Evaluating the role of mismatched unrelated donor transplantation

Stephen Spellman
CRP/DM Conference 2021
Conflict of Interest Disclosure

• Mr. Spellman has no conflicts to disclose
Selection of unrelated donors and cord blood units for hematopoietic cell transplantation: guidelines from the NMDP/CIBMTR

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2003 (Hurley, BBMT), 2008 (Bray, BBMT), 2012 (Spellman, Blood)
<table>
<thead>
<tr>
<th></th>
<th>Multiple HLA-A, HLA-B, HLA-C, and HLA-DRB1 (8/8) HLA matched unrelated donors available</th>
<th>8/8 match unavailable; multiple 7/8 unrelated donors available</th>
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<tbody>
<tr>
<td>1.</td>
<td>Resolution of typing HLA-A, HLA-B, HLA-C, and HLA-DRB1</td>
<td>High-resolution matches for ARDs for 7 matched alleles;</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Select HLA-C<em>03:03 vs C</em>03:04 mismatch, if present;</td>
</tr>
<tr>
<td></td>
<td></td>
<td>No other preference for mismatched loci (HLA-A/B/ C/DRB1) or other allele combinations</td>
</tr>
<tr>
<td>2.</td>
<td>Donor age</td>
<td>Select donors of younger age</td>
</tr>
<tr>
<td>3.</td>
<td>Permissive mismatching HLA-DPB1</td>
<td>Select matched/permissive DPB1 mismatch based on the algorithm developed by Crivello et al <a href="http://www.ebi.ac.uk/cgi-bin/ipd/imgt/hla/dpb_v2.cgi">66,70</a></td>
</tr>
<tr>
<td>4.</td>
<td>Matching HLA-DRB3/4/5 and HLA-DQB1</td>
<td>Minimize mismatches</td>
</tr>
<tr>
<td>5.</td>
<td>Vector of mismatch</td>
<td>Select donor with single allele mismatched at patient’s homozygous locus (HLA-A/B/C/DRB1), if applicable</td>
</tr>
<tr>
<td>6.</td>
<td>DSA in patient</td>
<td>Avoid mismatches of allotypes targeted by DSAs, including DQA1 and DPA1</td>
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Impact of Donor Type on One-year mortality after HCTs done in 2016-2018

P=0.09

No significant difference

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<tr>
<th>Odds Ratio</th>
<th>Availability</th>
<th>Sib N=6467</th>
<th>8/8 MUD N=9535</th>
</tr>
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<tbody>
<tr>
<td>0.9</td>
<td>~30%</td>
<td>Blue</td>
<td>Green</td>
</tr>
<tr>
<td>0.94</td>
<td>20-70%</td>
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CIBMTR
CENTER FOR INTERNATIONAL BLOOD & MARROW TRANSPLANT RESEARCH
Likelihood of finding a match

- **8/8** – 20-70%
- **7/8** – 70-90%
HLA impact on overall survival

- 8/8 = High resolution match at HLA-A, B, C and DRB1
- 7/8 = 1 mismatched at HLA-A, B, C or DRB1

Lee et al., Blood 2007
Validated in a European cohort

Furst et al., Blood. 2013 Oct 31;122(18):3220-29
Impact of Donor Type on One-year mortality after HCTs done in 2016-2018

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<th>P-value</th>
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<tr>
<td>Sib N=6467</td>
<td>1.00</td>
<td>P=0.09</td>
</tr>
<tr>
<td>7/8 MUD N=1492</td>
<td>0.91</td>
<td></td>
</tr>
<tr>
<td>Haplo N=3999</td>
<td>0.76</td>
<td>P&lt;0.001</td>
</tr>
<tr>
<td>Multi cord N=506</td>
<td>0.53</td>
<td></td>
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8/8 MUD N=9535
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Strategies for using $\leq 7/8$ donors

• Optimizing selection
  – Permissive mismatches
  – Younger donors
  – Minimize mismatching at low expression loci (HLA-DQA/B, DPA/B, DRB3/4/5) (Fernandez-Viña Blood 2013)
  – Avoid donor specific antibodies (Spellman et al Blood 2010)

• Alternative Graft vs Host Disease prophylaxis strategies
Permissive HLA-DPB1 T cell epitope mismatches

Fleischhauer & Shaw et al, Lancet Oncology 2012
Permissive HLA-C mismatch

- C*03:03 vs C*03:04 mismatch (MM) DOES NOT elicit CTL responses (Oudshoorn, et. al. Human Immunology, 2002)

- C*03:03/03:04 is the predominant allele level MM in patients and donors with European ancestry

- 69% of HLA-C MM in Lee, et al. Blood 2007 were C*03:03/03:04
  - HLA-C allele mismatches not sig. associated with OS
Overall survival – HLA-C*03:03/03:04

Fernandez-Viña et. al. Blood 2014
**Validation: C*03:03/03:04 MM Permissive**

<table>
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<th>Matching</th>
<th>RR (95% CI)</th>
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</tr>
</thead>
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<tr>
<td>8/8 N=5447) – reference</td>
<td></td>
<td></td>
</tr>
<tr>
<td>03:03/03:04 mm (N=86)</td>
<td>1.1 (0.8-1.4)</td>
<td>0.98 (0.78-1.23)</td>
</tr>
<tr>
<td>Other C allele mm (N=74)</td>
<td>1.3 (1.0-1.8)</td>
<td>1.43 (1.06-1.92)</td>
</tr>
<tr>
<td>Other C Antigen mm (N=606)</td>
<td>1.4 (1.2-1.5)</td>
<td>1.37 (1.24-1.51)</td>
</tr>
<tr>
<td>Other non-C mm (N=1305)</td>
<td>1.2 (1.1-1.4)</td>
<td>1.30 (1.19-1.43)</td>
</tr>
</tbody>
</table>

- **Fernandez-Viña**
  - Blood 2014

- **Pidala**
  - Blood 2014

\( p<0.01 \)
Evaluation of Permissive mismatches at HLA-A, B, C and DRB1

- Cross-reactive Antigen (CREG) groups (Wade et al Blood 2007)
- HLA Matchmaker (Duquesnoy et al BBMT 2008)
- Histocheck (Spellman et al BBMT 2012)
- Supertype matching (Lazaryan et al Haematologica 2016)
- Predicted indirectly recognizable HLA epitopes (PIRCHÉ) (Spierings et al BBMT 2017)
## HLA Mismatch Algorithms - Results

<table>
<thead>
<tr>
<th>Algorithm</th>
<th>Results vs 8/8 (or 10/10)</th>
<th>Results among mismatched groups</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cross-reactive Groups (CREG) (Wade et al Blood 2007)</td>
<td>p&lt;0.001</td>
<td>p=0.47</td>
</tr>
<tr>
<td>HLA Matchmaker (Duquesnoy et al BBMT 2008)</td>
<td>p&lt;0.01</td>
<td>p=0.62</td>
</tr>
<tr>
<td>Histocheck (Spellman et al BBMT 2012)</td>
<td>p&lt;0.01</td>
<td>p=0.36</td>
</tr>
<tr>
<td>HLA Supertypes (Lazaryan et al Haem. 2016)</td>
<td>NT</td>
<td>Class I p&gt;0.1 Class II p=0.04</td>
</tr>
<tr>
<td>Predicted indirectly recognizable HLA epitopes (PIRCHÉ) (Spierings et al BBMT 2017)</td>
<td>p&lt;0.01</td>
<td>p&gt;0.8</td>
</tr>
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What about patients without a 7/8 permissive mismatch?

• New research to minimize the impact of HLA mismatches using novel agents for GVHD prophylaxis
  – Post-transplant cyclophosphamide
  – Sirolimus
  – Abatacept
  – Graft engineering
15-MMUD – PIs: B Shaw and J Bolañes-Meade (NCT02793544)

• Multi-center, single arm Phase II study to assess the safety and efficacy of MMUD (4/8 – 7/8) bone marrow transplantation using PTCy, sirolimus and MMF for GVHD prophylaxis
  – Patients with a suitable HLA matched related or URD were excluded.
  – Patients received a fresh BM graft, followed by PTCY on days +3, +4, Sirolimus/MMF starting on Day+5.
  – Regimen intensity was at the center’s discretion

• Enrolled 80 patients at 11 transplant centers in the U.S. between Dec 2016 and March 2019:
  – 40 full intensity conditioning [FIC]
  – 40 reduced intensity conditioning [RIC]
### 15MMUD - Population characteristics

<table>
<thead>
<tr>
<th></th>
<th>FIC</th>
<th>RIC</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Patient race/ethnicity</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Non-white</td>
<td>23 (58)</td>
<td>15 (37)</td>
<td>38 (48)</td>
</tr>
<tr>
<td><strong>Disease</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Acute Leukemia</td>
<td>37 (92.5)</td>
<td>21 (52.5)</td>
<td>58 (72.5)</td>
</tr>
<tr>
<td><strong>Patient age</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median (min-max)</td>
<td>48.5 (18-66)</td>
<td>59.5 (23-70)</td>
<td>51.5 (18-70)</td>
</tr>
<tr>
<td><strong>Donor age</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median (min-max)</td>
<td>27 (18-56)</td>
<td>29 (21-44)</td>
<td>29 (18-56)</td>
</tr>
<tr>
<td><strong>HLA Match</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>7/8</td>
<td>26 (65)</td>
<td>23 (58)</td>
<td>49 (61)</td>
</tr>
<tr>
<td>≤6/8</td>
<td>14 (35)</td>
<td>17 (32)</td>
<td>31 (39)</td>
</tr>
</tbody>
</table>

HIV+ patients (n=4) 100% received CCR5Δ32-/- grafts
Ethnically diverse
- 48% of participants
- Post-transplant outcomes were not significantly different across ethnicities

<7/8 match
- 40% of participants
- Post-transplant outcomes were not significantly different between 7/8 and <7/8 match

Results:
- 75% survival rate after one year
- 11% aGVHD III-IV at 100 days
- >90% engraftment
Phase II Trial of PTCy in 7/8 URD
Pl: Monzr Al Malki (NCT 03128359)

- Single center (COH) Phase II study of 7/8 URD using PTCy, tacrolimus and MMF for GVHD prophylaxis
  - Patients with a suitable HLA matched related or URD were excluded
  - Patients received a PBSC graft, followed by PTCY and Tac/MMF
  - Patient age 0-75 with hematological malignancy and an available 7/8 URD
  - Two strata:
    - MAC group (n=19) using Flu/TBI, if patient ≤60 years old
    - RIC group (n=19) using Flu/Mel, if patient >60 years old
Results of NCT 03128359

Population characteristics
- Median pt age: 53 (21-72)
- Disease risk: low (47%), intermediate (37%), and high (6%)
- CR at HCT: 76%
- Median donor age: 32 (19-53)
- Female→male: 11%

No severe cGvHD by the NIH criteria

M. Al Malki, submitted
Sirolimus combined with cyclosporine and mycophenolate mofetil as GVHD prophylaxis after nonmyeloablative conditioning with HLA class I or II antigen mismatched donors: Results from a phase II multi-center trial

Brian Kornblit, MD, PhD; Barry E. Storer, PhD; Michael B. Maris; MD, Niels Andersen, MD, DMSc; Thomas Chauncey, MD; Effie W. Petersdorf, MD; Ann E. Woolfrey, MD; Rainer Storb, MD; David G. Maloney, MD, PhD; Brenda M. Sandmaier, MD

This work was supported by NIH/NCI CA018029 and CA078902

Fred Hutch protocol 2206: donor selection

- Related or unrelated donor
- G-CSF mobilized PBSC only
- HLA matching criteria:
  - Single antigen mismatch at HLAA, B or C +/- an class I allele level mismatch.
  - Mismatched at the allele level for 2 HLA class I loci
  - Mismatched at the antigen or allele level for any HLA DRB1 and/or DQB1
Summary: HLA mismatched PBSC HCT

**Historic: CSP/MMF**

- **Grades 2-4:** 69%
- **Grades 3-4:** 26%
- **NRM:** 47%
- **Relapse:** 26%

**Current: CSP/MMF + sirolimus**

- **Grades 2-4:** 34%
- **Grades 3-4:** 3%
- **Survival:** 68%
- **Relapse:** 26%
- **NRM:** 15%
CTLA4-Ig (Abatacept) can Inhibit T cell Costimulation and Prevent T cell Activation

In Vivo T Cell Costimulation Blockade with Abatacept for Acute Graft-versus-Host Disease Prevention: A First-in-Disease Trial


Bio Blood Marrow Transplant 19 (2013) 1638–1649
Study Design of Aba2

The Phase II Abatacept For GvHD Prevention Trial: Randomization and Clinical Pathway

**8/8 HLA Match**
- 140 Patients
- Randomize Double-Blind
- GvHD Prophylaxis:
  - Calcineurin Inhibitor
  - Methotrexate (Day +1, +3, +6, +11)
  - Abatacept (10mg/kg Day -1, +5, +14, +28)

**7/8 HLA Match**
- 40 Patients
- Compared to a Pre-Specified Matched Cohort from the CIBMTR Study Design of Aba2
ABA2: Significant Decrease in AGVHD

7/8 Cohort

Grade 2-4 AGVHD

Grade 3-4 AGVHD

6 month p = 0.03

6 month p < 0.001

ABA ITT
ABA vs. Control
CIBMTR Control
Results from ABA2 Suggests that Abatacept Could Level the Playing Field For Patients With HLA-Mismatched Donors

Relapse-Free Survival

FDA Breakthrough Therapy Designation for Abatacept for the Prevention of Mod-Severe AGVHD in Unrelated-Donor Transplant

Use of mismatched URD expands donor choice

- Younger age
- Sex match
- CMV status
- ABO match

- Avoid donor specific antibodies
- CCR5 Δ32 -/-
- KIR
- Other factors
Increasing donor age impacts survival

- Donor 18-30 (n = 1923)
- Donor 31-45 (n = 3924)
- Donor 46+ (n = 1131)

p-value = 0.0002
Increasing unrelated donor age is associated with higher mortality

- 2 year survival decreased ~4% per decade of donor age

Shaw et al, BBMT, 2018
Global Unrelated Donor Registry Composition

>16M Donors ≤35 years old
Likelihood of finding a match

100%

- 8/8 – 20-70%
- 7/8 – 70-90%
- ≤7/8 – 100%
  + Cord
  + Haplo
Impact of new approaches to prevent GVHD

• Potential to transplant across HLA barriers

• Expanded donor choice – younger donors

• Faster donor selection

• A donor available for all in need
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