AGENDA
CIBMTR WORKING COMMITTEE FOR DONOR HEALTH AND SAFETY
Orlando, Florida
Saturday, February 27, 2010, 2:45 pm– 4:45 pm

Co-chair: Susan Leitman, MD, National Institutes of Health
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Co-chair: David Stroncek, MD, National Institutes of Health
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Co-chair: Steven Goldstein, MD, University of Pennsylvania
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Statistician: Tanya Pedersen, CIBMTR Minneapolis
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Ph.D. Statistician: Brent Logan, PhD, CIBMTR Statistical Center
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CIBMTR Sci. Dir: Dennis Confer, MD, National Marrow Donor Program
Telephone: 612-362-3425; Fax: 612-627-8125; E-mail: dconfer@nmdp.org

1. Introduction
   a. Minutes of February, 2009 meeting (Attachment 1)

   b. Thank you outgoing Co-Chair: Susan Leitman, MD

   c. Welcome incoming Co-Chair: Michael Lankiewicz, MD, Blood Center of Wisconsin
      Phone: 414-937-6416; Fax: 414-933-6803; E-mail: michael.lankiewicz@bcw.edu

2. Accrual summary (Attachment 2)

3. Published or submitted papers
      Anderlini P, Haagenson M, Logan B, Horowitz MM, Confer DL. Adverse events among 2,408 unrelated
      donors of peripheral blood stem cells: results of a prospective trial from the National Marrow Donor

   b. D01-84b Pulsipher MA, Chitphakdithai P, Logan BR, Leitman SF, Anderlini P, Klein JP, Horowitz MM,
      Miller JP, King RJ, Confer DL. Donor, recipient, and transplant characteristics as risk factors after
      unrelated donor PBSC transplantation: beneficial effects of higher CD34+ cell dose. Blood 114:2606-
      2616, 2009.

   c. DS06-01 O'Donnell P, Pedersen TL, Confer DL, Rizzo JD, Pulsipher M, Stroncek D, Leitman S,
      Anderlini P. Practice patterns for evaluation, consent and care of related donors and recipients at
4. Studies in progress
   a. DS05-02 RDSafe: A multi-institutional study of HSC donor safety and
      quality of life (M Pulsipher) (Attachment 3)
   b. DS08-01 The identification of cytogenetic abnormalities in donor derived
      hematopoietic cells after unrelated donor stem cell transplantation
      (N Frey) (Attachment 4)
   c. DS09-01/GS09-01 Impact of Growth Factor Mobilization on Donor
      Bone Marrow Harvest (S Pincus) (Attachment 5)
   d. DS09-02 Prevalence and Clinical Significance of Monoclonal B Cell
      Lymphocytosis (MBL) in Unrelated Hematopoietic Stem Cell Donors
      (M Seftel) (Attachment 6)
   e. DS09-03 Effects of Second Donations on Marrow and PBSC donors
      (D Stroncek) (Attachment 7)
   f. DS09-04 The Effect of Race, Socioeconomic Status, and Donor Center
      Size on Bone Marrow and PBSC Donor Experiences (M Pulsipher)
      (Attachment 8)
   g. DS09-05 Early and Late Donor Toxicities Associated with BM vs. PBSC
      Collection in NMDP Donors (Attachment 9)

5. Future/proposed studies
   a. PROP1109-06 Effect of Demographics on Peripheral Blood CD34+ Counts and CD34+ Yields in
      Donors Undergoing Large Volume Leukapheresis (J Hsu / J Wingard) (Attachment 10)

6. Other business
   a. Donor Outcome Workshop, Berne, Switzerland (D Confer) (Attachment 11)
MINUTES
CIBMTR WORKING COMMITTEE FOR DONOR HEALTH AND SAFETY
Tampa, Florida
Thursday, February 12, 2009, 2:45 pm– 4:45 pm

Co-Chair: Michael Pulsipher, MD, University of Utah School of Medicine
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Co-Chair: David Stroncek, MD, National Institutes of Health
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Co-Chair: Susan Leitman, MD, NIH Clinical Center Blood Bank
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1. Introduction
David Stoncek called the meeting to order at 2:48 pm. Attendees were welcomed and introductions of the Working Committee (WC) staff were made (Susan Leitman was unable to attend). Minutes from the February, 2008 meeting were approved. Mike Pulsipher was recognized and thanked for his leadership contributions to the committee over the last five years and Steven Goldstein was welcomed as new co-chair.

2. Accrual summary
Mike Pulsipher reviewed the accrual table, explaining differences between donor data available between CIBMTR and NMDP databases. Significantly more comprehensive data (including degree of HLA match between donor and recipient) is available from the NMDP database.

3. Published or submitted papers
   Mike Pulsipher reported that this study has been prepublished online as a Blood First Edition paper.

   Dennis Confer informed the WC that this issue of BBMT reports on the 20-year experience of the National Marrow Donor Program and is available online free of charge.
4. Studies in progress
   a. **D01-84a**: Outcomes of a prospective trial of NMDP-facilitated unrelated donor PBSC hematopoietic cell transplantation for leukemia and myelodysplasia: comparable survival regardless of regimen intensity and improved survival with higher cell doses. (M Pulsipher)
      Mike Pulsipher reported that the manuscript is near submission.
   
   b. **DS05-02**: RDSafe: A Multicenter Study of Hematopoietic Stem Cell Donor Safety and Quality of Life (M Pulsipher)
      Mike Pulsipher informed the WC that this study has received funding from the federal government and will soon be open to enrollment. Centers interested in participating in the study were invited to attend an informational meeting held later during this BMT Tandem Meeting. The goals of the study include: comparing the incidence of adverse events and the quality of life (QoL) of related donors to unrelated donors. Both pediatric and adult donors will be enrolled. The initial forms would be completed by the transplant center, with long-term follow-up completed by the NMDP call center. Data reporting would be minimal on the part of transplant centers and would include: donor enrollment, baseline, and collection day forms, as well as any adverse event forms. Acknowledgement was given to Ed Snyder, present at this WC meeting, who raised the issue of related donor safety at a forum held in Arlington, VA in 2004. This study is a direct result of that meeting.
   
   c. **DS06-01**: Related donor and recipient management practice pattern survey (P O’Donnell)
      Paul O’Donnell presented his study aimed at determining if the potential for a conflict of interest exists when related donors are being treated by the same physician as the recipient. The survey was sent to medical directors at all U.S. transplant centers, with a response rate of 39%. The survey’s main finding is that transplant physicians in no less than 70% of centers were involved in overlapping care of the donor and the recipient during the donor evaluation, clearance, and collection phases. WC members were invited to attend the presentation of the full results of this study later that afternoon. 2009 goal for this study is to submit the manuscript.
   
   d. **DS07-01**: The effect of multiple hematopoietic progenitor cell collections on hematopoietic reserve in volunteer unrelated donors. (E Waller)
      Mike Pulsipher informed that committee that due to low numbers, this study has been dropped from the committee agenda.
   
   e. **DS08-01**: The identification of cytogenetic abnormalities in donor derived hematopoietic cells after unrelated donor stem cell transplantation. (N Frey)
      Noelle Frey presented the goals of the study: to characterize donor derived cytogenetic abnormalities that develop in the recipient after transplant, describe the outcomes, explain leukogenesis, and evaluate the process of informing the donor. Additional data will need to be collected from transplant/donor centers. 2009 goal for this study is to draft a data collection form and begin data collection.
5. Future/proposed studies

a. **PROP 1208-32** Prevalence and Clinical Significance of Monoclonal B Cell Lymphocytosis (MBL) in Unrelated Hematopoietic Stem Cell Donors (M Seftel)

Matthew Seftel presented his proposal, along with an alternative study design than the one outlined in his proposal. This cohort design would identify donors at risk (lymphocyte count > 4) and evaluate their recipients for new malignancies, graft failure, GVHD, relapse, etc. Most WC members preferred this study design, since the first design most likely would not be powered to detect a difference because unrelated donors are young (median age is 36) and the prevalence of MBL is low in younger populations. There is also a concern that samples would not be available on all the donors. Comment was made that the stepwise approach is good; if it is discovered that there aren’t any donors with lymphocyte count > 4 then it is not necessary to go further and the transplant community can be reassured that this is not a problem for donors and recipients. The concern was raised about consent to do this type of research with NMDP donors. NMDP consents donors for research using data and blood samples for transplant outcomes, but what is our ethical obligation to inform donors when we discover the abnormality, and should we have asked for their consent to look for the abnormality? And how do we handle informing the recipient if something is identified in the donor before donation? The NMDP’s consent form does not include verbiage that states if something is discovered that jeopardizes donor health we will inform the donor. However, there is an obligation to inform donors if we incidentally discover something, but not systematically discovered, as would be in the proposed study. If the study is prioritized to move forward, this consent issue would have to be clarified. Based on the proposal vote, this proposal is ranked #4.

b. **PROP 1208-45** Impact of Growth Factor Mobilization on Donor Bone Marrow Harvest (S Pincus)

Steve Pincus reviewed his proposal. This proposal will be considered jointly by this WC and the Graft Sources and Manipulation Working Committee. Very little data is available on the effects of giving growth factors to bone marrow donors. Growth factors are not allowed under NMDP bone marrow collection protocols. From what little data is available from related donors, mobilizing the bone marrow with growth factor results in increased marrow cellularity, more rapid engraftment, and shorter bone marrow harvest time (due to shorter anesthesia time and fewer aspirations). It also does not appear to affect GVHD rates, and decreases the need for autologous blood collection/transfusions. Dosing regimen at proponent’s institution is 10 mg/kg over 3 days. Proposal aims are three-fold: 1) determining donor safety, 2) describing the marrow graft, and 3) analyzing patient outcomes. The donor safety portion would compare the G-primed donors with standard marrow donors for complications. The CIBMTR database is limited to whether donor received blood transfusions, whether donor was hospitalized, and what complications arose from the donation. Recipient outcomes would be focused on the Graft Sources Working Committee. This issue could be considered as a clinical trial by the NMDP in the future. A suggestion was made to compare not only to standard bone marrow grafts but also to PBSC grafts. Proponent clarified that the intent with this proposal would be to establish differences between the two bone marrow groups. The bulk of the study would focus on the recipient outcomes, and a secondary aim would be to describe whatever donor information is available. Based on the proposal vote, this proposal is ranked #1.

c. **PROP 1208-57** Effects of Second Donations on Marrow and PBSC donors (D Stroncek)

Dave Stroncek presented his proposal. The study aims to determine the effects of second donations on pre-post blood counts, collection yield, and post-donation symptoms. There is very little data available
describing the effects of second donations, even from related donors. Since the number of cases are low, one possible study could be a matched control design comparing these donors with those who have donated only once. Hypothesis is that there won’t be a difference between blood counts, collection yield, and symptoms. If this hypothesis is upheld, it would be valuable information to pass on to a donor who is approached to donate a second time. Based on the proposal vote, this proposal is ranked #2.

d. PROP 1208-65 The Effect of Race, Socioeconomic Status, and Donor Center Size on Bone Marrow and PBSC Donor Experiences (M Pulsipher)

Mike Pulsipher presented his proposal. We know that women, older and obese unrelated donors experience more toxicities associated with the donation procedure, but we do not know if this varies by race, socioeconomic status (SES) and donor center size. Hypotheses are that toxicities, perceptions of pain, and severe adverse events will not vary between donors of different races and SES status, but that these would be different in donor centers of varying size, i.e., smaller centers would report higher numbers of these measures than larger centers. The main purpose of the study is to determine if there are differences, and if there are, counsel donors appropriately and implement any preventative strategies.

Related donors were not included in this study because the toxicity data has not been collected on this population, but this is being studied as part of the RDSafe study. Center-specific analysis may be complicated because of variation in donor management at the donor center. Based on the proposal vote, this proposal is ranked #3.

The meeting was adjourned at 4:35 pm.

Working Committee Priorities for the coming year:

<table>
<thead>
<tr>
<th>Title</th>
<th>PI</th>
<th>Goal by 7/1/09</th>
<th>Goal by 6/30/10</th>
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<tbody>
<tr>
<td>DS05-02</td>
<td>Pulsipher</td>
<td>Data collection</td>
<td>Data collection</td>
</tr>
<tr>
<td>DS06-01</td>
<td>O'Donnell</td>
<td>Manuscript preparation</td>
<td>Submit</td>
</tr>
<tr>
<td>DS08-01</td>
<td>Frey</td>
<td>Data collection</td>
<td>Analysis</td>
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<tr>
<td>1208-32</td>
<td>Seftel</td>
<td>Define study design</td>
<td>Protocol development</td>
</tr>
<tr>
<td>1208-45</td>
<td>Pincus</td>
<td>Protocol development</td>
<td>Data file preparation</td>
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<td>1208-57</td>
<td>Stroncek</td>
<td>Protocol development</td>
<td>Data file preparation</td>
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<tr>
<td>1208-65</td>
<td>Pulsipher</td>
<td>Protocol development</td>
<td>Data file preparation</td>
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Accrual Summary for Donor Health and Safety Working Committee


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<thead>
<tr>
<th>Characteristic</th>
<th>N (%)</th>
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<td>Number of donors</td>
<td>29627</td>
</tr>
<tr>
<td>Donor age, median (range), years</td>
<td>35 (18-62)</td>
</tr>
<tr>
<td>Donor age at time of transplant</td>
<td></td>
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<tr>
<td>18 – 19</td>
<td>316 (1)</td>
</tr>
<tr>
<td>20 – 29</td>
<td>8422 (28)</td>
</tr>
<tr>
<td>30 – 39</td>
<td>10665 (36)</td>
</tr>
<tr>
<td>40 – 49</td>
<td>7883 (27)</td>
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<tr>
<td>50 – 59</td>
<td>2295 (8)</td>
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<tr>
<td>60 +</td>
<td>46 (0)</td>
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<td>Donor race/ethnicity</td>
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<td>Caucasian</td>
<td>23548 (79)</td>
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<td>Black/African-American</td>
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<td>Asian-American/Pacific Islander</td>
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<td>3</td>
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<td>Graft type</td>
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<td>Donor male sex</td>
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<tr>
<td>Donor/recipient sex match</td>
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<tr>
<td>Male/Male</td>
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<tr>
<td>Male/Female</td>
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<td>Female/Male</td>
<td>6166 (21)</td>
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<tr>
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<td>Donor CMV status</td>
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<td>Negative/Positive</td>
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<tr>
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<td>Positive/Positive</td>
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Characteristics of donors reported to the CIBMTR between 1987 and 2008. (Continued)

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<tr>
<td>2008</td>
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Related Donors: Quantifying the Experience

RDSafe: A Multicenter Study of Hematopoietic Stem Cell Donor Safety and Quality of Life

Study Overview:
There is evidence suggesting that related donors are accepted for stem cell collection with more co-morbid conditions compared to unrelated donors, which could lead to increased adverse events. The RDSafe study is designed to definitively measure the risks of stem cell or bone marrow collection. The study is a multicenter, observational, prospective study comparing acute stem cell donation toxicities and psychosocial effects in related and unrelated marrow and PBSC donors. The primary endpoint is to compare adverse events in related BM and PBSC donors defined by three age groups (<18, 18 to 60, >60) versus unrelated BM and PBSC donors ages 18 to 60. A smaller quality of life (QOL) cohort of both related and unrelated donors will track psychosocial adverse outcomes.

Study Sponsor:
The Center for International Blood and Marrow Transplant Research (CIBMTR) is sponsoring this study. Dr. Michael Pulsipher of the University of Utah is the Principal Investigator.

Protocol Highlights:
- Approximately 2,300 related donors from selected transplant centers will be enrolled on the study
- About 5,600 unrelated bone marrow and PBSC donors will serve as a control group
- All donors will be followed for acute toxicities up to one year after donation
- All follow-up data after day of collection will be centrally collected by a call center
- Donors randomized to the QOL cohort will also undergo psychosocial evaluations conducted by the University of Pittsburgh research team

Site Responsibilities:
- Offer study to all bone marrow and PBSC donors (no donor age restrictions)
- Consent donor
- Complete case report forms at the following time points:
  - Enrollment/Baseline
  - Collection day
- Report any adverse events and protocol deviations
- Provide donor contact information to call center (all donors) and QOL team (QOL cohort only)

Study Duration:
The study opened in January, 2010. The estimated accrual period is 3.5 years.

Enrollment Compensation:
Reimbursement per donor is $250.

Further Inquiry:
For more information about the RDSafe study, please contact Amy Hays at the CIBMTR: 612-884-8559 or ahays@nmdp.org.
CIBMTR DS08-01

THE IDENTIFICATION OF DONOR DERIVED CYTOGENETIC ABNORMALITIES AND MALIGNANCIES IN HEMATOPOIETIC CELLS AFTER UNRELATED DONOR HEMATOPOIETIC STEM CELL TRANSPLANTATION

DRAFT PROTOCOL

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1.0 SPECIFIC OBJECTIVES:

1.1 To describe presentation and natural history of cytogenetic abnormalities arising in unrelated donor derived hematopoietic cells after unrelated donor hematopoietic stem cell transplantation (HSCT).

1.2 To describe presentation and natural history of donor derived hematopoietic malignancies that arise in recipients after unrelated donor HSCT.

1.3 To correlate donor health status with recipient health status in patients who develop incidental cytogenetic abnormalities or hematologic malignancies in donor derived stem cells.

1.4 To describe current practice of donor evaluation and management in the event of donor derived abnormality in the recipient.

2.0 SCIENTIFIC JUSTIFICATION:

Secondary malignancies are increased in patients who undergo allogeneic stem cell transplant procedures. A number of studies have been performed retrospectively to identify these risks (1, 2). In rare cases these malignancies arise in cells of donor origin and may have existed subclinically in the donor before transplant (with malignant clones infused directly into the recipient) or acquired in donor cells at various times after transplant (3-8). Of the former type at least 5 cases have been well documented in the literature (3-7). The most commonly reported acquired donor derived malignancy after allogeneic stem cell transplant are EBV related post transplant lymphoproliferative disorders in patients with significant immune compromise. Less frequently seen are acquired donor derived myelodysplastic syndromes or leukemias. In one study from the EBMT, 14 cases of donor derived leukemia were clearly identified from the database of 10489 allogeneic procedures performed between 1982 and 2003 (8). In these particular patients, none of the stem cell donors developed hematologic malignancies with a median follow-up of nine years. The conditions by which these disorders develop in donor derived stem cells remain unclear and one can postulate that there are acquired defects in the microenvironment or that the immune status of the transplantation allows for the emergence of these malignancies. What is less well characterized are the degree of cytogenetic abnormalities that are identified in the recipient after allogeneic transplantation and as well what is their natural history. It is interesting to follow the literature in patients with CML treated with imatinib who gained cytogenetic remission and have the emergence of alternate clonal abnormalities. Many of these abnormalities do not seem to progress to malignant clones, or at least not yet under the observational time that they have been followed (9).

At our own centers we have identified a number of patients, higher than we would have anticipated, with cytogenetic abnormalities that have emerged in the donor derived stem cells. We have identified one patient who acquired a trisomy 8 abnormality from a donor who is likely an undiagnosed constitutional trisomy 8 mosaic. Additionally, we have three patients where a reproducible cytogenetic abnormality has been found in the donor derived stem cells which has emerged from a post transplant normal karyotype. Finally, we have a fifth patient who has been transplanted from her sister for myelodysplasia who has developed florid myelodysplasia and now acute leukemia in the donor derived stem cells and will be proceeding to her second allogeneic transplantation procedure, but this time to eradicate the donor derived myelodysplasia.
We hypothesize that this may be more common than previously appreciated and we plan to query the CIBMTR database regarding the degree of abnormal donor derived cytogenetics that are encountered and how frequently these evolve to donor derived malignant states.

Given the potential for selection bias (only those patients with significant abnormalities are likely to have cytogenetic studies performed, at least late after HSCT), and the small numbers of cases anticipated, a true incidence may not be determined. However, the study will be able to describe the number of cases, the recurrent abnormalities, highlight unique cases (such as benign mosaicism), and make estimates regarding the significance of these abnormalities. In addition, we can begin to describe follow up procedures if appropriate, and make use of these data to describe the impact on donor follow up, evaluation and care.

### 3.0 STUDY POPULATION:

The study will include recipients undergoing unrelated donor HSCT and reported to the CIBMTR from 1990 - 2005 who develop a new malignancy of donor origin, as well as recipients reported to NMDP as developing cytogenetic abnormalities of donor cell origin. Cord blood recipients will be excluded. Patients developing PTLD will be excluded.

### 4.0 VARIABLES TO BE DESCRIBED:

**Patient related:**
- Age: in decades
- Sex: male vs. female
- Disease at transplant
- Cytogenetic abnormalities associated with disease
- Disease stage at transplant: early vs. intermediate vs. advanced
- Prior chemotherapy and radiotherapy regimens

**Donor related:**
- Age: in decades
- Sex: male vs. female
- Date of stem cell collection
- CBC at original evaluation

**Transplant characteristics:**
- Year of transplant
- Donor-recipient sex match: M-M vs. M-F vs. F-M vs. F-F
- Source of stem cells: BM vs. PB
- Unrelated donor-recipient HLA match: well-matched vs. partially matched vs. mismatched vs. missing
- Conditioning regimen: Cy+TBI±other vs. TBI±other vs. Bu+Cy±other vs. Cy±other vs. Flu±other vs. other
- Conditioning intensity: ablative vs. nonablative vs. reduced intensity
- GVHD prophylaxis: T-cell depletion vs. other
- Days from transplant to neutrophil engraftment
- Days from transplant to platelet engraftment:
- Time from transplant to Acute (in days) or Chronic GVHD (in months)
Donor derived disease:
- Type of donor derived disease or cytogenetic abnormality
- Time from transplant to diagnosis of donor derived malignancy or cytogenetic abnormality
- Method of determination that cells were of donor origin (one or more may apply): sex mismatch observed on cytogenetics vs. interpretation of cytogenetics in conjunction with chimerism analysis vs. detection of cytogenetic abnormality in donor graft vs. identification of clinical or cytogenetic abnormality in the donor
- For subjects with cytogenetic abnormality only (no disease):
  - Abnormality history
  - Disease occurrence: yes vs. no
  - Date of last follow up
  - Results of follow up bone marrows and cytogenetic reports

Donor evaluation after identification of donor derived abnormality:
- Stored sample of donor graft evaluated: yes vs. no
- Donor contacted: yes vs. no
- Donor evaluated: yes vs. no
- Donor evaluation findings
- Donor bone marrow biopsy performed: yes vs. no

5.0 DATA COLLECTION:

Patient-, donor- and transplant-related variables will be captured using the standard CIBMTR/NMDP forms. A supplemental data collection form will be prepared that will capture donor derived disease and donor evaluation information. Bone marrow biopsy, cytogenetic, and chimerism reports will be requested along with supplemental data. Supplemental data will be abstracted from charts for cases reported to the NMDP, and transplant and donor centers will be contacted for additional data as needed. Transplant centers reporting eligible patients to the CIBMTR will be contacted for additional data.

6.0 STUDY DESIGN:

Descriptive tables of patient-, donor-, transplant-related characteristics will be prepared.

7.0 REFERENCES:


Study Proposal 1208-45

Study Title:
Impact of Growth Factor Mobilization on Donor Bone Marrow Harvest
Steven Pincus, MD, PhD, Saint Louis University, St. Louis, MO

Specific Aims:
The purpose of this exploratory study is to compare mobilized marrow to resting marrow as a hematopoietic progenitor cell (HPC) source for engraftment. Secondary objectives including assessing patient survival, GVHD, and effects on the donor.

Scientific Justification:
Donors receive filgrastim for peripheral blood HPC mobilization prior to leukapheresis. It is generally assumed that the benefits of PBHPC transplant are due to the larger number of cells harvested and subsequently available for transplant. However it is possible that at least part of the benefit is due to activation or modulation of donor HPCs. PBHPC as a transplant source leads to higher rates of cGVHD in the recipients.

Growth factor mobilized marrow provides many of the benefits of PBHPC without the increased number of T cells present in PB. A number of transplant programs have been using hematopoietic growth factors to mobilize marrow in healthy related donors. In pediatric patients, a randomized trial of mobilized versus non-mobilized marrow is being performed. Currently a CIBMTR study is being performed in patients with severe aplastic anemia (GS05-02).

In our institution, related donors routinely receive GCSF for mobilization. This leads to higher marrow cellularity and higher numbers of harvested cells while at the same time collecting smaller volumes and shortening the duration of the harvest procedure. Engraftment has been prompt and we have not seen any increase in post transplant morbidity or mortality.

It is likely that many of the benefits of PBSCT can be realized by using mobilized marrow without the increased risk of chronic GVHD. Furthermore, donor benefits may be realized by eliminating the need for donor blood banking, shorter anesthesia time and less postoperative pain due to fewer aspirations.

Patient Eligibility Criteria:
Patients receiving marrow mobilized by growth factors. Parameters to measure include neutrophil and platelet engraftment, 100 day and one year survival, acute and chronic GVHD, and transplant related mortality. Characteristics of the graft, such as volume, cellularity, and T cell content if available.

Study Design:
Initially a description of eligible patients would be obtained including year of transplant, age, diagnosis, sex, type of preparative regimen, and GVHD prophylaxis. If sufficient patients are available, a subset would be selected. This subset would then be matched to comparable patients who received non-mobilized marrow. Feasability and best statistical approach will be determined with the guidance of the statistical staff.
Characteristics of patients who received 1st allogeneic stem cell transplants with a related mobilized BM vs standard BM graft since 1995 and reported to the CIBMTR

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Mobilized BM</th>
<th>Standard BM</th>
</tr>
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<tbody>
<tr>
<td></td>
<td>N Eval</td>
<td>N (%)</td>
</tr>
<tr>
<td>Number of patients</td>
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<td></td>
</tr>
<tr>
<td>Number of centers</td>
<td>129</td>
<td></td>
</tr>
<tr>
<td>Age, median (range), year</td>
<td>525</td>
<td>31 (&lt;1-64)</td>
</tr>
<tr>
<td>0-10</td>
<td>70 (13)</td>
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<tr>
<td>11-20</td>
<td>118 (22)</td>
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<td>21-30</td>
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<td>31-40</td>
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<td>41-50</td>
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<td>51-60</td>
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<td></td>
</tr>
<tr>
<td>over 60</td>
<td>5 (1)</td>
<td></td>
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<tr>
<td>Sex, male</td>
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<td>298 (57)</td>
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<td>Performance score</td>
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<td>≥90</td>
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<tr>
<td>AML-acute myelogenous leukemia</td>
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<tr>
<td>ALL-acute lymphoblastic leukemia</td>
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<td>CML-chronic myelogenous leukemia</td>
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<td>MDS-myelodysplastic-myeloprolif.disorder</td>
<td>47 (9)</td>
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<td>Other acute leukemia</td>
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<tr>
<td>NHL-non hodgkin lymphoma</td>
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</tr>
<tr>
<td>HD-hodgkin lymphoma</td>
<td>2 (&lt;1)</td>
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</tr>
<tr>
<td>MYE-plasma cell disorder, multiple myeloma</td>
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<td></td>
</tr>
<tr>
<td>Other Malignancies</td>
<td>2 (&lt;1)</td>
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</tr>
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<td>BC-breast cancer</td>
<td>3 (1)</td>
<td></td>
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<td>22 (4)</td>
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<td>differentiation or function</td>
<td></td>
<td></td>
</tr>
<tr>
<td>SCID &amp; other immune system disorders</td>
<td>13 (2)</td>
<td></td>
</tr>
<tr>
<td>Inherited disorder of metabolism</td>
<td>2 (&lt;1)</td>
<td></td>
</tr>
<tr>
<td>Histiocytic disorders</td>
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Continued.

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Mobilized BM</th>
<th>Standard BM</th>
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<tbody>
<tr>
<td></td>
<td>N Eval</td>
<td>N (%)</td>
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<td>Conditioning regimen</td>
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<td>Myeloablative</td>
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<td>RIC/NST</td>
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<td>369 (5)</td>
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<tr>
<td>To be classified</td>
<td>23 (4)</td>
<td>372 (6)</td>
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<td>GVHD prophylaxis</td>
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<td>6728</td>
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<tr>
<td>T-cell depletion</td>
<td>39 (7)</td>
<td>616 (9)</td>
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<tr>
<td>FK506+/-others</td>
<td>52 (10)</td>
<td>305 (5)</td>
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<tr>
<td>CSA+MTX+/-others</td>
<td>361 (69)</td>
<td>4646 (69)</td>
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<tr>
<td>CSA+/-others (no MTX)</td>
<td>56 (11)</td>
<td>933 (14)</td>
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<tr>
<td>MTX+/-others (no CSA)</td>
<td>6 (1)</td>
<td>87 (1)</td>
</tr>
<tr>
<td>To be classified</td>
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<td>141 (2)</td>
</tr>
<tr>
<td>Donor/recipient HLA match</td>
<td>525</td>
<td>6728</td>
</tr>
<tr>
<td>HLA-identical sibling</td>
<td>452 (86)</td>
<td>5824 (87)</td>
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<tr>
<td>HLA-identical other relative</td>
<td>14 (3)</td>
<td>180 (3)</td>
</tr>
<tr>
<td>Related, 1-antigen mismatch</td>
<td>37 (7)</td>
<td>430 (6)</td>
</tr>
<tr>
<td>Related, 2 or more-antigen mismatch</td>
<td>22 (4)</td>
<td>294 (4)</td>
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<td>Donor age, median (range), year</td>
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</tr>
<tr>
<td>0-10</td>
<td>98 (19)</td>
<td>1244 (18)</td>
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<td>11-20</td>
<td>75 (14)</td>
<td>1250 (19)</td>
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<td>21-30</td>
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<td>31-40</td>
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<td>Over 60</td>
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<td>7 (1)</td>
<td>113 (2)</td>
</tr>
<tr>
<td>Year of transplant</td>
<td>525</td>
<td>6728</td>
</tr>
<tr>
<td>1995-1999</td>
<td>266 (51)</td>
<td>4875 (72)</td>
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<tr>
<td>2000-2004</td>
<td>205 (39)</td>
<td>1387 (21)</td>
</tr>
<tr>
<td>2005 and beyond</td>
<td>54 (10)</td>
<td>466 (7)</td>
</tr>
<tr>
<td>Median follow-up of survivors, months (range)</td>
<td>290</td>
<td>3785</td>
</tr>
</tbody>
</table>

Notes:
*Patients with severe aplastic anemia were deleted because we had another study in Graft Sources working committee looking at the same topic for patients with severe aplastic anemia.

Completeness index of follow-up: mobilized BM-61% Standard BM-64%.
Study Proposal 1208-32

Study Title:
Prevalence and Clinical Significance of Monoclonal B Cell Lymphocytosis (MBL) in Unrelated Hematopoietic Stem Cell Donors
Matthew Seftel, James Johnston, Clive Zent, Carmen Morales, Donna Wall
University of Manitoba, Winnipeg, Manitoba, Canada
Mayo Clinic, Rochester, MN

Specific Aims:
1. To establish the prevalence of MBL in unrelated hematopoietic stem cell donors.
2. To establish whether unrelated donors with MBL can transfer such cells to recipients, with the subsequent generation of post-transplant complications including donor derived lymphoproliferative disorders.

Scientific Justification:
CLL is the most common form of leukemia among adults in western countries. Diagnosis of CLL requires a count of > 5x10^9/litre circulating B cells. Asymptomatic persons with monoclonal circulating B cell populations are now defined as having monoclonal B-cell lymphocytosis (MBL). People with MBL can be further subdivided into those with lymphocytosis (“clinical MBL”) and those with normal lymphocyte counts in whom the diagnosis is often made as a result of population surveys. The clinical relevance of MBL is currently being investigated and remains uncertain.

MBL occurs in a large number of otherwise healthy people. Among adults with a normal lymphocyte count the prevalence of MBL is estimated to be 2-5% with a age-dependent increase from 2.1% of 40- to 59-year-olds to 5.0% of 60- to 89-year-olds. In contrast, MBL occurs in 13.9% in subjects with blood lymphocyte counts between 4 and 5x10^9/L. The risk of progression of MBL to CLL that requires treatment is currently under investigation. Current estimates are that patients with MBL and lymphocytosis have an approximately 1% annual risk of progression to CLL or another B cell lymphoproliferative disorder but the risk for patients without lymphocytosis is likely to be considerably lower.

Given the relatively high prevalence of MBL, recipients of matched unrelated donor allogeneic BMT could be at appreciable risk of receiving hematopoietic stem cells from a patient with unrecognized MBL. Transfer of CLL after allografting has been reported. In a registry study of 19 syngeneic transplants for CLL, there was one case of “relapsed” CLL post transplant in which the CLL cells were later found to be of donor origin. This supports the concept that familial CLL could be transferred from recipient to donor. Three cases of donor derived CLL were reported where non-syngeneic donors were used. More recently, CLL was diagnosed in a patient with AML who received an allograft from her brother. Marrow CLL cells were noted after 3 months post-transplant, with progression to frank CLL over the next year. The donor developed CLL 26 months after donating marrow and in retrospect had had MBL at the time of transplant.

In addition to concerns about pre-existing B cell clonality in donors, there is a possibility that exposure to myeloid growth factors may promote genetic and epigenetic abnormalities in donor hematopoietic cells. If this were the case, there may be a significant interaction between donor MBL cells and growth factor exposure, with potential clinical consequences both for donors (e.g. leukemia) and recipients (e.g. new malignancy, engraftment failure, poor immune reconstitution, or relapse of the primary malignancy from an attenuated graft-vs.-tumor effect).
Single BMT centres have described the use of routine bone marrow aspirate analysis to screen for occult malignant disease in related donors\textsuperscript{11,12}. However, this technique is considerably less sensitive than flow cytometry of peripheral blood cells for the diagnosis of MBL. Moreover, MBL may not be readily apparent using non-specific cytogenetic screening of blood or bone marrow aspirates.\textsuperscript{13} There is thus a need to determine if MBL is a risk for allogeneic BMT recipients and if routine screening of all donor blood for MBL should be instituted, particularly in older donors or those with a family history of CLL\textsuperscript{6,14}. Based on the data from case reports and small case series, a larger and more systematic evaluation of this issue is warranted. The results of this study would have practical implications for the safety of both unrelated donors and recipients.

**Patient Eligibility Criteria:**
NMDP registered unrelated donors aged $\geq 50$ years for whom data on recipients are also available. According to NMDP data, there are currently 666 donors aged $\geq 50$ for whom donor samples and recipient clinical details are available\textsuperscript{16}. Relevant clinical and demographic data will be obtained from this NMDP cohort including age, gender, medical history (if any), family history of malignancy, and whether donation was by GCSF-mobilized cells or by marrow harvest. The clinical outcomes of the recipients will also be recorded, specifically: relapse of their underlying malignancy; incidence of a new malignancies, incidence of engraftment failure, incidence of acute and chronic GVHD.

**Data Collection:**
Data on unrelated donor and recipients will be obtained from NMDP.

**Sample Requirements:**
Stored cellular specimens from the NMDP will be analysed at facilities of the Manitoba Institute of Cell Biology (University of Manitoba): Specimens will be analysed by flow cytometry to assess the number of B cells and evidence of clonality, as previously described\textsuperscript{6}. If clonality is present, then four color flow cytometry will be carried out to determine whether the patient has a CLL or non-CLL MBL \textsuperscript{6}. This assay is carried out routinely in our institute for the evaluation of minimal residual disease in CLL. In addition, abnormal populations will undergo FISH and IgVH gene mutational analysis. These assays are routinely carried out on samples for the Manitoba CLL Tumor Bank, which is housed in the Manitoba Institute of Cell Biology. These latter studies will demonstrate whether the MBL has biological markers of poor prognosis, e.g. unmutated IgVH and/or deletion 17p13.

**Study Design:**
1. We hypothesize that the prevalence of MBL in healthy unrelated donors aged $\geq 50$ will be in the range of 2-5%. If this hypothesis were correct, screening of unrelated donors for MBL may be warranted. The alternative outcome is that unrelated donors have a much lower prevalence of MBL; this would serve as reassurance to prospective recipients of unrelated donor transplants.
2. We will collect clinical and demographic data from the unrelated donors. We will obtain CBC with absolute lymphocyte count at donation (prior to any growth factors). All available samples will be analysed for MBL. Samples with B cell clonality will undergo four color flow cytometry, IgVH gene analysis and FISH testing.
3. Outcomes of recipients will be collected and analysed. Specific outcomes of interest include age, indication for transplant, type of BMT (PB vs. marrow), acute and chronic GVHD (with grade), engraftment data, cumulative incidence of relapse, treatment related toxicity, second malignancy, and overall survival.
4. For donors found to have MBL, long term outcomes of these donors will be collected if available. Specifically, we wish to know whether these donors subsequently developed CLL or other malignancies.
5. If any donors with MBL are found, the post BMT outcomes of their respective recipients will be compared to the other recipients whose donors were free of MBL. This comparison will primarily be
a descriptive one. Depending on the numbers of donors with MBL, detailed statistical analyses may not be indicated.

References:
Characteristics of donors ≥ 50 years and their recipients reported to the National Marrow Donor Program, 1988-2008.

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>N Eval</th>
<th>N (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of patients</td>
<td>1143</td>
<td>1143</td>
</tr>
<tr>
<td>Number of centers</td>
<td>135</td>
<td></td>
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<tr>
<td>Recipient age at transplant, median (range), years</td>
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<td>21 (&lt;1-75)</td>
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<td>Recipient age at transplant</td>
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<tr>
<td>0-9</td>
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<td>10-19</td>
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<td>20-29</td>
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<td></td>
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<tr>
<td>30-39</td>
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<td>40-49</td>
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<td>50-59</td>
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<td>60-69</td>
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<tr>
<td>Over 70</td>
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<td>Donor sex, male</td>
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<td>Female- male</td>
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<tr>
<td>Female-female</td>
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<tr>
<td>Disease</td>
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<tr>
<td>AML-acute myelogenous leukemia</td>
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</tr>
<tr>
<td>ALL-acute lymphoblastic leukemia</td>
<td>206 (18)</td>
<td></td>
</tr>
<tr>
<td>Other leukemia</td>
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</tr>
<tr>
<td>CML-chronic myelogenous leukemia</td>
<td>255 (22)</td>
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<tr>
<td>MDS-myelodysplastic-myeloprolif.disorder</td>
<td>131 (11)</td>
<td></td>
</tr>
<tr>
<td>NHL-non hodgkin lymphoma</td>
<td>59 (5)</td>
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<tr>
<td>HD-hodgkin lymphoma</td>
<td>3 (&lt;1)</td>
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<td>MYE-plasma cell disorder, multiple myeloma</td>
<td>11 (1)</td>
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</tr>
<tr>
<td>Other Malignancies</td>
<td>5 (&lt;1)</td>
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<tr>
<td>BC-breast cancer</td>
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<td>SAA-severe aplastic anemia</td>
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<tr>
<td>Inherited abnormalities of erythrocyte differentiation or function</td>
<td>2 (&lt;1)</td>
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<td>Inherited disorder of metabolism</td>
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<td>2003-2008</td>
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<tr>
<td>Median follow-up of survivors, (range), years</td>
<td>363</td>
<td>53 (&lt;1-231)</td>
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*Data have not been modeled for the NMDP Corrective Action Plan.

**Sample availability to be determined.
CIBMTR DS09-03

EFFECTS OF SECOND DONATIONS ON PBSC DONORS AND COLLECTION YIELDS

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1.0 **HYPOTHESIS:**

The effects on healthy subjects of the collection of bone marrow and mobilized peripheral blood stem cells (PBSCs) have been well documented. The collection yields, changes in blood counts associated with the donation and the symptoms and adverse effects associated with donation have all been well described. However, most studies have focused on a healthy subject’s first stem cell donation. Occasionally, a healthy subject donates stem cells more than one time. Based on the results of studies of a small number of people donating a second time, we believe that the effects of the second donation will not differ from those of the first donation.

2.0 **SPECIFIC OBJECTIVES:**

2.1 Compare unrelated donors making two PBSC donations with a control group of randomly selected NMDP PBSC donors.

2.2 Compare the first donation experience and first donation yield of people making two PBSC donations with the typical PBSC donor’s donation experience and collection yield.

2.3 For people making two PBSC donations compare the quantity of cells collected during the first and second PBSC donations.

2.4 For people making two PBSC donations compare the donor’s pre-mobilization blood counts, pre-collection blood counts, and post-donation blood counts between first and second PBSC donation.

2.5 For people making two PBSC donations compare donor symptoms and adverse events associated with the first and second PBSC donations.

3.0 **SCIENTIFIC JUSTIFICATION:**

The donation of the bone marrow or G-CSF-mobilized PBSC concentrates by healthy subjects is associated with many symptoms, changes in blood counts and occasional complications [1-11]. Most marrow and PBSC transplants involving HLA compatible unrelated donors and recipients are successful and only one donation is required. However, some unrelated donors are asked to donate a second time to treat graft failure or disease relapse in the same recipient or to treat another recipient [12]. Since the CD34+ cell collection yields are higher and rates of engraftment are faster when PBSC concentrates are transplanted rather than marrow, most second donations involve the collection PBSC concentrates rather than marrow. The effects of a single G-CSF-mobilization and PBSC donation on symptoms, time to recovery, complications, changes in blood counts and recovery of blood counts have been well documented, but little is known about the effects of a second PBSC donation on the donor and collection yield.

When healthy subjects are given 5 days of G-CSF to mobilize hematopoietic stem cells prior to apheresis, they experience headache, bone pain, myalgia, nausea, and insomnia [1-3,6]. Generally, these symptoms are mild and disappear within a few days of the collection [3,6], but 10% experience severe or intolerable pain [1].
During the collection of PBSC concentrates healthy subjects can experience citrate toxicity, thrombocytopenia, bleeding or hematoma [1,2]. The risk of a complication is greater in donors who have poor venous access and require central venous line placement for the apheresis procedure. The risk of side effects is also increased in women and obese donors [1]. PBSC donors also rarely experience severe chest or back pain [1]. PBSC donors given G-CSF also experience transient enlargement of their spleen [13,14] and approximately 1 in 10,000 experience spontaneous rupture of the spleen.

During the administration of G-CSF healthy subjects experience a slight fall in hemoglobin levels [1,4]. Following the donation of G-CSF-mobilized PBSC components healthy subjects experience an immediate fall in platelet counts due to the collection of platelets with the hematopoietic stem cells [3]. The recovery of platelet counts is delayed by approximately one week due to the suppression of platelet production by G-CSF [15]. Neutrophil counts also fall slightly approximately one month post donation [4,5]. The donor’s hemoglobin and platelet counts return to baseline levels 1 year post donation [1,16], but the white blood cell counts remain slightly elevated [1].

Less is known about second PBSC donations. Studies of small numbers of healthy subjects who have donated PBSC concentrates twice have found that when the first and second donations are separated by more than 3 months, the pre-apheresis concentration of CD34+ cells and mononuclear cells and collections yield are similar for the first and second donations [16,17]. However, the recoveries of blood counts, donor symptoms, and adverse events associated with second PBSC donations have not been investigated.

Studies of second PBSC donations must consider that the people making two PBSC donations may not be the same as typical NMDP PBSC donors. There may be a selection bias involving second donations. People who have a difficult first donation or who experience more severe adverse effects or symptoms may not be asked by their donor center to donate a second time or they may not agree to donate again if asked. Since gender and body mass index effect the PBSC donor’s experience [1], the gender and body mass index may differ between those making 2 PBSC donations and those who have made only one donation. In addition, the donor’s age, gender, and race effects the number of CD34+ cells mobilized and collected [18]. Since the dose of CD34+ transplanted effects engraftment, graft failure may be more common with PBSC concentrates collected from certain donor subsets.

The purpose of this study is to compare the effects of first and second donations on PBSC donor symptoms, adverse events, blood counts, and collection yields. Since most healthy subjects who donated stem cells on more than one occasion have donated PBSCs, only people donating G-CSF mobilized PBSC concentrates twice will be studied. Since donor factors affect the donation experience, the age, race, gender and body mass index of people donating PBSCs twice will be compared to the typical NMDP donor.

4.0 STUDY POPULATION:

Subjects donating G-CSF mobilized-PBSC for two unrelated donor transplants will be eligible.
5.0 OUTCOMES:

5.1 First and second PBSC donation collection procedures. Each donation of PBSCs involves one or two apheresis procedures and each apheresis procedure involves the processing of a variable amount of whole blood. For the first and second donations the number of apheresis procedures performed, the volume of whole blood processed during each apheresis procedure and total volume of blood processed for each donation will be assessed.

5.2 PBSC collection yields of the first and second donation. Each apheresis procedure the number of mononuclear cells and CD34+ cells collected and the number of cells collected per liter of whole blood processed will be assessed. The total number of mononuclear and CD34+ cells and number per volume of whole blood processed for each donation will also be assessed.

5.3 Blood counts pre- and post-donation. The hemoglobin, white blood cell counts (WBC), absolute neutrophil counts (ANC), and absolute mononuclear cells count will be assessed at baseline, pre-donation, immediately post-donation, and one, six and 12 months following the first and second donations.

5.4 Collection related adverse events: Incidence of severe adverse events as reported by the collection center, reported rates of citrate toxicity, bleeding, rates of the need for placement of a central line for the first and second donations.

5.5 Incidence of grade II-IV and grade III-IV Cancer and Leukemia Group B (CALGB) toxicity and Eastern Cooperative Oncology Group (ECOG) Performance Status. Peak toxicity levels during the mobilization and collection process for the following categories will be assessed: fever, fatigue, skin rash, local-site reaction, nausea, vomiting, anorexia, insomnia, dizziness, syncope, infection, headache, and pain for the first and second donations. In addition, maximum ECOG performance status score during the course of mobilization and donation should be compared.

5.6 Serious unexpected or life-threatening events. Events that were fatal or immediately life threatening, resulted in prolonged hospitalization, or permanent disability, was a congenital abnormality, cancer or death.

5.7 Long-term pain or disability: pain or disability associated with donation that has not resolved by 1 month post-donation

6.0 VARIABLES TO BE ANALYZED:

Donor related:
- Age at donation: continuous
- Gender: female vs. male
- Weight/body mass Index: underweight vs. normal vs. overweight vs. obese
- Race: Caucasian vs. non-Caucasian
Collection related:
- WBC: change in counts from pre-donation to pre-collection to follow-up
- Platelets: change in counts from pre-donation to pre-collection to follow-up
- Hemoglobin: change in counts from pre-donation to follow-up
- % Neutrophils: change in counts from pre-donation to precollection to follow-up
- % Mononuclear cells: change in counts from pre-donation to pre-collection to follow-up
- Duration of procedure: in minutes
- Year of procedure
- Center location: international vs. domestic
- Filgrastim dose
- Volume of whole blood processed: small (< 12 L) vs. standard (12-18 L) vs. large (18+ L)
- Number of apheresis procedures for each donation: 1 vs. 2
- Duration of time between donations: continuous

7.0 STUDY DESIGN:

Compare the characteristics of the people donating twice and their donation experiences with the characteristics and experiences of typical NMDP PBSC donors. The characteristics of the people making two PBSC donations will be compared with a randomly selected control group of NMDP PBSC donors. The age, gender, race, and body mass index will be compared between groups. The PBSC donation experiences and collection yields of the randomly selected control donors will also be compared with the donation experience and collection yields of the first donation by people making two PBSC donations.

Comparison of the first and second donations: effects of the donors. For NMDP donors making 2 PBSC donations their symptoms, adverse events, changes in blood counts and collection yields will be compared between the first and second donations. Since all subjects studied will be donating PBSC concentrates twice, paired analysis tools can be used. The effects of donor gender, age, race, and body mass index on donation symptoms and toxicities, collection yields and blood counts will be investigated. The number of collections requiring central line placement, peak CALGB toxicities and ECOG performance status will be compared between the first and second donations.

Comparison of the first and second donations: the collection. The total volume of blood processed for each donation, the total duration of apheresis procedures for each donation, filgrastim dose, and collection yields will be compared between donations.

Effects of time between donation on donor experiences and collection outcome. The effects of differences in duration of time between the two donations on differences between donations in donor symptoms, adverse events, and change in performance status will be evaluated. The effects of differences in duration between the two donations on differences between collection yields between the first and second donation should also be evaluated.

Limitations on the number of subjects eligible for the study may prevent the analysis of an effect of age and race.

When randomly selecting a group of NMDP PBSC donors as a control group, it may be best to select 2 or 3 control donors for each person making 2 PBSC donations.
Descriptive tables of donor- and collection-related variables will be prepared by first and second donation. Variables will be compared between groups using the Chi-square test for categorical variables and the Kruskal-Wallis test for continuous variables.

Donor and control group gender, race and body mass index will be compared using the Chi-square test. Donor and control groups maximum CALGB toxicity and ECOG performance status will be compared using XXXX. Donor and control group age and collection yields will be compared using t-tests.

Donor WBC, platelet, hemoglobin, neutrophils, and mononuclear cell recovery after donation will be analyzed via paired t test. Logistic regression using the step-wise model selection method will be used to evaluate risk factors that might have an influence on donor symptoms and adverse events.

8.0 REFERENCES:


### Characteristics of NMDP donors donating twice and who have a 1 year follow-up form for each donation.

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<tbody>
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<td>Bone marrow-Bone marrow</td>
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<td>50+</td>
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<td>Interval from Donation 1 to Donation 2, median (range), months</td>
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<td>16 (&lt;1-52)</td>
</tr>
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Study Proposal 1208-65

Study Title:
The Effect of Race, Socioeconomic Status, and Donor Center Size on Bone Marrow and PBSC Donor Experiences
Michael Pulsipher, MD, Primary Children’s Medical Center, Salt Lake City, UT
David Stroncek, MD, Department of Transfusion Medicine, CC, NIH, Bethesda, MD

Hypothesis:
1. Though gender differences may persist, rates of CALGB/CTC toxicities, levels of pain, and percentage of patients experiencing severe or unexpected events after BM and PBSC donation will not vary based upon the donor's reported race.

2. Rates of CALGB/CTC toxicities, levels of pain, and percentage of patients experiencing severe or unexpected events after BM and PBSC donation will not vary based upon perceived SEC status as ascertained by local zip code.

3. Rates of CALGB/CTC toxicities and levels of reported pain will be similar in larger vs. smaller collection centers, but levels of severe or unexpected events after BM and PBSC donation will be increased at smaller centers.

Specific Aims:
1. Compare early donation associated toxicities (grades II-IV CALGB/CTC toxicities, peak levels of pain) in donors of BM or PBSC between:
   A. Donors reporting themselves as Black, Hispanic, (asian if there are enough) and other races with Caucasian donors,
   B. Donors living in low SEC zip codes vs. middle SEC zip codes vs. high SEC zip codes,
   C. Donors collected/harvested at centers who perform less than 10 procedures/year vs. 10-50?? procedures/year vs. higher numbers.

2. Compare apheresis collection associated toxicities (reported "severe" toxicities, need for placement of a central line, significant bleeding, etc.) for the groups outlined in 1 above.

3. Compare percentage and types of serious unexpected or life threatening adverse events after BM and PBSC for the groups outlined in 1 above.

Scientific Justification:
Recent publications have described in detail acute toxicities associated with volunteer unrelated donation of BM and PBSCs.1,2 The peak of toxicities occurs at different time points for BM and PBSC and is well understood. For BM donors, increased risks for toxicities have been noted in older donors, women, and those who used local anesthetics. For PBSC donors, increased risk of side effects were documented in women and obese donors. These studies form a baseline for further study in this area.

Studies have demonstrated lower thresholds to pain in Hispanic and African American patients;3 one study linked the differing pain thresholds to differences in oxytocin levels in African Americans.4 Other studies have shown that chronic pain differences in ethnic groups disappear when variables are appropriately controlled.5 Understanding whether there is a difference in pain risk during the process of donation based upon ethnicity could assist donor centers in advising donors prior to donation and appropriately treating donors during the process. Studies have also linked pain risk to SEC status,6 and a
study looking at risk of adverse events and pain in different SEC groups could similarly benefit donors and donor centers who council them.

Finally, donor centers vary tremendously in volume and experience. To date, a comprehensive study looking at the toxicity outcomes of donors has not looked at the variable of donor center size and experience. Such a study is important to the NMDP to assist in accreditation and quality control of centers.

Patient Eligibility Population:
The study population will include all donors of BM and PBSC for whom appropriate data is available. Full data from PBSC patients is available starting in 1999 and more detailed data from BM donors has been collected since forms were revised in 2004. Second donations will be excluded as they are being studied in a different proposal.

Data Collection:
A number of donor related variables will be assessed including:
- Age at donation: Age as a continuous variable.
- Gender: female vs. male
- Weight/body mass Index
- SEC status of low vs. middle vs. high based upon zip code
- Reported ethnicity: Black vs. Hispanic vs. Caucasian vs. other
- Donor center size (<10 vs. 10-50 vs. >50)
- PBSC and BM will be assessed separately

The following outcomes will be assessed:

Incidence of grade II-IV and grade III-IV CALGB or CTC. Peak toxicity levels during the harvest process of the following categories will be assessed: fever in the absence of signs of infection, fatigue, skin rash, local-site reaction, nausea, vomiting, anorexia, insomnia, dizziness, syncope, infection and pain.

Collection related adverse events: Incidence of SAEs as reported by the collection center, reported rates of citrate toxicity, bleeding, rates of the need for placement of a central line.

Serious unexpected or Life-threatening Events: As defined by the FDA and explained on collection forms.

Study Design:
For each of the analyses of different ethnicities, different SEC groups, and differently sized centers, BM donors will be compared with other BM donors and PBSC donors with PBSC. After univariate analyses of relevant variables, multivariate analysis will be performed to test for interactions.

References:


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</table>
CIBMTR DS09-05

EARLY AND LATE DONOR TOXICITIES ASSOCIATED WITH BM VS. PBSC COLLECTION IN NMDP DONORS

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1.0 SPECIFIC OBJECTIVES:

1.1. Compare peri-donation and post-donation associated toxicities (grades II-IV CALGB/CTC toxicities, peak levels of pain) in NMDP donors of bone marrow (BM) with NMDP donors of peripheral blood stem cells (PBSC).

1.2. Compare percentage and types of serious unexpected or life threatening adverse events after BM and PBSC donation.

1.3. Compare rates of long-term disability and chronic pain in BM vs. PBSC donors.

1.4. Identify risk factors for adverse events.

2.0 SCIENTIFIC JUSTIFICATION:

Recent publications have described acute toxicities associated with volunteer unrelated donation of BM and PBSCs. 1, 2 While the studies describe that the peak of toxicities occurs at different time points for BM and PBSC, a direct comparison of BM with PBSC using similar instruments has not been performed. For BM donors, past studies have shown increased risks for toxicities in older donors, women, and those who used local anesthetics. Long-term toxicities, including disabling pain were noted in a small percentage of donors. For PBSC donors, increased risk of side effects was documented in women and obese donors. Long-term disability has not been described.

Since 2004 the toxicity reporting for NMDP BM donors has been updated to reflect the careful toxicity reporting that has occurred with NMDP PBSC donors since 1999. This presents an opportunity to directly compare BM and PBSC donors to give a more accurate, up to date comparison of toxicities between the two methods of harvest. Such a comparison is important to define risk patterns that may point to one method as more safe for an individual donor compared to another. In addition, this direct comparison will provide the most accurate data to date for informing a donor of risks versus benefits of each approach when they are required to choose between the two approaches.

3.0 STUDY POPULATION:

The study population will include all BM and PBSC from the National Marrow Donor Program for whom data is available from baseline to 1 month post-donation on the 700 series forms. The study will include only first donations and exclude donors who donated within one month of their first donation. Donors enrolled on the BMT CTN protocol 02-01 will be excluded.

4.0 OUTCOMES:

4.1 Incidence of grade II-IV and grade III-IV CALGB or CTC. Peak toxicity levels for the following categories will be assessed from day 1 of filgrastim administration to 2 days post-donation for PB donors and from day of collection to 2 days post-donation for BM donors: fever in the absence of signs of infection, fatigue, skin rash, local-site reaction, nausea, vomiting, anorexia, insomnia, dizziness, syncope, infection and pain.

4.1.1 Risk factors for Grades II-IV bone pain and fatigue will be assessed separately for donors at their peak toxicity level during the time period outlined above and
at 1 week and 1 month post-donation (and additional timepoints if data allows).

4.1.2 Risk factors for Grades III-IV bone pain and fatigue will be assessed separately for donors at their peak toxicity level during the time period outlined above and at 1 week and 1 month post-donation.

4.1.3 Risk factors for maximum grade II-IV across all toxicities will be assessed separately for donors at their peak toxicity level during the time period outlined above and at 1 week and 1 month post-donation (and additional timepoints if data allows).

4.1.4 Risk factors for maximum grade III-IV across all toxicities will be assessed separately for donors at their peak toxicity level during the time period outlined above and at 1 week and 1 month post-donation.

4.2 Unexpected but not uncommon adverse events: Incidence of collection-related AEs within the first 30 days after harvest, such as: citrate toxicity, length of hospital stay, receipt of allogeneic red cells, and placement of a central line for the collection procedure.

4.3 Serious unexpected or Life-threatening Events: events that were fatal or life threatening or resulted in prolonged hospitalization immediately associated with or as a direct result of the harvest procedure. Permanent disability, congenital abnormality, cancer, or death occurring at any time after the harvest procedure that is possibly, probably, or definitely associated with the harvest procedure and/or G-CSF administration.

4.4 Long-term pain or disability: pain or disability associated with donation that has not returned to baseline by 1 month post-donation.

4.5 Changes in counts from pre-donation to 1 month, 1 year and 2 years post-donation (dependent on available follow-up)
- WBC
- Platelets
- Hemoglobin
- % Neutrophils
- % Mononuclear cells

4.6 Time to recovery: time from donation to report of complete recovery.

5.0 VARIABLES TO BE ANALYZED:

Main effect:
- Stem cell product donated: BM vs. PB

Donor related:
- Age at donation: 18-34 vs. 35-44 vs. 45-61
- Gender: female vs. male
- Weight/body mass Index: underweight vs. normal vs. overweight vs. obese
- Race: Caucasian vs. Black/African American vs. Hispanic/Latino vs. Asian/Pacific Islander vs. American Indian/Alaska Native vs. other
- CMV status: positive vs. negative
- WBC at baseline
- Platelet count at baseline
- Hemoglobin at baseline
- % Neutrophils at baseline
- % Mononuclear cells at baseline

**Bone marrow collection related:**
- Duration of harvest procedure: in minutes
- Year of procedure
- Center location: international vs. domestic
- Volume collected/kg and total volume
- Anesthesia type: general vs. epidural/local/spinal

**Peripheral blood apheresis related:**
- Duration of apheresis procedure: in minutes
- Year of procedure
- Center location: international vs. domestic
- Filgrastim dose
- Volume of whole blood processed: small (< 12 L) vs. standard (12-18 L) vs. large (18+ L)
- Number of collections: 1 vs. 2
- Central line placement: yes vs. no
- WBC: change in counts from baseline to pre-collection
- Platelets: change in counts from baseline to pre-collection
- Hemoglobin: change in counts from baseline to pre-collection
- % Neutrophils: change in counts from baseline to pre-collection
- % Mononuclear cells: change in counts from baseline to pre-collection

**6.0 STUDY DESIGN:**

Descriptive tables of donor- and collection-related variables will be prepared by product type. Variables will be compared between groups using the Chi-square test for categorical variables and the Kruskal-Wallis test for continuous variables.

Donors will be censored at the time of second donation: for subsequent bone marrow donations at time of second collection and for subsequent peripheral blood donations at Day 1 of filgrastim administration.

Mean changes in donor WBC, platelet, hemoglobin, neutrophils, and mononuclear cell recovery from pre- to each post-donation time point will be compared between the PB and BM groups using a 2-sample t-test. Mixed models will be used to compare these measurements between the PB and BM groups after adjusting for patient characteristics. Logistic regression will be used to compare donor symptoms and toxicities between PB and BM donors, after adjusting for donor/collection factors. Step-wise model selection will be used after forcing PB vs. BM into the model.
7.0 REFERENCES:


Study Title:
Effect of Demographics on Peripheral Blood CD34+ counts and CD34+ Cell Yields in Donors Undergoing Large Volume Leukapheresis

Specific Aims:
To determine the influence of race and ethnicity on CD34+ cell yields in allogeneic peripheral blood donors after G-CSF administration. Donors will be analyzed according to the following endpoints:
- Peripheral Blood WBC and neutrophil counts prior to start of GCSF
- Peripheral Blood CD34+ cell count on day 1 collection
- Total CD34+ cell collection on day 1 collection
- Graft composition (TNC, CD3, CD4, CD8) on day 1

Scientific Justification:
Peripheral blood stem cells (PBSC) collected after G-CSF administration are now the most common source of stem cells for allogeneic transplants due to their relative ease of collection and more rapid hematopoietic recovery. However, a small percentage of healthy donors will have a poor mobilization response to GCSF, resulting in additional apheresis or a second mobilization. Analysis of donor factors have identified age, weight, and gender as possible variables affecting the efficiency of collection. Except for age, however, results have not been consistent.

The effect of ethnicity on stem cell collections has not been extensively investigated. The only published series consists of 639 allogeneic donors who had PBSC collections using G-CSF alone. Donors were self-categorized as white (412), black (75), Hispanic (116), and Asian/Pacific (36). Univariate analysis identified white donors had a blunted CD34+ mobilization response which remained significant in multivariate analysis. Black donors had the highest CD34+ cell counts after mobilization while Asian/Pacific donors had the highest CD34+ cell counts after adjustment for BMI and body weight. The observation that black donors appear to mobilize better than white donors is surprising and is in contrast to the lower CD34+ cell count in black cord blood donors and the lower baseline neutrophil counts in African Americans. We have performed a case control analysis of 22 African Americans and 12 Hispanic donors matched with 34 Caucasian donors from our center and confirm baseline lower WBC and ANC prior to apheresis. Our results also confirm the increased CD34+ cell yield in African Americans over Caucasians (see table). We also noted CD34+ cell collections of Hispanic donors fall between African Americans and Caucasians.

<table>
<thead>
<tr>
<th>Pre-mobilization WBC</th>
<th>African American</th>
<th>Hispanic</th>
<th>Caucasian</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pre-apheresis peripheral blood WBC</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total CD34+ (x10^6)</td>
<td>9.5</td>
<td>7.0</td>
<td>6.4</td>
</tr>
<tr>
<td>% CD34+ of TNC</td>
<td>0.9</td>
<td>0.8</td>
<td>0.7</td>
</tr>
<tr>
<td>CD34+ cells/kg (x10^6)</td>
<td>10.7</td>
<td>9.2</td>
<td>8.0</td>
</tr>
</tbody>
</table>

Because there is minimal published information on the effect of race and ethnicity on mobilization, we would like to determine whether there is a correlation between this factor and successful stem cell collections. If there is enough information, we would also like to analyze the composition of the graft to determine if there is any ethnic variation.
Patient Eligibility Population:
Since insufficient data is collected about sibling donor collection and unrelated donor forms are more complete, we will confine the study to unrelated donors. The study will include all unrelated peripheral blood donors reported to the CIBMTR. We will investigate all race and ethnic types identified in the CIBMTR. Cord blood units will be excluded from the analysis.

Predictor Variables to be Analyzed:

Donor Factors
- Gender (male vs. female)
- Age
- Weight (BMI, kg/m²)
- WBC count (baseline, if available)
- Neutrophil count (baseline, if available)
- Platelet count (baseline, if available)

GCSF Factors
- Dose, Dose/kg
- Dose schedule

Procedure Factors
- Pre-apheresis (day 1) WBC count (if available)
- Pre-apheresis (day 1) Platelet count (if available)
- Pre-apheresis (day 1) CD34+ count (if available)
- Number days of apheresis
- Apheresis volume (on day 1 and total)

Product Factors
- TNC count on day 1 and total (total and per kg)
- CD34+ count on day 1 and total (total and per kg)
- CD3+ count on day 1 and total (total and per kg)
- CD4+ count on day 1 and total (total and per kg)
- CD8+ count on day 1 and total (total and per kg)

Data collection:
Donor and graft characteristics will be obtained from the CIBMTR database. No additional supplemental data collection is anticipated.

Study Design:
This is a descriptive study to determine whether a significant difference occurs between donor ethnicity and efficiency of stem cell collections. This study will also examine whether there are differences in graft composition based on race and ethnicity. Both univariate and multivariate analysis will be performed on predictor variables to control for potential confounding factors such as age, GCSF, weight, and gender.

References:
## Characteristics of NMDP peripheral blood donors

<table>
<thead>
<tr>
<th></th>
<th>Caucasian</th>
<th>Black</th>
<th>Asian</th>
<th>Hispanic</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N eval</td>
<td>Median (range)</td>
<td>N eval</td>
<td>Median (range)</td>
</tr>
<tr>
<td><strong>Number of donors</strong></td>
<td>5329</td>
<td>338</td>
<td>310</td>
<td>649</td>
</tr>
<tr>
<td><strong>Prior to start of GCSF</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>WBC (x 10^9/L)</td>
<td>5329</td>
<td>6.3 (2.8-16)</td>
<td>338</td>
<td>5.9 (2.4-15.0)</td>
</tr>
<tr>
<td>Neutrophil (x 10^9/L)</td>
<td>5328</td>
<td>3.9 (1.1-12.9)</td>
<td>338</td>
<td>3.3 (1.0-12.2)</td>
</tr>
<tr>
<td><strong>Day 1 Collection</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Peripheral blood CD34+ (x 10^6/L)</td>
<td>4045</td>
<td>82.6 (&lt;1-670.3)</td>
<td>266</td>
<td>111.9 (5.4-1088.7)</td>
</tr>
<tr>
<td>Total CD34+ cells collected (x 10^6)</td>
<td>4595</td>
<td>590.6 (0.8-6748.1)</td>
<td>301</td>
<td>699 (7.9-3984.5)</td>
</tr>
<tr>
<td>Total TNC (x 10^9/L)</td>
<td>5322</td>
<td>76.6 (6.1-379.1)</td>
<td>338</td>
<td>80.5 (8.0-275.3)</td>
</tr>
</tbody>
</table>
Donor Outcome Workshop  
Berne, August 27th/28th, 2009

Minutes

Attendees:
Audat F (France Greffe de Moelle), Ball L (LUMC), Bengtsson M (Tobias Registry), Brezinova L (Czech Stem Cells Registry), Bozic L (Austrian Bone Marrow Donor Registry), Buhrfeind E (SBSC), Buser A (Blood transfusion center Basel), Confer D (NMDP/CIBMTR), Fechter M (Europodonor), Gratwohl A (University hospital Basel), Hägglund H (Karolinska University hospital, Huddinge/Nordic donor registry), Halter J (University hospital Basel), King R (NMDP/CIBMTR), Korthof E (LUMC), Lawlor E (IBTS), Marry E (France Greffe de Moelle), Mengling T (DKMS), Ng-McClelland J (C.W. Bill Young DOD Marrow Donor Program), Nicoloso de Faveri G (SBSC), Rajadhayasksha S (Tata Memorial Hospital), Rosenmayr A (Austrian Bone Marrow Registry), Reti M (Szent Istvan and Szent Laszlo University hospital Budapest), Schmidt A (DKMS), Tassi C (University hospital Bologna), van Walraven AM (LUMC), Worel N (University hospital Vienna), Zahlavova L (Czech Stem Cells Registry)

1. **Thursday, August 27th, 2009**

During the first day of the workshop, the participating members from the different countries presented their donor follow-up procedures, completed by a presentation of Anne-Marie vanWalraven about the SEAR/SPEAR, the WMDA adverse event reporting system. These reports showed a wide range of donor follow-up procedures, strategies and expectations, giving first inputs and fundamental issues for the discussion on the requested minimal data the following morning.

Participants agreed that large data sets are necessary for reliable analyses. However, limitation of resources are a reality for all teams and has to be accounted for future data collection.

2. **Friday, August 28th, 2009**

The goal of this session was to get a consent to a minimal data set (called A-data) which should be collected globally. The lively and very constructive discussions led to the proposal listed in table 1 and 2.

The items should be entered in a database. How these items will be “extracted” from a donor questionnaire has to be discussed later on and will finally be defined by each group. Participants pointed out the importance of an adequate wording for the donor, e.g. using open questions and avoiding a list of severe illnesses.

**Further tasks**

- The minimal data set (table 1 and 2) will be compiled as a paper draft to be presented at the WBMT meeting during the WMDA meeting, 6th of November 2009 in Minneapolis.
- Publish the consensus on a minimal data set on behalf of WBMT. A draft of the paper will be prepared by Jörg Halter. Members of the writing committee are (in alphabetical order): Mats Bengtson, Dennis Confer, Mirjam Fechter, Alois Gratwohl,
Hans Hägglund, Jörg Halter, Roberta King, Evelyne Marry, Grazia Nicoloso de Faveri, Alexander Schmidt, Bronwen Shaw, Annemarie van Walraven, Nina Worel, a representative from APBMT and a representative from EMBMT

- The final content of the database and rules for data analysis will be further decided by WBMT
- Dietger Niederwieser will be asked to distribute this protocol within WBMT, and inform EBMT, CIBMTR, WMDA, APBMT, EMBMT
- All participants of the donor outcome workshop agreed to work further on the definition of a more detailed donor outcome dataset (B-data).

For the protocol:

Dennis Confer, Alois Gratwohl, Jörg Halter
Table 1: minimal data set to be reported after the end of the donation procedure

Data reporting includes donor and procedure characteristics. The time interval covers the period from the beginning of the donation procedure until day 30 after the completion of the procedure. The data should be reported between 30 and 100 days after the donation procedure.

Donor data:
- Donor ID: there is no global unique donor identifier yet. Each center/registry defines the unique donor ID by its own
- Age at donation
- Sex
- Relationship to the recipient:
  - Twin
  - Sibling
  - Other family donor
  - Unrelated donor

Harvest data
- Start date of the procedure
- Was the product collection completed?
  - yes/no
- Number of harvest/subsequent donation
- Were hematopoietic growth factors used (eg. GCSF)?
  - yes/no
- Were cell binding inhibitors used (eg. plerixafor)?
  - yes/no
- Was erythropoietin used?
  - yes/no
- Were other drugs used for mobilization?
  - yes/no (without further specification)

Product:
- BM (including harvest of MSC)
- PBSC
- Both (BM and PBSC)
- Unstimulated leucapheresis (eg. DLI)
- Others

Complications in temporal association with the donation procedure:
- report only severe adverse events (SAE) with ICD coding
  (A list with a selection of the anticipated most frequent events will be prepared)
- every SAE occurring in the interval between start of the donation procedure and day 30 after end of the donation procedure must be reported
Definitions:
1. Definition of donation procedure: procedure with the objective of harvest an adequate number of therapeutic cells (HSC, MSC, DLI (T, NK), others). The donation procedure starts with the first injection of mobilizing agents, start of anesthesia or start of apheresis (in case of non-stimulated leucapheresis, eg. for DLI) and usually ends with one or multiple harvests. However, the accomplishment of a harvest is not a requirement. Even if the preparative actions are stopped prematurely (due to donor's or recipient's reasons) the activity fulfils the definition of a donation procedure and the donor will have to be registered and followed.

2. Definition of SAE is the same as in WMDA and includes:
   - death
   - life-threatening event
   - require in-patient hospitalization or prolongation of existing hospitalization due to WHO grade 3 or 4 toxicity (Miller AB et al. Cancer 1981; 47: 207-214)
   - persistent or significant disability/incapacity

3. The current ICD10 code should be used. ICD coding should include the letter and the first two numbers (eg. I21 for acute myocardial infarction). For more details and ICD online search please go to www.who.int/classifications/icd/en/
Table 2: minimal data set to be reported for long term follow up

Data on long term follow up should be reported on a regular basis up to 10 years after completion of the last donation procedure. Minimal reporting includes reports after 1 year, 5 years and 10 years but annual or biannual reporting is recommended.

Donor survival status
- Date of last follow up or death
- Donor alive?
  - yes/no
    - If no: cause of death: ICD code

Malignancy
- Hematologic malignancy?
  - yes/no/unknown
    - if yes: certainty of the diagnosis: confirmed/unconfirmed by medical data
    - ICD code
- Non-hematologic malignancy?
  - yes/no/unknown
    - if yes: certainty of the diagnosis: confirmed/unconfirmed by medical data
    - ICD code

Autoimmune disease
- Autoimmune disease? (a list with a selection of the anticipated most frequent events will be provided)
  - yes/no/unknown
    - if yes: certainty of the diagnosis: confirmed/unconfirmed by medical data
    - ICD code