Donor Selection and Release Criteria for Cellular Therapy Products

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Barcelona, March 6, 2014
Learning Objectives

• How to select the best HSC donor for a particular patient to achieve the best *clinical outcome* of transplantation
• How to select the best HSC donor for a particular patient for *optimal donor, product and patient safety*
• Describe the impact of donor selection by transplant physicians on future donor recruitment
• Understand the medical evaluation process for HSC donors to *ensure donor safety*
• Discuss *release criteria* for cellular therapy products once they have been collected
# Differences Between HSC and Blood Donors

<table>
<thead>
<tr>
<th></th>
<th>Blood</th>
<th>HSC</th>
</tr>
</thead>
<tbody>
<tr>
<td>Annual # of Events</td>
<td>More than 20,000,000 in the US alone</td>
<td>30,000 alloHSCT/yr worldwide</td>
</tr>
<tr>
<td>Donor → Patient</td>
<td>1:1, 1:2, 1:3 whole blood</td>
<td>Usually 1:1</td>
</tr>
<tr>
<td>Donor Testing</td>
<td>Day of Collection, strict release criteria</td>
<td>Up to 30 days prior to donation, flexible release criteria, DOC not available for release</td>
</tr>
<tr>
<td>Donor Assessment</td>
<td>HHQ, limited physical assessment</td>
<td>HHQ, complete H&amp;P, labs, EKG, CXR and extended testing possible</td>
</tr>
<tr>
<td>Matching</td>
<td>ABO/Rh +/- RBC Ag</td>
<td>HLA, ABO, KIR Only/best match</td>
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High-resolution donor-recipient HLA matching contributes to the success of unrelated donor marrow transplantation

BLOOD (2007) 110: 4576-83

Probability of Overall Survival by HLA Matching for Early Disease Stage

- 8/8 HLA Matched (n=835)
- 7/8 HLA Matched (n=379)
- 6/8 HLA Matched (n=241)

Log-rank p-value = < 0.0001
Probability of Overall Survival by HLA Matching for Intermediate Disease Stage

Log-rank p-value < 0.0001

- 8/8 HLA Matched (n=674)
- 7/8 HLA Matched (n=412)
- 6/8 HLA Matched (n=268)

Survival rates:
- 32%
- 27%
- 22%

Months after transplant
Probability of Overall Survival by HLA Matching for Advanced Disease Stage

- 8/8 HLA Matched (n=327)
- 7/8 HLA Matched (n=195)
- 6/8 HLA Matched (n=123)

Log-rank p-value = 0.02

Probability of Overall Survival by HLA Matching for Advanced Disease Stage

- 17%
- 15%
- 10%
Impact of Donor Age on Survival

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

p-value = 0.0002

Kollman 2001
Impact of Donor Age on Survival

5 yr Survival

Kollman 2013
## Impact of Donor Factors on Survival

<table>
<thead>
<tr>
<th>Donor Age</th>
<th>Hazard Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>18-32</td>
<td>1.00</td>
</tr>
<tr>
<td>32-50</td>
<td>1.13*</td>
</tr>
<tr>
<td>&gt; 50</td>
<td>1.29*</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>HLA Mismatch</th>
<th>Hazard Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>1.00</td>
</tr>
<tr>
<td>1</td>
<td>1.24*</td>
</tr>
<tr>
<td>2</td>
<td>1.62*</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>ABO Matching</th>
<th>Hazard Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>Matched</td>
<td>1.00</td>
</tr>
<tr>
<td>Minor Mismatch</td>
<td>1.10*</td>
</tr>
<tr>
<td>Major Mismatch</td>
<td>1.23*</td>
</tr>
</tbody>
</table>
Donor Sex and Parity Impact cGVHD

Cumulative Incidence

- Female Donor/2+ Pregnancies (n = 921)
- Female Donor/1 Pregnancy (n = 295)
- Female Donor/No Pregnancies (n = 779)
- Male Donor (n = 2802)

P value < 0.0001
## Age/Gender and Donor Selection 2004-2009

### Donor Age

<table>
<thead>
<tr>
<th>Donor Age</th>
<th>Marrow</th>
<th>PBSC</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>18 to 30</td>
<td>973 (36)</td>
<td>2380 (35)</td>
<td>0.100</td>
</tr>
<tr>
<td>31 to 40</td>
<td>878 (32)</td>
<td>2202 (33)</td>
<td></td>
</tr>
<tr>
<td>41 to 50</td>
<td>684 (25)</td>
<td>1616 (24)</td>
<td></td>
</tr>
<tr>
<td>51 to 61</td>
<td>191 (7)</td>
<td>570 (8)</td>
<td></td>
</tr>
<tr>
<td>Median Age</td>
<td>35</td>
<td>35</td>
<td>0.377</td>
</tr>
</tbody>
</table>

### Donor Gender

<table>
<thead>
<tr>
<th>Donor Gender</th>
<th>Marrow</th>
<th>PBSC</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male</td>
<td>1638 (60)</td>
<td>4170 (62)</td>
<td>0.168</td>
</tr>
<tr>
<td>Female</td>
<td>1088 (40)</td>
<td>2598 (38)</td>
<td></td>
</tr>
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Increasingly Focused on Adding Young Adults to the Registry

Effective October 1, 2012:

- Be the Match began concentrating efforts and resources on **adding 18 – 44 year olds** to the registry
- **Registry remains open to age 60**
  - Allowing those 45 – 60 who are interested in joining and willing to pay the ability to join
  - Individuals ages 45 – 60 **must join online**
  - $100 payment required for new members ages 45 – 60 (those already on the registry do not need to pay)
Evaluate an individual's suitability to serve as a donor of marrow and/or PBSC

Donor Safety
- Unrelated volunteer
- Risks of donation process

Recipient Safety
- Infectious or genetic disease transmission
- Product quality
Assessment Components and Steps

• At Recruitment, Preliminary, DR, HR, CT, & WU
  Donor Health History Screening Questionnaire

• At CT, Workup, Day of Collection
  Donor Infectious Disease Testing

• At Workup
  History, Physical Examination & Testing (CBC, Chemistries, UA, Pregnancy, Sickle screen, CXR, EKG)
Additional NMDP PE Requirements

- Identify conditions that may put donor or recipient at risk such as
  - Sensitivity to filgrastim or E. Coli-derived protein products
  - History of autoimmune conditions
  - History of DVTs
  - History of iritis/episcleritis
  - Thrombocytopenia <150 x 10^6 L at baseline
  - Current treatment with Lithium
  - Positive screening test for Hemoglobin S
  - Receiving experimental therapy
  - Anesthesia risks (sleep apnea, asthma)
  - Bone marrow harvest risks (anatomy, h/o back issues)
Evaluation Considerations

Does any information affect

1. Donor Safety?
2. Product Quality?
3. Recipient Safety?
Keeping in mind assessment goals:

**Safe donation & Safe product**

**DATA**
- HHQ
- IDMs
- H&P
- Labs
- CXR
- EKG
- UA

**ANALYSIS**
- Clinical Correlation
- Medical Experience

**CONCLUSION**
- Accept for both products
- Accept for 1 Product-only
- “Extended” med testing
- Temporary Unavailable
- Medically Defer
- Treat & Wait
TC Notification Considerations

Is the potential risk significant enough to warrant notifying Transplant Center?

- Is it possibly transmissible?
- Is there a risk the TC MD must weigh against the known risks of transplant?
- Is this providing “too” much info?
Extended Medical Testing Utilization: 2011

- 1306 Workups
- 706 Ext Med Requests
- 402 Donors
- 31% Workups
Extended Medical Testing Utilization: 2011

Range of Costs

- 248 donors evaluated for <$100
- 307 donors evaluated for $101-$500
- 70 donors evaluated for $501-$1000
- 76 donors evaluated for $1001-$5000
- 4 donors evaluated for >$5001

402 Donors evaluated for 390 Patients
Issue to Consider with Extended Testing

- Is the donor becoming a patient (counseling, f/u care)?
- Are we testing the donor into suitability (repeat tests)
- What is the risk of the additional test(s), e.g. marrow Bx?
- Will the testing influence the donor’s decision whether to donate (e.g. monetary incentive if no insurance)?

- What is the impact on the patient – will this delay the transplant?
- Cost – ultimately borne by patients
HSC Product Release Criteria
Considerations

Product Safety (SQuIPP)
- Safety
- Quality
- Identity
- Purity
- Potency

Product Efficacy
- Dose/Potency: TNC, CD34
- HLA matching
HSC Product Release Criteria: Reality

Release (almost) all products:

• Patient has received their conditioning regimen
• Replacement product from this donor or another, may not available, at least in the short term
• Products need to be released to the courier within hours of collection
• Day of collection IDM results and product testing may not be complete prior to release
• Patients are on broad spectrum antibiotics
• What is the minimum dose for engraftment?
• No rapidly available HLA test for identity/efficacy
Validation of short-term handling and storage conditions for marrow and peripheral blood stem cell products

Transfusion
Volume 51, Issue 1, pages 137-147, 1 JUL 2010 DOI: 10.1111/j.1537-2995.2010.02758.x
Emergency Subsequent Request?

What is the cutoff dose to determine **Emergency Subsequent Donation** versus **Monitor For Engraftment**?

<table>
<thead>
<tr>
<th>Dose</th>
<th>Approach</th>
</tr>
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<tbody>
<tr>
<td>( \geq 2 )</td>
<td>Monitor for engraftment ( \times 4 ) wks</td>
</tr>
<tr>
<td>( 1 - &lt; 2 )</td>
<td>Evaluate request</td>
</tr>
<tr>
<td>( &lt; 1 )</td>
<td>Approve request</td>
</tr>
</tbody>
</table>

Dose:
- \( x10^6 \) for PBSC
- \( x10^8 \) for Marrow
Summary

• HLA matching is the major factor affecting clinical outcomes in HSCT, followed by donor age, gender, and ABO matching
• Careful donor evaluation is essential to ensure donor, product and recipient safety; medical evaluation and judgment is required for each donor
• Strict product release criteria are hard to define for HSC products
• Urgent subsequent donations may be requested if the primary donation cell count is low, and are routinely requested for graft failure, relapse, to enhance immune reconstitution and treat certain viral infections (CTLs)