Robert Hartzman, M.D., J. Douglas Rizzo, M.D., Mary Horowitz, M.D., Dennis Confer, M.D., and Martin Maiers, B.A.

## Table 2. Adult-Donor Availability in 2010, According to Broad Racial and Ethnic Category.

<table>
<thead>
<tr>
<th>Racial and Ethnic Category</th>
<th>Confirmatory Typing Available</th>
<th>Typing Not Discrepant</th>
<th>Workup Available</th>
<th>Available Overall</th>
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<tbody>
<tr>
<td>White</td>
<td>62</td>
<td>98</td>
<td>83</td>
<td>51</td>
</tr>
<tr>
<td>Black</td>
<td>36</td>
<td>95</td>
<td>69</td>
<td>23</td>
</tr>
<tr>
<td>Asian or Pacific Islander</td>
<td>42</td>
<td>97</td>
<td>73</td>
<td>29</td>
</tr>
<tr>
<td>Hispanic</td>
<td>44</td>
<td>96</td>
<td>68</td>
<td>29</td>
</tr>
<tr>
<td>Native American</td>
<td>45</td>
<td>98</td>
<td>63</td>
<td>28</td>
</tr>
</tbody>
</table>

\(^a\) percentage of donors
The effect of donor characteristics on survival after unrelated donor transplantation for hematologic malignancy


Donor Age in 10 year increments, RR 1.055 (1.013-10.99), p=0.01
Matching Likelihoods According to Racial and Ethnic Groups

Search strategy: 8/8 URD → 7/8 URD → cord blood

Registry studies demonstrate similar outcomes for all donor types
HCT Donor Transplantation

• Each donor type has pros and cons

• Choice of donor is based on availability and institutional preference

• There is no adequate prospective data to support one donor type over the other

• Institutional practice is influenced by previous experience and research interests

• Technological and supportive care improvements over the years have improved allogeneic HCT transplantation in general
The “Silver” Standard
Unrelated Adult Donors

Pros
• 25 million of volunteers in the registries
• Obtaining adequate graft is the rule
• Low risk of graft rejection
• Additional progenitor and/or immune cells potentially available
The “silver” standard
Unrelated Adult Donors

Cons

• Donor choice limited by HLA-matching
  • Minorities poorly represented
• Donor may not available 30-60% of the time
• Higher risk of graft-vs.-host disease
  • In particular if mismatched
Registry studies have established current standard of unrelated adult donor selection

High-resolution donor-recipient HLA matching contributes to the success of unrelated donor marrow transplantation

Stephanie J. Lee,1 John Klein,2 Michael Haagenson,3 Lee Ann Baxter-Lowe,4 Dennis L. Confer,5 Mary Eapen,2 Marcelo Fernandez-Vina,6 Neal Flomenberg,7 Mary Horowitz,2 Carolyn K. Hurley,8 Harriet Noreen,9 Machteld Oudshoorn,10 Effie Petersdorf,1 Michelle Setterholm,5 Stephen Spellman,5 Daniel Weisdorf,11 Thomas M. Williams,12 and Claudio Anasetti13

Blood 2007

HLA-C Antigen Mismatch Is Associated with Worse Outcome in Unrelated Donor Peripheral Blood Stem Cell Transplantation

Ann Woolfrey,1 John P. Klein,2 Michael Haagenson,3 Stephen Spellman,4 Effie Petersdorf,1 Machteld Oudshoorn,5 James Gajewski,6 Gregory A. Hale,7 John Horan,8 Minoo Battiwalla,9 Susana R. Marino,10 Michelle Setterholm,4 Olle Ringden,11 Carolyn Hurley,12 Neal Flomenberg,13 Claudio Anasetti,14 Marcelo Fernandez-Vina,15 Stephanie J. Lee1

BBMT 2011
Registry studies have established current standard of unrelated adult donor selection

Bone Marrow
- 3,800 patients patient donor pairs
- Acute leukemia, MDS and CML
- Myeloablative only
- Younger fit patients

Peripheral Blood
- 1933 patient-donor pairs
- Very few CML, Acute leukemia and Lymphomas
- Reduced intensity
- Older patients
Any Single Antigen or Allele Mismatch Adversely Impacts Outcomes Unrelated Donor Bone Marrow Transplant

<table>
<thead>
<tr>
<th>Outcome</th>
<th>8/8</th>
<th>7/8</th>
<th>6/8</th>
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<tr>
<td>5 yr survival (%)</td>
<td>37</td>
<td>29</td>
<td>22</td>
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<tr>
<td>TRM (%)</td>
<td>36</td>
<td>45</td>
<td>55</td>
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<tr>
<td>Relapse (%)</td>
<td>18</td>
<td>16</td>
<td>15</td>
</tr>
<tr>
<td>Chronic GVHD</td>
<td>44</td>
<td>36</td>
<td>32</td>
</tr>
<tr>
<td>Acute GVHD</td>
<td>28</td>
<td>37</td>
<td>44</td>
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<tr>
<td>Graft Failure</td>
<td>10</td>
<td>13</td>
<td>17</td>
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</table>

Lee et al Blood 2007
Definition of HLA-Mismatch Direction

Host vs. Graft: increases risk of rejection

Graft vs. Host: increases risk of GVHD

Bidirectional: increases risk of both
It seems that not HLA-mismatches are the same

<table>
<thead>
<tr>
<th></th>
<th>Survival</th>
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<tr>
<td></td>
<td>n*</td>
<td>RR</td>
<td>95% CI</td>
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<tr>
<td>Matched</td>
<td>1840</td>
<td>1.00</td>
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<tr>
<td>HLA-A</td>
<td></td>
<td></td>
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<tr>
<td>Allele</td>
<td>113</td>
<td>1.50</td>
<td>1.20-1.88</td>
</tr>
<tr>
<td>Antigen</td>
<td>161</td>
<td>1.24</td>
<td>1.02-1.52</td>
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<tr>
<td>Allele vs antigen</td>
<td>—</td>
<td>0.83</td>
<td>0.62-1.10</td>
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<tr>
<td>HLA-B</td>
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<td></td>
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<tr>
<td>Allele</td>
<td>99</td>
<td>1.25</td>
<td>0.97-1.60</td>
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<tr>
<td>Antigen</td>
<td>17</td>
<td>0.78</td>
<td>0.42-1.45</td>
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<tr>
<td>Allele vs antigen</td>
<td>—</td>
<td>0.62</td>
<td>0.32-1.21</td>
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<tr>
<td>HLA-C</td>
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<tr>
<td>Allele</td>
<td>96</td>
<td>1.03</td>
<td>0.79-1.34</td>
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<tr>
<td>Antigen</td>
<td>382</td>
<td>1.22</td>
<td>1.06-1.39</td>
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<tr>
<td>Allele vs antigen</td>
<td>—</td>
<td>1.18</td>
<td>0.89-1.57</td>
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<td>HLA-DRB1</td>
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<tr>
<td>Allele</td>
<td>104</td>
<td>1.42</td>
<td>1.13-1.80</td>
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<tr>
<td>Antigen</td>
<td>13</td>
<td>1.81</td>
<td>0.96-3.41</td>
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<tr>
<td>Allele vs antigen</td>
<td>—</td>
<td>1.27</td>
<td>0.64-2.48</td>
</tr>
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</table>

Lee et al Blood 2007
The permissive HLA-mismatch concept

Nonpermissive HLA-DPB1 mismatch increases mortality after myeloablative unrelated allogeneic hematopoietic cell transplantation

Joseph Pidala,1 Stephanie J. Lee,2 Kwang Woo Ahn,3 Stephen Spellman,4 Hai-Lin Wang,3 Mahmoud Aljurf,5 Medhat Askar,6 Jason Dehn,7 Marcelo Fernandez Viña,8 Alois Gratwohl,9 Vikas Gupta,10 Rabi Hanna,6 Mary M. Horowitz,3 Carolyn K. Hurley,11 Yoshihiro Inamoto,2 Adetola A. Kassim,12 Taiga Nishihori,1 Carlheinz Mueller,13 Machteld Oudshoorn,14 Effie W. Petersdorf,2 Vinod Prasad,15 James Robinson,16,17 Wael Saber,3 Kirk R. Schultz,18 Bronwen Shaw,16,17,19 Jan Storek,20 William A. Wood,21 Ann E. Woolfrey,2 and Claudio Anasetti1

- The recognition of a mismatch depends on the antigen recognition site.
- Certain DNA sequence substitutions do not change the antigen recognition.
- Thus, they are well tolerated or permissive

High HLA-DP Expression and Graft-versus-Host Disease

Effie W. Petersdorf, M.D., Mari Malkki, Ph.D., Colm O’hUigin, Ph.D., Mary Carrington, Ph.D., Ted Gooley, Ph.D., Michael D. Haagenson, M.S., Mary M. Horowitz, M.D., Stephen R. Spellman, M.B.S., Tao Wang, Ph.D., and Philip Stevenson, M.S.
Haploidentical Related Donors

Pros

• Almost everyone has at least one
• Rapidly available and motivated donors
• Additional progenitor and/or immune cells potentially available
• May favor NK cell alloreactivity
Haploidentical Related Donors

Cons

• Requires in vitro or in vivo T cell depletion
• High risk of infections and relapse
• Delayed immune reconstitution
There are multiple haploidentical related donors platforms

- Unmodified BM or PB
  - Post-transplant cyclophosphamide
  - Very intensive immuno suppression
- Mega CD34+ cell dose
- Depletion of αβ T cells
Haploidentical transplants favor the expansion of NK cells potentiating the graft-vs.-leukemia effect

Ruggeri et al Blood 2007
Unmodified Graft Haploidentical Transplantation with Post-Transplant Cyclophosphamide

Luznik, Fuchs, and Jones
Haploidentical transplantation with post-transplant cyclophosphamide results in low incidence of acute and chronic GVHD

*Supported by Pfizer*
The trade off between low non-relapse mortality and high rate of relapse results in promising survival.
Haploidentical transplant with posttransplant cyclophosphamide vs matched unrelated donor transplant for acute myeloid leukemia

Stefan O. Ciurea,1 Mei-Jie Zhang,2,3 Andrea A. Bacigalupo,4 Asad Bashey,5 Frederick R. Appelbaum,6 Omar S. Aljitawi,7 Philippe Armand,8 Joseph H. Antin,6 Junfang Chen,2 Steven M. Devine,9 Daniel H. Fowler,10 Leo Luznik,11 Ryotaro Nakamura,12 Paul V. O'Donnell,6 Miguel-Angel Perales,13 Sai Ravi Pingali,1 David L. Porter,14 Marce R. Richos,15 Olle T. H. Ringdén,16 Vanderson Rocha,17 Ravi Vij,18 Daniel J. Weisdorf,10 Richard E. Champlin,1 Mary M. Horowitz,2 Ephraim J. Fuchs,11 and Mary Eapen2

Reduced Intensity Myeloablative

- Unrelated donor 20% (18-22)
- Haploidentical donor 14% (8-22)

Cumulative incidence, %

Years

Unrelated donor 23% (19-26)
- Haploidentical donor 9% (4-16)

Cumulative incidence, %

Years

Unrelated donor 46% (35-56)
- Haploidentical donor 46% (35-56)

Probability, %

Years

Unrelated donor 44% (40-47)
Risk-stratified outcomes of nonmyeloablative HLA-haploidentical BMT with high-dose posttransplantation cyclophosphamide


Progression-Free Survival

Relapse

Blood. 2015;125(19):3024-3031
Mismatched Umbilical Cord Blood

Pros
- UCB units are rapidly available
- HLA matching is less frequently a barrier to finding a donor
- Risk of acute and chronic GVHD is low in the presence of HLA mismatch
- Low risk of infection transmission
- No risk for the donor
Mismatched Umbilical Cord Blood

Cons

• Delayed engraftment with higher risk of early non-relapse mortality
• No donor lymphocytes for treatment of relapse or low chimerism
• Fixed cell dose
• Elevated cost of procurement
Refining Cord Blood Selection

- **Cryopreserved nucleated cell dose** $2.5-3.0 \times 10^7$/kg
- **HLA DRB1 at allele level**
- **HLA A and B at antigen level**

- **CD34 cell dose** (Sanz et al BBMT 2010;16:86)
- **High resolution HLA matching** (Eapen et al Blood 2014;123:133)
- **Matching at HLA-C** (Eapen et al Lancet Oncol 2011;12:1214)
- **Anti-HLA antibodies** (Cutler et al Blood 2011;118:6691)
- **Red cell depleted** (Ballen et al. BBMT 2015;21:688)
- **Experience with the cord blood bank** (center dependent)
- **Direction of mismatch** (Stevens et al. Blood 2011;118:3969)
- **Kir-ligand matching** (Willenze et al. Leukemia 2009;23:492)
- **Non-inherited maternal allele (NIMA)** (van Rood et al. PNAS 2009;106:19952)
- **Licensed vs. unlicensed cord blood** (no data available)
In cord blood transplant the cell dose of the graft is critical for the outcomes

- In children, a single adequately dosed cord blood unit is often available
- In adults, a single adequately dosed cord blood unit is rarely available
- Thus, the double cord blood strategy was used to extend cord blood transplantation to adults
Single vs. Double

Children

- Single-unit group at month 12: 73% (95% CI, 63–80)
- Double-unit group at month 12: 65% (95% CI, 56–74)

Adults

- Double UCB transplant
- Single UCB unit transplant

Wagner et. al. NEJM 2014

Scaradavou et. al. Blood 2013
# The Art of Graft Selection in Cord Blood Transplantation

## Single vs Double

<table>
<thead>
<tr>
<th>Number CB units</th>
<th>Positive</th>
<th>Negative</th>
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<tr>
<td>Anti-HLA antibodies</td>
<td>Cutler et al Blood 2011</td>
<td>Brunstein et al BBMT 2011</td>
</tr>
<tr>
<td>Kerlingand Match</td>
<td>Wilenze et al Leukemia 2009</td>
<td>Brunstein et al Blood 2009</td>
</tr>
<tr>
<td>Matching HLA-C</td>
<td>Eapen et al Lancet Oncol 2011</td>
<td>However,...</td>
</tr>
<tr>
<td></td>
<td>Brunstein et al In the works</td>
<td></td>
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</table>
Impact of Allele-Level HLA Mismatch on Outcomes in Recipients of Double Umbilical Cord Blood Transplantation

Claudio G. Brunstein, Ette W. Petersdorf, Todd E. Defor, Harriet Noreen, David Maurer, Margaret L. MacMillan, Celalettin Ustun, Michael R. Verneris, Jeffrey S. Miller, Bruce R. Blazar, Philip B. McGlave, Daniel J. Weisdorf, John E. Wagner

Relapse acute leukemia by conventional HLA

```
P=0.14
5/6
4/6

Cumulative Incidence
0 1 2 3 4 5
Years Post Transplant
```

Relapse acute leukemia by allele level HLA

```
P=0.03
9-10/10
6-8/10
2-5/10

Cumulative Incidence
0 1 2 3 4 5
Years Post Transplant
```

DFS of acute leukemia by conventional HLA

```
P=0.27
4/6
5/6
6/6

Cumulative Proportion
0 1 2 3 4 5
Years Post Transplant
```

DFS of acute leukemia by allele level HLA

```
P=0.06
2-5/10
6-8/10
9-10/10

Cumulative Proportion
0 1 2 3 4 5
Years Post Transplant
```
Cord-Blood Transplantation in Patients with Minimal Residual Disease

Filippo Milano, M.D., Ph.D., Ted Gooley, Ph.D., Brent Wood, M.D., Ann Woolfrey, M.D., Mary E. Flowers, M.D., Kristine Doney, M.D., Robert Witherspoon, M.D., Marco Mielcarek, M.D., Joachim H. Deeg, M.D., Mohamed Sorror, M.D., Ann Dahlberg, M.D., Brenda M. Sandmaier, M.D., Rachel Salit, M.D., Effie Petersdorf, M.D., Frederick R. Appelbaum, M.D., and Colleen Delaney, M.D.

P = 0.08 for comparison of HLA-matched vs. cord blood
P = 0.001 for comparison of HLA-mismatched vs. cord blood

P = 0.007 for comparison of HLA-matched vs. cord blood
P = 0.02 for comparison of HLA-mismatched vs. cord blood
Cord blood recipients who take longer to recover neutrophils have higher non-relapse mortality

P = 0.04

Days ≥ 26: 35%
Days < 26: 19%
Novel strategies such as SR1 expansion accelerate neutrophil recovery and can potentially reduce risk of non-relapse mortality

- Cord blood cell dose directly correlates with speed of neutrophil recovery
- The cell dose in cord blood units is fixed
- Novel methods allow us to grow more stem cells from a single cord blood unit
- More stem cells shorten time to neutrophil recovery
Finding a Donor

- Patient evaluated for Allogeneic Transplant
  - Suitable Matched Sibling Donor?
    - Go to Transplant
    - Start Unrelated Donor and UCB Search
      - 7-8/8 URD Donor within 8 weeks
      - UCB
    - Haploidentical Sibling Donor
    - Suitable Biological Parent or Child
      - Haploidentical Related Donor
        - Go to Transplant
Conclusions

• Alternative donors are valuable alternatives to sibling donors and can bridge the gap in donor availability
• Today we can find a donor, if not for every, for almost every patient
• At this point, the choice of alternative donor type to be used is driven by donor availability, urgency of transplantation and transplant center experience and research priorities
• In the future, donor type choice will hopefully be driven by prospective randomized data
BMT CTN Protocol 1101

Multi-center, Phase III, Randomized Trial of Reduced Intensity Conditioning and Transplantation Of Double Unrelated Umbilical Cord Blood versus HLA-Haploidentical Related Bone Marrow for Patients with Hematologic Malignancies