Non-HLA donor characteristics

Bronwen Shaw, MD PhD, CIBMTR
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Disclosures

The following faculty and planning committee staff have no financial disclosures:

<table>
<thead>
<tr>
<th>Name</th>
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<tr>
<td>Bronwen Shaw, MD PhD</td>
<td>CIBMTR</td>
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<td>Abeer Madbouly, PhD</td>
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<tr>
<td>Martin Maiers</td>
<td>NMDP/Be The Match</td>
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<tr>
<td>Michael Wright</td>
<td>NMDP/Be The Match</td>
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Learning objectives

At the conclusion of this session, attendees will be able to:

• List multiple non-HLA donor characteristics that could influence transplant outcomes

• Identify key differences between how we self-report our ancestral origin and our genetic structure

• Prioritize donor characteristics to impact transplant outcome
Beyond HLA: What non-HLA characteristics are being considered in donor selection today?

Bronwen Shaw, MD PhD
Professor of Medicine, MCW
Senior Scientific Director, CIBMTR
Introduction

• HLA matching is the key variable when selecting an URD
• The ‘gold standard’ is an 8/8 match
• Other HLA loci may be considered
• Several studies show an impact of ‘secondary donor factors’
• These are especially important when more than one 8/8 URD is available:
  – Approximately 70% of Caucasian patients searches through NMDP, Kevin Tram, personal communication, July 2017
Which donor factors are we talking about?

- Age
- CMV serostatus
- Gender
- ABO type
- Is there an algorithm/hierarchy for selection
Donor Age: Does this affect OS?

• Several studies show that a younger donor results in a better survival
• 2001 NMDP study:
  – 6978 pts, 1987-1999, BM
• Updated population:
  – 6349 pts, 1988-2006, BM/PBSC
• Validation population:
  – 4690 pts, 2007-2011, BM/PBSC
Overall survival decreased with increasing donor age. This effect was highly significant.
Proportional hazards regression models for grade III or IV acute graft-versus-host disease (GVHD) (n = 6978) and chronic GVHD (n = 4819 evaluable patients surviving at least 80 days)

<table>
<thead>
<tr>
<th>Factor</th>
<th>Grade III-IV acute GVHD</th>
<th>Chronic GVHD</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>RR</td>
<td>95% CI</td>
</tr>
<tr>
<td>Donor age (per decade)</td>
<td>1.08</td>
<td>1.03-1.14</td>
</tr>
</tbody>
</table>
Summary: Donor Age

• This matters for all outcomes and should always be considered when selecting a donor
• Consider age next in importance after HLA for OS
• Every year younger is better:
  e.g. equal HLA match pick 19 yo before 33 yo
Donor Gender: Does this affect OS?

- Three CIBMTR studies mentioned
  - NO
The cumulative incidence of chronic GVHD was higher with multiparous female donors. Results with male donors and female donors without pregnancies were similar, whereas an increasing incidence of chronic GVHD was associated with female donors with one or more pregnancies.

Craig Kollman et al. Blood 2001;98:2043-2051

©2001 by American Society of Hematology
<table>
<thead>
<tr>
<th>Non-relapse Mortality</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Male</td>
<td>1.00</td>
<td></td>
</tr>
<tr>
<td>Female, no pregnancies</td>
<td>1.02 (0.91 – 1.14)</td>
<td>0.75</td>
</tr>
<tr>
<td>Female, 1 or more pregnancies</td>
<td>1.29 (1.18 – 1.41)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Chronic GvHD</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Male</td>
<td>1.00</td>
<td></td>
</tr>
<tr>
<td>Female, no pregnancies</td>
<td>1.01 (0.91 – 1.12)</td>
<td>0.88</td>
</tr>
<tr>
<td>Female, 1 or more pregnancies</td>
<td>1.22 (1.11 – 1.34)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Relapse</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Male</td>
<td>1.00</td>
<td></td>
</tr>
<tr>
<td>Female, no pregnancies</td>
<td>0.96 (0.84 – 1.10)</td>
<td>0.57</td>
</tr>
<tr>
<td>Female, 1 or more pregnancies</td>
<td>0.84 (0.74 – 0.95)</td>
<td>0.007</td>
</tr>
</tbody>
</table>

No impact on Overall Survival
Donor Gender: Does this affect other outcomes?

Male vs Female donor

- Higher cell numbers – may be related to weight and difference between patient and donor weight*
- Higher engraftment rates
- Less primary graft failure
- No difference in acute GVHD
- Lower Chronic GVHD than females with 1 or more pregnancies
- Female donor into male recipient: Some studies show higher GVHD

* Billen, Transfusion, 2014
Summary: Donor Gender

- Does not impact survival, but may impact other outcomes
- Due to lower cell numbers and weight MIGHT prefer PBSC
- Is lower on the list of factors to consider
CMV serostatus: Does this affect OS?

- Three NMDP/CIBMTR studies mentioned
  - NO
- Other studies do show a difference
  - 8003 AL, CML, MDS: worst outcome in CMV R+/D-(Pidala, 2014)
  - Large EBMT study, 49542 showed: R+/ D+ had improved OS (HR, 0.92; 95% CI, .86-.98; P < .01) compared with R+/D- (Ljungman, 2014)
  - Anthony Nolan cohort (2016)

- Controversial results GVHD/Relapse
CMV serostatus: Does this affect OS?

A : R/D CMV M / HLA M (N=676)
B : R/D CMV MM / HLA M (N=223)
C : R/D CMV M / HLA MM (N=207)
D : R/D CMV MM / HLA MM (N=122)

p <0.0001

Years post SCT

0 1 2 3 4 5
CMV serostatus: Does this affect OS?

A : R/D CMV M / HLA M (N=676)
B : R/D CMV MM / HLA M (N=223)
C : R/D CMV M / HLA MM (N=207)
D : R/D CMV MM / HLA MM (N=122)

Years post SCT
Probabilty of survival
CMV serostatus: Does this affect OS?

Probability of Survival

Patient / Donor CMV Match (N=863)

Patient / Donor CMV Mismatch (N=331)

Years post SCT
CMV serostatus: Does this make the transplant more difficult for everyone?

- Post transplant CMV reactivation and persistent more common in R+/D- than R+/D-
  - No CMV specific T cells if D-/multiple reactivations
  - Increase morbidity with CMV treatment

Summary: Donor CMV status

- Impact may be very dependent on the type of transplantation (e.g. conditioning/T cell depletion)
- A match is better than a mismatch if possible
ABO Match: Does this affect OS?

- Kollman, 2001 and validation, 2015 CIBMTR: NO
- Second study: ~10% increase mortality with ABO mismatch
- Variable results in other studies
  - 5179, all AML or MDS, major mm = ~20% increase TRM (Luger, 2012)
  - 1679 lymphoma, minor mm = shorter OS
  - 8003 AL, CML, MDS, any mm = ~10% increased mortality (Pidala, 2014)
- Several other studies show no impact
Multivariate Analysis
- Donor-recipient ABO match -

Validation cohort: \( p = 0.43 \)

Baseline: ABO Match

Overall survival

Minor ABO MM: 1.18
Major ABO MM: 1.05

\( P < 0.001 \)

Kollman, et al.
Overall Survival
8/8 HLA-matched Transplants

Overall Survival for 8/8 HLA-matched Transplants. The graph shows the probability of survival over time for different ABO match categories:

- ABO match/18-32
- ABO match/33-50
- ABO match/>50
- ABO MM/18-32
- ABO MM/33-50
- ABO MM/>50

The p-value for the comparison is 0.02.
Overall Survival
7/8 HLA-matched Transplants

Probability, %

0 12 24 36

Months after Transplant

ABO match/18-32
ABO match/33-50
ABO match/>50
ABO MM/18-32
ABO MM/33-50
ABO MM/>50

p = 0.008

CIBMTR
**ABO Match: Does this affect other outcomes?**

Table 1. Nomenclature for ABO Mismatching Observed and Theoretical Adverse Outcomes in Allogeneic BMT Reported in Previous Studies

<table>
<thead>
<tr>
<th>ABO Mismatch</th>
<th>Donor</th>
<th>Recipient</th>
<th>Known and Postulated Consequences</th>
</tr>
</thead>
<tbody>
<tr>
<td>Minor</td>
<td>O</td>
<td>A, B or AB</td>
<td>Recipient hemolysis</td>
</tr>
<tr>
<td></td>
<td>A, B</td>
<td>AB</td>
<td>Reports of increased GVHD</td>
</tr>
<tr>
<td>Major</td>
<td>A, B or AB</td>
<td>O</td>
<td>Posttransplantation pure red blood cell aplasia</td>
</tr>
<tr>
<td></td>
<td>AB</td>
<td>A, B</td>
<td>Reports of impaired engraftment and increased GVHD</td>
</tr>
<tr>
<td>Bidirectional</td>
<td>A</td>
<td>B</td>
<td>Recipient hemolysis and red blood cell aplasia</td>
</tr>
<tr>
<td></td>
<td>B</td>
<td>A</td>
<td>Reports of reduced overall survival</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Reports of impaired engraftment and increased GVHD</td>
</tr>
</tbody>
</table>

Seebach et al, BBMT 2005
ABO Match: Does this make the transplant more difficult for everyone?

a) Major ABO incompatible

- Recipient anti-donor titer
  - ≥ 1:32
    - PBSC
      - Infuse without modification.
      - Monitor for acute hemolytic reaction
  - ≤ 1:16
    - BM
      - Infuse without modification.
      - Monitor for acute hemolytic reaction
  - BM
    - ≥ 20 ml RBC
      - RBC depletion of component, or isoagglutinin depletion of recipient.
      - Monitor for acute hemolytic reaction
  - PBSC
    - < 20 ml RBC
      - Infuse without modification.
      - Monitor for acute hemolytic reaction

b) Minor ABO incompatible

- Donor anti-recipient titer
  - ≥ 1:256
    - Plasma depletion of component
  - ≤ 1:128
    - Infuse without modification
  - Infuse without modification

Rowley, BMT 2001
Summary: non-HLA

• Not controversial: it matters for outcomes!
  – Age

• Controversial impact on OS and other outcomes – selection practice relatively consistent – even if for logistic reasons
  – CMV serostatus: match is better
  – ABO type: match is better

• May not affect outcomes – selection practice varies
  – Gender: may impact cell numbers/GvHD (parity only)

• Other considerations
  – DSA, race/ethnicity, donor weight/discrepancy
Summary

• Some factors are interdependent
  – ABO or CMV match may ‘matter’ more depending on HLA match status
  – Gender and ABO may matter more in BM vs PBSC for logistic reasons

• Unfavorable donor characteristics are often a ‘package’

• Factors may differ in different transplant settings
  – BM vs PBSC
  – TCD vs T cell replete
  – Disease stage
Is there an algorithm? My thoughts

• First tier (survival benefit repeatedly shown):
  – 8/8 HLA match
Is there an algorithm? My thoughts

• First tier (survival benefit repeatedly shown):
  – 8/8 HLA match

• Second tier (survival benefit repeatedly shown):
  – Donor age = linear effect (younger is better)
Is there an algorithm? My thoughts

- First tier (survival benefit repeatedly shown):
  - 8/8 HLA match
- Second tier (survival benefit repeatedly shown):
  - Donor age = linear effect (younger is better)
- Third tier (survival benefit inconsistent):
  - DPB1 TCE permissive/match
  - CMV
  - ABO
  - Males or non-parous females
Is there an algorithm? My thoughts

- First tier (survival benefit repeatedly shown):
  - 8/8 HLA match
- Second tier (survival benefit repeatedly shown):
  - Donor age = linear effect (younger is better)
- Third tier (survival benefit inconsistent):
  - DPB1 TCE permissive/match
  - CMV
  - ABO
  - Males or non-parous females
- Fourth tier (survival benefit not shown)
  - Gender
  - DQB1
Is there an algorithm? My thoughts

• First tier (survival benefit repeatedly shown):
  – 8/8 HLA match
• Second tier (survival benefit repeatedly shown):
  – Donor age = linear effect (younger is better)
• Third tier (survival benefit inconsistent):
  – DPB1 TCE permissive/match
  – CMV
  – ABO
  – Males or non-parous females
• Fourth tier (survival benefit not shown)
  – Gender
  – DQB1
• TRUMPS
  – DSA/Clinical trial
Effect of Genetic Ancestry on HSCT Outcome

Abeer Madbouly, PhD

Senior Bioinformatics Scientist
Bioinformatics Research, CIBMTR
Race and HCT outcomes

Figure 1. Probability of OS by race.

Baker et al, BBMT 2009

Ustun et al, Leukemia & Lymphoma 2013
Race and HCT

Does race influence HCT outcome? **Yes**

Does race matching influence HCT outcome? **We don’t know**
HapLogic® starts by searching potentially matched donors of the same race group as the patient.

- The odds are higher to find a match within the same race group as the patient.
- We have more European Caucasian donors. HLA-matched/race-mismatched transplants often happen.
- Prior studies addressed racial disparities in HLA matched HCT outcome.
- No studies to date analyzed disparities due to genetically defined ancestral groups.
Investigating the Association of Genetic Admixture and Donor/Recipient Genetic Disparity with Transplant Outcomes

Abeer Madbouly 1,4, Tao Wang 2, Michael Haagenson 3, Vanja Paunic 1, Cynthia Vierra-Green 3, Katharina Fleischhauer 4, Katharine C. Hsu 2, Michael R. Verneris 6, Navneet S. Majhail 7, Stephanie J. Lee 2,8, Stephen R. Spellman 3, Martin Maiers 1

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2 Center for International Blood and Marrow Transplant Research, Medical College of Wisconsin, Milwaukee, Wisconsin
3 Center for International Blood and Marrow Transplant Research, Minneapolis, Minnesota
4 Institute for Experimental Cellular Therapy, University Hospital, Essen, Germany
5 Memorial Sloan Kettering Cancer Center, New York, New York
6 University of Colorado-Denver, Denver, Colorado
7 Cleveland Clinic, Cleveland, Ohio
8 Fred Hutchinson Cancer Research Center, Seattle, Washington
Study Objectives

• Does difference in donor/recipient genetic ancestry affect HCT outcome?

• Does recipient/donor genetic ancestry affect HCT outcomes?
Study Objectives

• Does difference in donor/recipient genetic ancestry affect HCT outcome?

• Does recipient/donor genetic ancestry affect HCT outcomes?
### Study cohort

<table>
<thead>
<tr>
<th>Variable</th>
<th>N (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of patients</td>
<td>1378</td>
</tr>
<tr>
<td>Number of centers</td>
<td>146</td>
</tr>
<tr>
<td>Age, median (range), years</td>
<td>39 (&lt;1-70)</td>
</tr>
</tbody>
</table>

**Disease at transplant**

<table>
<thead>
<tr>
<th>Disease at transplant</th>
<th>N (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>AML</td>
<td>461 (33)</td>
</tr>
<tr>
<td>ALL</td>
<td>216 (16)</td>
</tr>
<tr>
<td>CML</td>
<td>436 (32)</td>
</tr>
<tr>
<td>MDS</td>
<td>265 (19)</td>
</tr>
</tbody>
</table>

**Graft type**

<table>
<thead>
<tr>
<th>Graft type</th>
<th>N (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bone marrow</td>
<td>777 (56)</td>
</tr>
<tr>
<td>Peripheral blood</td>
<td>601 (44)</td>
</tr>
</tbody>
</table>

1378 10/10 HLA matched donor/recipient pairs
What did we study?

- We genotyped the study samples for 500 Ancestry Informative Markers (AIMs) single nucleotide polymorphisms (SNPs)
  - Genetic markers that differ in allele frequencies across different populations within or across world continents.
  - Designed to distinguish continental and/or sub-continental groups
- What does this mean?
- What does this look like?
Your genetic admixture

This is a consumer genetics example. We have the same pipeline in-house.
Does our race reflect our genetic admixture?
Clinical Results
Genetic Admixture

• Studied the following genetic admixtures for donors and recipients:
  – European (EUR)
  – African (AFR)
  – Asian (ASI)
  – South European/Amerindian (SEUR/AMER)

• *Recipient* EUR and ASI failed linearity test and were excluded
Recipient admixture – multivariate analysis

Hazard ratios and confidence intervals for recipient AFR admixture associations with HCT outcomes

- P = 0.005
- P = 0.0003
Recipient admixture

- When evaluated as a continuous variable, increasing recipient AFR admixture was associated with worse OS and TRM at p<0.01
- When tested as categorical variables, no significant associations were found
- Because of this discrepancy, we tested for a cut-point for AFR admixture.
- The optimal cut point was >14% AFR admixture
- This *risk group* included 2.8% of the study population (N=34 recipients) and 90% of the self-identified African-American recipients in the study
Recipient admixture

- Overall Survival
- Transplant Related Mortality

P-values shown for 5-year OS and TRM.

p = 0.004

p = 0.02
Donor admixture

• Similar effects were seen in the multivariate analysis when admixture was analyzed as a continuous variable but not categorical.

• We tested for a cut-point for the donor AFR admixture.

• The optimal cut point was >23% AFR admixture.

• This included 2% of the study population (N=24 donor) and 89% of the self-identified African-American donors.
Donor admixture

p – values shown for 5-year OS and TRM.

**Overall Survival**

- Donor AFR admixture < 23% (n=1229)
- Donor AFR admixture > 23% (n=24)

**Transplant related mortality**

- Donor AFR admixture ≤ 23% (n=1219)
- Donor AFR admixture > 23% (n=24)

P < 0.001
Donor admixture

Disease-Free Survival

- Donor AFR admixture ≤ 23% (n=1219)
- Donor AFR admixture > 23% (n=24)

$P < 0.001$

$p$ – value shown for 5-year DFS.
Putting it all together

• Investigated effect of genetic ancestry and donor/recipient genetic distance on HCT outcome

• No association was found between genetic distance and outcome

• Increased *recipient* AFR admixture was found to have an adverse effect on OS and TRM

• Increased *donor* AFR admixture was found to have an adverse effect on OS, DFS and TRM

Donor Genetic Driver?  Hard to tell
Race, ethnicity and genetics

• The average AFR admixture in self-identified African-Americans in the US ranges from 73% to 93% (Bryc et al., AJHG 2015)

• Admixture thresholds (>14% and >23%) in this study are cohort driven, and ARE NOT indicative of African-American race (or any other group).

• AFR admixture of >14% can exist in several Latino populations or multiethnic individuals.

• However, high-risk groups included 89% self-identified African-American individuals. This was mainly driven by the study design.
Impact on HCT - Caution

• One should be careful when considering the findings of this study in selecting 10/10 matched donors for HCT, especially if multiple 10/10 donors of different race/ethnicity are available and the recipient is of AFA race.

• While the findings are in favor of selecting a non-AFA donor, the sample size driving these findings is NOT sufficiently large to settle this issue. Further analysis is required to validate these findings.
Study limitations

• Cohort 10/10 HLA allele-matched URD transplants, therefore a small subset of individuals was of non-CAU race/ethnicity.

• A larger, more diverse sample could help validate our findings

• The 10/10 HLA allele-matched selection criteria raised the odds of race-matched donor-recipient pairs.

• Expanding the study to mismatched transplants could increase the diversity in the sample race groups and race/ethnic match patterns.
Messages

• Genetic ancestry matters
• Self-identified race is complicated and occasionally misleading
• We need to collect race information in more detailed and consistent ways
• Transplant outcomes are affected by ancestry
• More work and bigger, more diverse cohorts are needed to investigate the effect on outcomes
Acknowledgements

**NMDP**
- Martin Maiers
- Mark Albrecht
- Vanja Paunić
- Michael Heuer
- Kelsey Besse

**CIBMTR**
- Stephen Spellman
- Tao Wang
- Michael Haagenson
- Cynthia Vierra-Green
- Heather Severance

**Immunobiology WG**
- Stephanie Lee
- Katharina Fleischhauer
- Katharine Hsu
- Michael Verneris

**Cleveland Clinic**
- Navneet Majhail

Office of Naval Research: N00014-12-1-0142
Evaluation Reminder

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We appreciate your feedback!