Stem Cell Procurement and Donor Safety

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Seattle, WA November 20, 2015

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Disclosure Information

Michael Linenberger, MD

I have no financial relationships to disclose

Other

• I am a member of the Hematology Board Exam Committee of ABIM
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Hematopoietic Progenitor Cell Donors
Nalini Ambady, a social psychologist whose research on the surprising accuracy of first impressions was popularized by Malcolm Gladwell in “Blink,” his best-selling nonfiction book of 2005, died on Oct. 28 in Boston.

“Beating the odds of one in over 20,000, the unexpected happened last week when city-based Marrow Donor Registry of India (MDRI) found the Human Leukocyte Antigens (HLAs) match in a software engineer. But Ambady's hopes crashed when after initially giving consent and registering as a donor, the engineer refused to go ahead with the donation citing health and later family problems. 

….this was the sixth instance where the registry failed to convert a match into a transplant.

"Since we started the registry in 2010, there have been 55 requests for a match and we have managed to find six matches so far. But barring one instance, the donors backed out in all cases“

…donor attrition has emerged as the biggest problem in the way of unrelated stem-cell transplants…”
Objectives

- Review donor *eligibility* and infectious disease screening
- Understand donor *suitability* and relevance to safety of PBSC collection
- Review the PBSC donor experience, toxicities and adverse events (AEs)
- Discuss ethical and psychological aspects of PBSC donation & their relevance to AEs and enhancing donor confidence and commitment
Donor Eligibility: Safety for the recipient
### 3-Step Donor Eligibility: Risk for Communicable Disease Transmission

<table>
<thead>
<tr>
<th>(1) Donor Health Questionnaire</th>
<th>(2) Screening Labs</th>
<th>(3) PE Signs</th>
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</thead>
<tbody>
<tr>
<td><strong>Risk behavior for:</strong></td>
<td><strong>Hep B</strong> (s Ag; c AB; NAT)</td>
<td><strong>IV Drug use</strong></td>
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<tr>
<td>HIV</td>
<td><strong>Hep C</strong> (AB; NAT)</td>
<td><strong>Tattoo/piercings</strong></td>
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<tr>
<td>Hepatitis</td>
<td><strong>HIV 1/2</strong> (AB; HIV 1 NAT)</td>
<td><strong>Lymphadenopathy</strong></td>
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<tr>
<td>STDs</td>
<td><strong>HTLV I/II</strong> (AB)</td>
<td><strong>Oral thrush</strong></td>
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<tr>
<td>Malaria; Chagas</td>
<td><strong>Syphilis</strong> (TP AB)</td>
<td><strong>Kaposi’s</strong></td>
</tr>
<tr>
<td>Babesiosis</td>
<td><strong>West Nile Virus</strong> (NAT)</td>
<td><strong>Jaundice; ↑ liver</strong></td>
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<tr>
<td>CJD (mad cow)</td>
<td><strong>Chagas</strong> <em>(T. cruzi AB)</em></td>
<td><strong>Sepsis/rash</strong></td>
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<tr>
<td>Xenotransplant</td>
<td><strong>CMV</strong> (AB)</td>
<td><strong>Smallpox vaccine complications</strong></td>
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</table>

*Emerging ID risks*
(Relatively) Common Scenario

Healthy sib donor: DHQ (–) (no travel/risks); PE (–)

ID lab panel: (+) Hep Bc AB; (–) sAg; (–) NAT; others (–)

Confirmatory testing: (–) HBV DNA Quant (PCR)

? WHY IS THIS IMPORTANT ?

Hep Bc AB (+): Interpretation varies
- Healthy US blood donors: 0.4 - 1% (false +)
- Endemic HBV: 10 - 20% (resolved HBV)

FDA: (+) is “ineligible” criterion
- Donor requires “justification” to proceed
- Institutional policy regarding further testing

http://depts.washington.edu/hepstudy/hepB/clindx/core/discussion.html
Hep B Reactivation in NHL Pts in China: Hep Bc AB(+)/Hep B DNA PCR(−) on Rituximab + Chemo

Seto W-K et al. JCO 2014;32:3736

Original Investigation

Entecavir vs Lamivudine for Prevention of Hepatitis B Virus Reactivation Among Patients With Untreated Diffuse Large B-Cell Lymphoma Receiving R-CHOP Chemotherapy A Randomized Clinical Trial

He Huang, MD; Xueying Lu, MD; Jun Zhu, MD, PhD; Sheng Ye, MD; Hongyu Zhang, MD; Wei Wang, MD; Xiangyuan Wu, MD; Jiewen Peng, MD; Bing Xu, MD; Yingcheng Lin, MD; Yabing Cao, MD; Haoran Li, MD, PhD; Xiuwu Lin, MD; Qing Liu, PhD; Tongyu Lin, MD, PhD

JAMA 2014;312:2521
FHCRC SPM: Allo Donor Anti-HBc (+)

- HBV DNA $^{pos}$
  - Check HBV DNA by PCR in donor
    - HBV DNA negative
      - Check donor hematopoietic cells for HBV DNA by PCR
        - Hematopoietic cells HBV DNA $^{pos}$
          - Proceed with hematopoietic cell harvest and transplant
            - Monitor serum ALT of recipient at monthly intervals post-transplant
              - Increased serum ALT
                - Evaluate possible causes
                  - HBV DNA by PCR
                    - HBV DNA $^{pos}$
                      - Treat recipient with entecavir
                    - HBV DNA $^{neg}$
                      - Proceed with transplant
        - Hematopoietic cells HBV DNA $^{neg}$
          - Proceed with transplant
    - Is an equally well-HLA-matched HBsAg $^{neg}$ donor available?
      - NO
        - Treat donor with entecavir
          - Consider Hepatitis B Immune Globulin (HBIG) before infusion of cells.
        - Entecavir prophylaxis of recipient, begin a few days before hematopoietic stem cell infusion and continue for at least 30 days, pending HBV DNA results in recipient.
      - YES
        - Use alternate donor
          - Proceed with transplant
          - Monitor serum ALT and HBV DNA of recipient at monthly intervals to 6 months post-transplant
Emerging IDs: Threat to Transfusion Safety w/o Effective Screening &/or Intervention

ID Agent Attributes: Found in blood during asymptomatic phase; survives processing/storage; transmission causes sequelae

ISBT List\(^1\): 74 EID agents with regional/global relevance

Current Major Considerations

- *Babesia (US)*: Target screen for high-risk recip. $713,000/QALY\(^2\)
- Dengue viruses: Endemic in 110 countries (40% world pop); sporadic in the Rio Grande, Hawaii, Florida Keys, Puerto Rico
- Chikungunya virus: Distribution & clinical signs \(\approx\) dengue
- Middle East respiratory syndrome coronavirus (MERS-CoV)
- Hepatitis E virus: Most common cause of acute hepatitis

\(^1\)ISBT Science Series 2014; 9:30
\(^2\)Simon et al. Transfusion 2014; 54:889
Donor Suitability:
Safety for the donor
Donor Suitability / Comorbidities

- **Donor risks:** BM, PBSC, MNC (DLI)
- **Recipient risks:** ID, cancer, autoimmune, genetic dz
- **Health questionnaires & checklists**
- **Medical fitness guidelines & request for review:**
  www.worldmarrowdonor.org/donorsuitability (similar to NMDP tools)
- **Assessments:** Timing; clinical/lab criteria; re-evals
- **Deferrals & exclusions**
Suitability Criteria for Adult Related Donors: A Consensus Statement from the Worldwide Network for Blood and Marrow Transplantation Standing Committee on Donor Issues

PBSC Mobilization and Collection by Apheresis
Mobilization

CD34+ marrow cell

Cytokines (G-CSF) → MMPs (4 days)
+/- Plerixafor → reversible CXCR4 blocker

Kronenwett, R et al. Stem Cells 2000; 18:320
Filgrastim (G-CSF)-Mobilized Peripheral Blood Stem Cells

FHCRC: 16 µg/kg/day  
NMDP: 10 µg/kg/day

G-CSF

Apheresis

FHCRC: Start 4th d G (transplant day -1 \(\rightarrow\) goal)  
NMDP: Start 5th d G; 1 d (ideal) or 2 d of apheresis
What are the Risks of G-CSF?

- **Common**
  - MS pain, arthralgias
  - HA, nausea, malaise
  - Mild ↓ plts + ↑ spleen
  - ↑ LDH

- **Uncommon**
  - Fever, rash, arthritis

- **Rare**
  - ↓↓↓ plts - Spleen infarct
  - Splenic bleed/rupture

Dincer et al. J Ped Hematol Oncol 2004; 26:761
Transfusion 2015;55:708
G-CSF-Induced Bone Pain

Anecdotal cases of refractory G-CSF-induced bone pain relieved by antihistamines

- Loratidine (Claritin®) 10 mg/day
- Clinical trials
  - CALGB: Loratidine to prevent pegfilgrastim-induced pain
  - AMGEN trial: Naproxen vs loratidine to prevent pegfilgrastim bone pain in breast Ca patients
What are the Risks of Apheresis?

NMDP Prospective Trial (N=2408)

- Citrate (↓ Ca++): 51%
- Nausea: 20%
- Venous Access: 22%
- Pain, HA, ↓ BP: 1 - 6%

Frequency of all AE scores

Blood 2009;113:3604
Symptoms & AEs during Apheresis

Age not associated with donor toxicity

- MS pain
- Headache
- Nausea
- IV site pain
- Paresthesia

Linenberger et al. JCA 2009;24:69 (abstr)
PBSC Mobilization/Harvest Sx’s-NMDP

Days 5 = Mobilization & Apheresis d1.

Greater Risks for Females
- Require CVC (21% vs 5% males)
- Apheresis-related AEs (2-fold)
  - N/V; citrate reactions
- Hospitalization (3.3% vs 0.6%)

Pulsipher et al. Blood 2013;121:197
**PBSC Serious Adverse Events (NMDP)**

- **Persist (>3m) or Disabling (0.06%)**
  - Muscle pain, rash (1)
  - Numbness or neuropathic pain (1)
  - Dizziness (1)
  - Bone/joint pain (1)

- **Life-Threatening Events (0.03%)**
  - Intracranial hemorrhage
  - Syncope/pericarditis

**Fewer Cancers in URDs (G-CSF)**

<table>
<thead>
<tr>
<th>Result</th>
<th>BM</th>
<th>PB</th>
</tr>
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<tbody>
<tr>
<td>Observed number of cancers</td>
<td>11</td>
<td>29</td>
</tr>
<tr>
<td>Expected number of cancers</td>
<td>19.89</td>
<td>47.95</td>
</tr>
<tr>
<td>Standardized incidence ratio</td>
<td>0.55</td>
<td>0.60</td>
</tr>
<tr>
<td>95% confidence interval</td>
<td>0.28-0.99</td>
<td>0.41-0.87</td>
</tr>
<tr>
<td>P value</td>
<td>0.045</td>
<td>.004</td>
</tr>
</tbody>
</table>

*Pulsipher MA et al. Blood 2014;123:3655*
PBSC Donation: “How long before I’m back to normal?”

- BM & PBSC donors experience overall similar levels of discomfort
- Variations in intensity & time-course of toxicities occur
- Donor age, gender and obesity variably impact experience & toxicity
Long-Term Risks for Donors?

- **Single center studies:** No ↑ incidence of AML or MDS
- **URD registries:** No ↑ heme malignancies
- **WMDA recommends Informed Consent language:** Unknown long-term risk of G-CSF
- **Chromosomal effect of G-CSF?**
  - CD34+ & PHA-stim T cells: No aneuploidy or replication asynchrony
  - NIH study (35 PBSC & 38 PMN donors): No abnormal chr 7 or 8

References:

3. Olnes et al. Transfusion 2012;52:537
But wait....
Biosimilar G-CSF in the U.S.

- **Tbo-filgrastim (Granix®)**: Approved in Aug, 2012 via full BLA (not biosimilar path) only for chemoRx-induced neutropenia
  - Efficacy in breast Ca (n=348) – Safety in 3 RCTs of various Ca (n=680)

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**FDA panel backs approval of filgrastim biosimilar**

**By: ELIZABETH MECHCATIE, Oncology Practice Digital Network**

**Jan 8, 2015**

At a meeting on Jan. 7, the FDA’s Oncologic Drugs Advisory Committee voted 14-0 that the filgrastim biosimilar should be approved for the five indications approved for Neupogen in the United States, based on “the totality of the evidence,” which includes pharmacokinetic, pharmacodynamic, immunogenicity, and clinical data.

**EP2006 (Zarxio®): In Europe since 2009; 1st US biosimilar**

- PK/PD study: EP06-109
- Safety/efficacy: RCT breast Ca
- Suppl: URD PBSC study EP06-501

URD Donors for Nalini Amady

Match likelihood

- 8/8 HLA adult donor
- 7/8 HLA adult donor
- 6/6 HLA cord blood
- 5/6 HLA cord blood
- 4/6 HLA cord blood

Research Operations Department of the National Marrow Donor Program® (www.marrow.org)

https://bethematchclinical.org/resources-and-education/hct-presentation-slides/#/
Psychological Impact of Donation on Donor Populations

- Equivalent pain/anxiety with BM vs PBSC
- Most related donors have positive emotional outcomes
  - (+) Donor attitude/relationship; known risks/pain
- Ambivalence predicts negative outcome, & is related to...
  - ↑ Education; ↓ happiness; pessimistic of prognosis
- RD risks: Female, younger, not a blood donor
- URD benefit: Altruistic, intense counseling

**REVIEW**
Bone Marrow Transplantation (2014) 49, 729–736

A review of the haematopoietic stem cell donation experience: is there room for improvement?

A Billen¹,², JA Madrigal¹,² and BE Shaw¹,²,³
URD Recovery Time is Linked to Predonation Quality of Life

Prospective study of URDs in Anthony Nolan registry (UK)

SF-36 PCS: Physical Component Summary
(Higher score = more positive health states)

SF-36 MCS: Mental Component Summary
(Higher score = more positive health states)
Related Donor Recovery is Linked to Gender, Age & Baseline Status

- **BM donor skeletal pain**

- **BM Donor peak toxicity**

- **↑ PBSC pain/sxs at apheresis** ≈ Female, (+) baseline pain; 30-39 yo
- **PBSC pain & toxicity persisting out 1 yr:**
  - (+) Baseline pain/symptoms (OR=4)
  - Female > male (OR=1.7)

Pulsipher et al. RDSafe Study; ASH 2014; Abstract 3847
Donor Motivation:
Can we raise incentive?
Ban on bone marrow sales challenged

A lawsuit urges compensation for those who give the life-saving stem cells, hoping to broaden the pool of donors.

Kumud Majumder & 11-year-old Arya
Remuneration of hematopoietic stem cell donors: principles and perspective of the World Marrow Donor Association

Michael Boo, Suzanna M. van Walraven, Jeremy Chapman, Brian Lindberg, Alexander H. Schmidt, Bronwen E. Shaw, Galen E. Switzer, Edward Yang, and Torstein Egeland, on behalf of the World Marrow Donor Association

- Remuneration is undesirable & may be deleterious
- Raises ethical dilemmas & challenges
- Risk of safety to patients (nondisclosure of ID risk)
- Damages the public will to act altruistically
- Reward removes autonomy & value of motivation
- Compromises free exchange between registries

Ninth Circuit Says Bone Marrow Compensation is Legal
By Robyn Hagan Cain on December 5, 2011 3:07 PM
DEPARTMENT OF HEALTH AND HUMAN SERVICES    October 2, 2013
42 CFR Part 121 RIN 0906-AB02 Change to the Definition of ``Human Organ'' Under
Section 301 of the National Organ Transplant Act of 1984 AGENCY: Health Resources
and Services Administration, HHS.

SUMMARY: This notice seeks public comment on the proposed change in the definition of ``human organ'' in section [[Page 60811]] 301 of the National Organ and Transplant Act of 1984, as amended, (NOTA) to explicitly incorporate hematopoietic stem cells (HSCs) within peripheral blood in the definition of ``bone marrow.''

Next Step: Revise the National Organ Transplant Act
Summary

• ID screening & donor suitability assessment are key elements to successful PBSC collections

• Pre-donation factors may identify higher-risk donors who may benefit from targeted screening & counseling → ↑ URD retention & experience

• PBSC mobilization & collection are relatively safe & effective for the vast majority of donors

• Donor & collection centers must protect donor autonomy and optimize ethical treatment
“I went to the woods because I wanted to live deliberately, I wanted to live deep and suck out all the marrow in life....”

Henry David Thoreau (1817 – 1862)