- Schedule and request services
- Symptom assessment using the Modified Toxicity Criteria*
- Document a list of the donor's medications
- Height and weight*
- Vital signs (pulse, blood pressure, temperature)*
- Venous access assessment*
- Review health history including deferral of voluntary blood donation, and prior experiences/problems with anesthetic agents
- Hematology tests: Complete blood count (CBC) with differential*, (will include hemoglobin and hematocrit), ABO and Rh, and screening for Hemoglobin S*
- Chemistry tests: Electrolytes, (sodium, potassium, carbon dioxide, chloride), glucose, blood urea nitrogen (BUN) and creatinine, serum total protein plus albumin or serum protein electrophoresis, lactate dehydrogenase (LDH), alanine aminotransferase (ALT, SGPT), alkaline phosphatase, and serum beta-HCG pregnancy*
- Urinalysis
- EKG
- Chest x-ray
- Infectious disease markers - not required at the time of PE, but within 30 days of collection date. Note: Effective December 1, 2008, Chagas testing is required
- Physical assessment for FDA eligibility criteria, if risks were identified by health history screening or other medical records

*Reported on the Form 700

Results of the PE and completed forms should be made available to the donor center no more than five business days of the examination. See the *Donor Suitability and Clearance* section of this chapter for additional information.

9.18. Outcome of the Physical Examination

Urgent workups require that the donor center contact the SCU with the PE results no more than five business days from the examination. Standard workups require that the donor center contact the SCU with the PE results within seven calendar days. Outcomes include the following:

- Donor Clearance: Information session completed, consent signed and the donor is deemed medically suitable to donate PBSC.
- Extended Physical Examination: PE Results are inconclusive and require further medical evaluation/testing.
- Ineligible Donor Determination: The donor is suitable but a risk factor is identified for a relevant communicable disease.
- Clinically Significant Abnormal Findings: The donor is medically suitable but requires additional consideration.
- Donor Deferral: The donor is medically deferred from all stem cell donations.

All documentation related to the PE must be maintained in the donor chart according to record management practices. Source documents may include, but are not limited to lab reports, physician notes, and all test results.

9.18.1. Donor Suitability and Clearance

Typically, the donor passes the PE and is deemed medically suitable by both the apheresis center and donor center physicians to donate PBSC. The donor is determined to be eligible or ineligible based on the relevant communicable disease risk assessments. The donor center communicates this outcome by submitting the following to the SCU:

- Form 700, *Determination of Stem Cell Donor Suitability*. This form is signed by both the apheresis center and donor center physicians.
- NMDP Verification of PBSC Request. This form is signed by both the apheresis center and donor center personnel. The apheresis center's physician is not required to sign the form. Apheresis centers should examine the data from the *Donor Workup Request* form (or original *TC Donor Request Report*, if electronic workup) and *Verification of PBSC Request* forms to carefully assess if the donor can safely provide the volume requested by the transplant center.
- Form 50, *Repeat Donor Infectious Disease Marker* (not required for clearance but should be submitted as soon as available)
- *Summary of Donor Eligibility*, Section One (indicating whether relevant donor screening communicable disease risk factors have been identified).

Upon receipt of this paperwork, the SCU verifies the information and notifies the transplant center of donor clearance. The donor center will receive a copy of the *Notification of Donor Clearance for PBSC Donation* form. Prior to the collection date, Sections Two and Three of the *Summary of Donor Eligibility* will be completed by the SCU and faxed to the donor center.

A collection date(s) may have been tentatively negotiated during an earlier phase of the workup. All collection dates should be entered in the STAR Link application. If no tentative dates have been negotiated, see *Setting a Date for PBSC Collection* section of this chapter for additional information on scheduling the collection.

9.18.2. Extended Physical Examination and Testing

As a result of the physical exam, it may be determined that the donor requires additional evaluation before being deemed medically suitable to donate. The donor center must notify the SCU of any extended medical testing expenses and receive approval in advance of the procedure. To facilitate the extended physical exam process, the donor center must:

A. Obtain information about the additional tests required from the apheresis or collection center or third party physician.

B. Receive an estimated cost of the required testing from the apheresis center or third party physician.

C. Counsel the donor about the need for additional tests.

D. Create a tentative plan but DO NOT proceed until authorization is granted.

E. Contact the SCU with the information and estimated costs. Note: All estimated costs must be preauthorized by the NMDP, regardless of the amount.

The SCU will provide written approval to the donor center whether or not the additional costs have been approved. The form used to communicate the outcome is the *Approval of Extended Medical Fees*. If approved, the appointment(s) may occur. If not approved, counsel the donor appropriately. Document the decision in STAR Link.

9.18.3. Clinically Significant Abnormal Findings

As a result of the donor evaluation, an underlying condition or unusual test result may be identified, which is not cause for deferral but is clinically significant enough to require that the appropriate parties are informed. Clinically significant abnormalities usually fall into one of two categories: increased donor risk or increased recipient risk.

9.18.3.1. Clinically Significant Abnormal Findings: Increased Donor Risk

Medical conditions or findings that are "out of the norm" are evaluated by the apheresis or donor center physician and may be found acceptable. Such conditions are not necessarily cause for deferral nor will they impact the quality of the stem cells. For example, the donor exceeds the weight guidelines or has insulin-dependent diabetes. In

such cases, the donor center must communicate the condition to the SCU for documentation. The donor center is provided guidance for common conditions which require notification in the *Assessment Tools* and *Rationale and Action Guide*. The transplant center is not usually informed of abnormal findings that are an increased risk for the donor.

When appropriate, the SCU will generate a *Donor Center Abnormal Findings Letter* to the donor center. The letter requires that the donor be counseled. The donor may be counseled by the donor center, apheresis center, or collection center medical director, or designee.

The letter must be signed and returned to the SCU. The original must be maintained in the donor chart. All applicable parties should be informed of the decision.

9.18.3.2. Clinically Significant Abnormal Findings: Increased Recipient Risk

Medical conditions or findings that are "out of the norm" are evaluated by a physician and may be found acceptable with little or no risk for the donor, but a slight increase risk to the potential recipient. Examples include a donor who has had malaria in the past three years, and animal bite in the past 12 months, received vaccinations recently, or a donor unsuitable to donate marrow, even when PBSC is the preferred stem cell choice.

In such cases, the donor center must communicate the condition to the SCU when discovered, but no later than donor clearance. The donor center is provided guidance for common conditions would require notification in the *Assessment Tools* and *Rationale and Action Guide*. In addition, using medical judgment, the DC or AC Medical Director may recommend that the transplant center be informed of a condition. The SCU will present the relevant information to the transplant center so the physician can determine if the finding presents an acceptable or unacceptable risk. The transplant center will evaluate the information, counsel the recipient, and document their decision to proceed. The SCU will inform the donor center of the outcome. The donor center should then inform the apheresis center of the decision.

9.18.4. Donor Deferral

As a result of the physical exam, the donor may be permanently or temporarily medically deferred as a stem cell donor. The examining physician may determine donation is not safe for the donor, or that a condition exists that is not safe for the recipient. Notify the SCU immediately and release the donor as "Permanently Medically Deferred" or "Temporarily Unavailable" and enter the date the donor anticipates being available in the STAR Link application. All applicable parties should be informed of the decision.

9.19. Determining Donor Eligibility

Within 30 days of the planned PBSC collection, the NMDP and the managing donor center make a final determination regarding the donor's eligibility status, eligible or ineligible. This determination takes into account screening and testing information accumulated throughout the workup process.

Medical conditions or findings that present a potential risk of transmitting a relevant communicable disease defines the donor as ineligible and must be relayed to the transplant center physician for evaluation. The donor center is provided guidance for conditions that affect donor eligibility based on responses to the HHQ and require notification in the *Rationale and Action Guide*. Examples include a donor who has lived in the United Kingdom for more than three months, or a donor who had a tattoo in the past 12 months.

In such cases, the donor center must communicate the condition to the SCU, preferably prior to or at a minimum, at the time of donor clearance. This is accomplished by completing and submitting the Summary of Donor Eligibility form with the appropriate attachments to the SCU. The reporting process must include at least a two-step review process to ensure accuracy. The SCU will present the relevant information to the transplant center physician to determine if there is an acceptable or unacceptable risk. The SCU will inform the donor center of the outcome. The donor center should inform the apheresis center.

Note: If a donor tests reactive for Chagas, administer F00658, *Follow-up Questions for Reactive Chagas Screening Test Result*. Report responses to the SCU. The donor's eligibility status will be ineligible even if the supplemental testing is non-reactive.

9.19.1. Summary of Donor Eligibility

The donor center is required to complete Section One of the *Summary of Donor Eligibility* form at the time of donor clearance. This form documents the donor's partial eligibility status based on the health history questionnaire, physical assessment and review of other readily available medical records.

The donor center is responsible for the following:

- If the donor is <u>eligible</u>, mark "eligible" on the form. Sign, date, and submit page one of the Summary of Donor Eligibility to the NMDP.
- If the donor is <u>ineligible</u>, check all appropriate reasons for the donor being "ineligible" on the form. Sign, date, and submit page one of the *Summary of Donor Eligibility* along with any of the following applicable attachments to the NMDP.

Table 9-2: Documentation of Donor Ineligibility

Form	General Description	General Instructions
For US Donors: Ineligible Donor: Health History Screening (A1) Form #: F00310 **OR** Ineligible Donor: Health History Screening (A2) Form #: F00309	Use to describe health history screening responses that indicate that a donor is ineligible. Use to transcribe health history screening responses that indicate that a donor is ineligible.	Complete form and fax to the NMDP SCU with Section 2: Communicable Disease Assessment of the Donor Health History Screening Questionnaire. Transcribe all "yes/no" responses from Section 3: Communicable Disease Assessment of the Donor Health History Screening Questionnaire to this form. Fax form to the NMDP SCU.
For International Donors: International Health History Questionnaire (A3)	Use to describe health history screening responses that indicate that a donor is ineligible.	Transcribe the donor's health history questionnaire yes/no responses to this form. Fax form to the NMDP SCU. Answers to all questions must be provided.
Ineligible Donor: Physical Assessment (B) Form #: F00311	Use to communicate physical exam findings that indicate that a donor is ineligible.	Answers to all assessments must be provided. If applicable, complete and fax to the NMDP SCU.
Ineligible Donor: Other Medical Records (C) Form #: F00313	Use to communicate information obtained from other sources, personal medical records, previous testing greater than 30 days, etc.	Complete and fax to the NMDP

9.19.2. Final Eligibility Determination

When collection dates are firmly established and the final IDM results have been reviewed, the SCU completes Sections Two and Three of the *Summary of Donor Eligibility* and returns it to the donor center. Prior to patient prep and filgrastim administration, the donor center reviews Section Two (Infectious Disease Testing Assessment) and Section Three (Final Donor Eligibility Recommendation) of the *Summary of Donor Eligibility*. Upon reviewing the form, the donor center is responsible for the following:

- Perform a second review of the completed HHSQ and IDM results.
- Complete Section Four, *Final Donor Eligibility Determination*, by checking the appropriate response (agree/disagree).
- If <u>agree</u>, sign, date, and return document to the NMDP.
- If <u>disagree</u>, complete information in the text box on the form to indicate the donor center's eligibility assessment. Mark applicable reasons to support assessment. Sign, date, and return document to the NMDP and discuss discrepancy with the SCU as soon as possible.

9.19.3. Declaration of Urgent Medical Need

If the donor is ineligible, the SCU initiates the *Declaration of Urgent Medical Need, Ineligible Donor* and receives the transplant center's signature. The transplant center physician must indicate whether or not to receive a stem cell product by signing and returning this form to the SCU prior to the start of the patient' s conditioning regimen. The donor center receives a copy of this form to file in the donor chart. This form does not accompany the product.

9.19.4. Final Declaration of Donor Eligibility

Review the completed HHSQ, source documents from the laboratory, and the PE provider's medical evaluation to determine the donor's eligibility. Once final eligibility is determined, the donor center or apheresis center is responsible for completing the *Final Declaration of Donor Eligibility*, which is considered labeling and must accompany the product. See *Instructions for Completing the Final Declaration of Donor Eligibility* and the *Cellular Product Labeling and Transport* chapter of this manual.

In the event that the donor's suitability and/or eligibility status changes prior to collection, contact the *SCU* immediately.

9.20. Donor Exclusion Criteria for PBSC Protocol

The PBSC protocol for primary donation outlines the donor exclusion criteria. See the *Filgrastim-Mobilized Peripheral Blood Stem Cells for Allogeneic Transplantation with Unrelated Donors* and the *Rationale for PBSC Donor Exclusion Criteria for DC Staff*, which indicates when a planned protocol deviation is allowed.

9.21. NMDP Verification of PBSC Request

The *NMDP Verification of PBSC Request* is a tool used by the donor and collection center to communicate a plan for the PBSC collection. By taking into account the weight of the patient or the desired CD34+ cell dose, the centers determine the number of collection procedures needed, product transport temperature, and/or the donor blood volume to be processed.

The donor and apheresis center complete and sign the *NMDP Verification of PBSC Request* as a part of the donor clearance and submit it to the NMDP along with the Form 700 and the *Summary of Donor Eligibility*. The SCU obtains the transplant center's signature and faxes the completed form back to the donor center.

9.22. Setting a Date for PBSC Collection

Confidentiality guidelines prohibit direct communication between donor and the transplant centers prior to the receipt of the *Notification of Donor Clearance for PBSC Donation* form. This requirement ensures the donor is medically suitable and willing to donate before the transplant center can begin final preparations for transplant.

Many times collection dates are tentatively scheduled, pending donor clearance, early in the workup phase. Once the donor is cleared for PBSC donation, a collection date(s) may be established based on transplant center request, donor availability, and apheresis center availability. The donor center should enter, or confirm that the date is entered by the SCU and viewable in the STAR Link application. The *Notification of Donor Clearance for PBSC Donation* form will reflect prior date negotiations when applicable. Donor and transplant centers may communicate directly at this time, however, centers usually prefer to negotiate and establish collection dates through the SCU.

The NMDP recommends that the PBSC collection occurs within three months of donor clearance. For situations that fall outside of these guidelines, transplant center rationale for postponement will be communicated to the donor center.

The donor center is responsible for the following:

A. Affirm the proposed collection date with the donor.

B. Verify apheresis center and physician availability.

C. Provide the donor with information regarding the details for the day of collection.

D. Enter collection date(s) and apheresis center in the STAR Link application.

E. Educate all medical providers caring for donor during the PE and/or product collection process regarding the billing requirements. A letter template is available on the NMDP Network Web site that can be customized for each center. Refer to the *Suggested Letter to Medical Providers and Collection Centers*.

9.22.1. Interval Evaluation

The *NMDP Standards* require that an "interval" evaluation take place to reassess the donor's health and eligibility status if the PBSC collection does not occur within eight weeks of the initial PE. The elements required in the interval evaluation depend on the amount of time elapsed since the most recent complete physical examination.

Interval evaluation requirements are as follows:

- If there are between eight and 12 weeks from the most recent complete physical examination to the scheduled collection date, the collection center physician or designee will conduct a telephone follow-up to

determine if there are any changes to the donor's condition/medical history. The timing of the repeat IDMs and pregnancy testing (if applicable) must be considered.

- If there are between 12 weeks and six months from the most recent complete physical examination to the scheduled collection date, the collection center physician or designee will complete a telephone or in-person interview to determine if there are any changes to the donor's condition/medical history. Blood testing, as outlined in the *NMDP Standards* and the Physical Examination Requirements section of this chapter must be repeated. The timing of repeat IDM and pregnancy testing (if applicable) must be considered.
- If it is more than six months from the most recent complete physical examination, the health history screening questionnaire, and the entire physical examination, including pregnancy testing (if applicable) must be repeated, including all testing outlined in the Physical Examination Requirements of this chapter.
- .Infectious disease testing must be repeated if the results are from testing more than 30 days prior to the scheduled marrow or PBSC donation. The IDM panel must include Chagas testing.

If it is determined that the donor requires an interval evaluation, the donor center is responsible for the following:

A. Schedule the interval evaluation and enter the interval evaluation date in STAR Link.

B. Coordinate the completion of the appropriate interval evaluation. The donor center and/or collection center can complete this assessment and determine if the donor is still healthy and suitable for PBSC donation.

C. Report the outcome of the interval evaluation as follows:

1. Complete the *Form 702, Determination of Stem Cell Donor Suitability, Greater Than 8—12 Weeks Post Medical Evaluation*, if there are between eight and 12 weeks from the most recent complete physical examination to the scheduled collection date.
2. Complete the *Form 703, Determination of Stem Cell Donor Suitability, Greater Than 12 Weeks—6 Months Post Medical Evaluation*, if there are between 12 weeks and six months from the most recent complete physical examination to the scheduled collection date.
3. Complete a new *Form 700, Determination of Stem Cell Donor Suitability*, and the *Donor Health History Screening Questionnaire for Use at HR/CT/Workup* if has been more than six months since the original PE.

D. Submit the appropriate form to the SCU at least two business days before the recipient's preparative regimen begins.

1. The SCU notifies the transplant center coordinator of the outcome of donor's interval evaluation and verifies continued suitability for PBSC donation.
2. If the PBSC collection is further postponed, the interval evaluation requirements may change.

9.23. NMDP Research Database & Research Sample Repository Protocols

Donors providing stem cells are asked to consider participation in the NMDP Research Database and Research Sample Repository studies. Although participation is optional for the donor, donors should be informed of and offered the opportunity to participate in research, which may benefit the field of transplantation.

To ensure compliance with Federal Regulations, donor centers must use a current IRB-approved consent form. The NMDP protocols and informed consent documents for the Research Sample Repository and Research Database have been approved by the NMDP IRB. If a donor center does not designate the NMDP IRB on the Federalwide Assurance (FWA), the center must submit the protocol and consent forms to their local IRB for review and approval. The donor center must send their IRB's approval notice, a copy of the approved consent form, and protocol to NMDP Research Administration. The protocols and consent forms are available to transplant centers and donor centers on the Network Web site. These documents are:

- *Protocol for a Research Database for Allogeneic Unrelated Hematopoietic Stem Cell Transplantation and Marrow Toxic Injuries*
- *Protocol for a Research Sample Repository for Allogeneic Unrelated Hematopoietic Stem Cell Transplantation*
- *Research Database for Unrelated Donor Transplant Donor/Subject Research Consent Form*
- *Contribution of a Blood Sample to the National Marrow Donor Program's Research Sample Repository Donor/Subject Research Consent Form*

9.24. Obtaining Donor Consent for Research Studies

Donors providing stem cells should be asked to consider participation in the following NMDP research studies:

- **Research Database**: Donor search and follow-up data are stored in the NMDP database for each donor and recipient pair. Donors are asked to consider permitting the data to be used in future research studies. Consent must be obtained with each additional workup request because new data are collected.
- **Research Samples**: Donors are asked to consider providing a blood sample for storage in the NMDP Research Repository for future studies. A donor only needs to provide one research sample, regardless of the number of stem cell donations provided. Donor centers are monitored for their compliance in providing donor research blood samples (or excuse codes) as part of the NMDP's Continuous Process Improvement (CPI) program.

The donor center is responsible for the following:

A. Educate the donor about the research studies.

B. Provide the donor with the NMDP brochure entitled *Opportunity to Participate in the Research Sample Repository* informational brochure, available through the *NMDP Materials Catalog*.

C. Review both the research database and research sample repository consent forms with the donor.

D. If the donor agrees to provide research samples:

1. The donor shall read, sign and date the consent form(s).
2. Enter the research sample draw date and record the shipping number in the STAR Link application.
3. Provide the donor with a copy of the consent and file the original completed consent form at the donor center.
4. Collect the specified amount of blood in ACD tubes prior to the PBSC donation. See the *Research Repository Critical Facts Sheet* for specifics.
5. Affix research sample labels.
6. Package tubes to comply with International Air Transport Association (IATA) requirements for shipping blood.
7. Complete the airbill using FedEx account number and ship the samples to the designated research repository. See shipping instructions titled *FedEx Pointers on Shipping: Clinical Samples, Diagnostic Specimens and Environmental Test Samples*. See the *Product Transport and Specimen Shipment Web page* on the Network Web site for a direct link to the FedEx Web site.
8. Record the appropriate internal billing code on the FedEx airbill.

9. Ship the samples by overnight carrier to the designated research repository. See the *Overnight Carrier Shipping Instructions* and the *Research Repository Critical Facts Sheet*.

E. If a donor declines to participate in providing research samples:

1. Complete the appropriate *NMDP Research Sample Excuse Code Form: NMDP Research Sample Not Available* and fax to the NMDP.
2. File in donor chart.
3. Document the donor's decision not to contribute a Research Repository Sample in donor's chart in STAR Link.

F. If the donor agrees to participate in the Research Database:

1. The donor shall read, sign and date the consent form.
2. Provide the donor with a copy of the consent and file the original completed consent form at the donor center.

G. Document the donor's decision to consent to the use of their data on the F700, *Determination of Stem Cell Donor Suitability*.

1. Document the donor's decision to participate in the research database in donor's chart in STAR Link.

   Note: Submission of the donor data collection forms (700 series) to the NMDP is required whether or not the donor agrees to participate in the research database. If the donor declines to participate, his/her data will not be included in future research studies, however, the data is required as part of the PBSC clinical trial requirements and for monitoring of donor safety.

9.25. Participation in Other Research Studies

Donors may be asked to consider participation in other NMDP research studies or in research studies sponsored by the transplant center. Although participation is optional, donors shall be educated on the research study. The donor center will receive notification about the study from the SC at the time of the request. The NMDP Research Administration will then send specific instructions about the study

9.26. Pre-collection Samples

The transplant center may request blood samples prior to the PBSC donation for pre-transplant testing required by the transplant center's institutional guidelines. The samples may be used for testing such as IDMs, ABO/Rh type and cross-match. The request is indicated on the *Donor Workup Request* form. Donors

consented to donate pre-collection samples when they signed the *NMDP Study of Filgrastim-Mobilized Blood Stem Cells For a First Transplant Donor/Subject Release Form.*

The donor center is responsible for the following:

A. Review the workup request for pre-collection tube requirements and time frame.

B. Schedule sample collection. Samples should be drawn to arrive at the transplant center on a week day. Consider drawing at the time of the information session or physical exam.

C. Collect blood sample.

D. Affix pre-collection sample labels.

E. Package tubes to comply with IATA requirements for shipping blood.

F. Ship tubes using the address identified on the workup request. Use the appropriate FedEx reference code for pre-collection samples on the airbill.

G. Enter the pre-collection sample draw date and shipping number in the STAR Link application.

These duties may be performed by the apheresis center, if mutually agreed upon by both parties.

9.27. Infectious Disease Marker (IDM) Testing within 30 Days of PBSC Collection

Donor screening for infectious disease markers (IDM) is required within 30 days of PBSC donation. When more than 30 days elapse between the blood collection date for IDM testing and the PBSC collection date, the testing must be repeated.

Note: A second PBSC collection date is always assumed when determining if the IDMs meet the required testing time frame, regardless if only one collection is planned. If the potential (but unplanned) second PBSC collection is more than 30 days from the IDM blood sample collection date, repeat IDM testing should be performed.

IDM testing requirements established by the Food and Drug Administration (FDA), effective May 2005, include the following stipulations:

- Samples must be tested at a laboratory certified by Centers for Medicare & Medicaid Services (CMS) certified laboratory.
- Samples must be tested using kits that are FDA approved for NMDP donor screening and confirmatory testing. (The laboratory must use screening test kits; not diagnostic test kits.)

- Samples must be handled, tested, and shipped according to the manufacturer's instructions and meet IATA/DOT requirements.
- Laboratories performing IDM testing must hold current registration with the FDA as a Tissue Establishment, using FDA Form 3356.

The purpose of the testing is to assess the donor's exposure to and likelihood of transmitting an infectious disease to the recipient. The donor center must establish a process to ensure when a screening test is positive that the appropriate confirmatory test is performed. See Table 9-2, *U.S. Infectious Disease Testing Profile*, and Table 9-3, *International Infectious Disease Testing Profile.*

In addition, if a donor tests reactive for Chagas, additional follow-up questions must be asked. These questions are available on F00658, *Follow-up Questions for Reactive Chagas Screening Test Result.* Responses to the questions must be provided to the SCU to assist the transplant center in its decision making pending supplemental testing, which may take several weeks.

The donor center must be familiar with the laws of the state in which the donor resides that require the reporting of positive test results (i.e., reactive Anti-HIV) to a state agency such as the Department of Health. Refer to *IDM Eligibility and Labeling Guide* and *Basics of Infectious Disease Testing for Stem Cell Donors* available on the Network Web site.

International donor centers will receive a form titled *Special Instructions for International Donor Workup Requests* from the SCU. This form is to remind international centers of the US requirement to submit a sample to the NMDP contract laboratory for IDM testing. When the IDM testing is complete, the results are available for review by the NMDP and transplant center. The donor center is provided a copy of the IDM lab report and notified of any reactive results via a separate message.

The donor center is responsible for the following:

A. Schedule the blood draw for the repeat IDM testing. Testing may be coordinated to occur at the time of the PE or at the time of pregnancy testing.

B. Enter correct IDM draw date into the STAR Link application.

C. Send appropriate blood sample to the laboratory for IDM testing and ABO/Rh typing.

   a. The IDM panel must include testing for Chagas.

D. Receive and review IDM test results from the laboratory. Verify that the Donor ID number is recorded on the source document. If any IDM screening result is positive, perform the applicable confirmatory test, excluding anti-CMV.

   a. If the donor is reactive for Chagas, supplemental testing must be performed.

   b. If reactive, administer F00658, *Follow-up Questions for Reactive Chagas Screening Test Result.* Report responses to the SCU.

E. Record results on the Form 50, *Repeat Donor Infectious Disease Markers* taking care to ensure correct transfer of test information.

F. Perform a second review of the complete Form 50, preferably by a second person, to ensure accuracy. This information is used to determine eligibility of donors to donate their stem cells according to FDA regulatory requirements. The second review should be documented on the form with the reviewer's initials and date of review.

G. Submit the completed Form 50 to the SCU within one business day of receiving results. See *Instructions for Completion of Form 24 and Form 50.* Retain the laboratory report as a source document in the donor's chart.

H. The donor's IDM test results will affect the final eligibility determination. The SCU will review all results and make a final recommendation to the donor center. Inform and counsel donor of confirmed positive test results, excluding anti-CMV, according to center's procedures.

9.28. Pregnancy Testing

Females with childbearing potential must be counseled during the information session and throughout the workup process that pregnancy is a contraindication for receiving filgrastim. The donor center must reinforce the message that the donor must not become pregnant between the day of the pregnancy testing and the PBSC collection date. A donor with a positive serum Beta-HCG test (pregnancy test) must be temporarily unavailable for PBSC donation.

A serum Beta-HCG pregnancy test is required for all female donors who do not meet the following criteria:

- Celibate for at least 3 months
- Post-menopausal (no menstruation for more than 12 months)
- Having had surgical removal of uterus and/or both ovaries

9.28.1. Pregnancy Testing Within 15 Days Prior to Collection

A serum Beta-HCG pregnancy test must be performed within 15 days of the PBSC collection taking into account that results must be available prior to the first filgrastim injection and prior to the start of the patient's preparative regimen. The SCU initiates a Form 705, *Donor Pregnancy Testing and Screening,* and faxes the form to the donor center once a

collection date is scheduled and the preparative regimen start date is confirmed with the TC.

The results of the serum Beta-HCG pregnancy test must be communicated via the Form 705 to the SCU at least two days prior to the start of the patient's preparative regimen. See the Donor Forms Instruction Manual.

9.28.2. Pregnancy Assessment 2 Days Prior to Start of Filgrastim

The donor center must perform a verbal assessment two days prior to the start of filgrastim injections and report the outcome to the SCU on the Form 705. Repeat the serum pregnancy test if there is any possibility that the donor may be pregnant. If repeat testing is necessary, it must be performed urgently and the SCU must be notified immediately.

9.29. Infectious Disease Marker (IDM) Testing on Day of PBSC Collection

Donor testing for infectious diseases is required on the day of collection. As with IDM testing required within 30 days of collection, Day of Collection samples must be tested at a laboratory certified by Centers for Medicare & Medicaid Services (CMS) and tested using kits that are FDA approved for donor screening and confirmatory testing.

Apheresis centers may be asked to draw the donor blood sample for this required testing. Donor centers may use an NMDP contract laboratory, the collection center laboratory, or an independent laboratory to perform infectious disease marker testing.

West Nile Virus (WNV) testing is required year-round on the Day of Collection IDM panel as specified by NMDP policy. NAT methodologies for HIV and HCV IDM testing may be performed on pooled rather than single donor specimens, however, WNV testing must be performed on single donor samples.

The IDM results are not available prior to the product being infused. The length of time it takes to obtain IDM results varies, but it is important for the donor center to submit the completed Form 50 to the NMDP within five days of the donation. The SCU will report the results to the transplant center as soon as they are available.

9.30. Filgrastim Administration

Filgrastim is administered to all PBSC donors as a series of subcutaneous (under the skin) injections over a period of five consecutive days. It is recommended that a nurse or physician who is experienced with administration of the drug give filgrastim to the donor. The first dose should be given at an NMDP center or in a clinic setting, but other injections may be administered at the donor's home,

workplace or other location. In unique circumstances, injections may be self-administered if the donor so chooses and the donor center concurs.

Injections are given in the upper arms, thighs or abdomen using a small gauge needle. The combination of vials for each daily dose is specified in the protocol and in the instructions provided from the SCU. The entire contents of each vial must be administered, preferably at the same time each day when feasible. The fifth dose is administered on the first day of PBSC collection.

Amgen recommends storage of filgrastim at 2-8°C. Filgrastim should not be frozen. If circumstances arise that do not allow storage of the drug at 2 to 8°C, stability studies performed by Amgen show that filgrastim in unopened vials are stable at room temperature between 9 to 30°C (48 to 86°F) for a cumulative exposure not to exceed seven days without adverse effects on product integrity or shelf life. If filgrastim is inadvertently frozen, the vials can be thawed in the refrigerator for future use. Exposure to freezing temperatures for up to 24 hours does not adversely affect the stability of filgrastim, however, filgrastim should not be used if frozen beyond 24 hours or frozen more than once.

The donor center is responsible to:

- Create a plan for the filgrastim administration.
- Enter the Filgrastim Injection Start Date in the STAR Link application
- Coordinate the filgrastim injections.
- Monitor the donor's symptoms during filgrastim administration and modify dose according to protocol, if necessary.
- Complete and submit the NMDP data collection forms.

9.30.1. Receipt of Filgrastim

When a collection date is established, the SCU ships the appropriate dosage of filgrastim to the location(s) provided by the donor center. The donor's weight from the Form 700, *Determination of Stem Cell Donor Suitability,* is used to calculate the dosage of filgrastim required. The drug is shipped via overnight carrier to arrive 2-3 days prior to the date of the first injection. Frozen gel packs are used to maintain a temperature of 2-8°C during shipping of the drug. The gel packs may be reused for PBSC transport.

Where the drug is shipped will depend on individual donor circumstances. The donor center ensures that the following activities are performed:

- Drug is received at the designated location.
- The donor center is responsible for the storage and tracking of the filgrastim received from the NMDP. Shipments of donor-specific

filgrastim must be recorded. See *PBSC Resource Manual* for information on drug storage and accountability.

- The shipping box is returned to the NMDP according to the enclosed instructions.
- The *Administration of Filgrastim* and the *NMDP Verify Condition Drug Received* forms are included in the drug shipment. The *NMDP Verify Condition Drug Received* form must be completed and faxed to the SCU as soon as possible.
- The drug is transferred to a refrigerator and stored between 2-8°C.

9.30.2. Proper Disposal of Filgrastim Vials

Empty, partially used, or unused vials of filgrastim must be destroyed following completion of injection schedule or cancellation of planned collection. Document the drug volume and date vials were dispensed and/or destroyed according to procedures established at the donor center. Note the reason for the destruction of unused medication.

9.30.3. Donor Assessment During Filgrastim Administration

Donors are closely monitored during filgrastim administration. Observations are recorded on the Form 710, *Filgrastim Mobilized PBSC Days One, Two, Three and Four Donor Assessment.* Each day filgrastim is administered, vital signs and symptom assessment is required. Blood work is also required on days one, five and six, if a two day collection. For days five and six donor assessments, Form 730, *Filgrastim Mobilized PBSC Day Five and Day Six Donor Assessment/Apheresis Procedure* is used. See the *NMDP Donor Forms Instruction Manual.*

9.30.4. Treatment of Donor Symptoms

Most donors will experience discomfort during filgrastim administration. Bone pain is the most common symptom and is treated with acetaminophen, ibuprofen, naproxen and similar analgesics. Rarely, donors may require prescription analgesics. Aspirin and aspirin-containing drugs must be avoided during filgrastim administration and for 14 days following apheresis because the donor's platelet count will have decreased. Other symptoms that occur less frequently but may require treatment include headache, nausea, chills, night sweats, and body aches. All symptoms should disappear or diminish markedly 48 to 72 hours after the final filgrastim dose.

9.30.5. Filgrastim Dose Reduction

The protocol defines donor symptoms that are severe enough to warrant filgrastim dose reduction. When necessary, the physician follows the protocol guidelines and reduces filgrastim accordingly. Notify the SCU whenever filgrastim is reduced or withheld. Complete and submit the Form

710, *Filgrastim Mobilized PBSC Days One, Two, Three and Four Donor Assessment.*

A 24-hour emergency number (donor center coordinator or donor center medical director) must be provided to the donor for the time period during the filgrastim injections.

9.31. PBSC Collection Protocol Guidelines

PBSC collections consist of one or two apheresis procedures on consecutive days, with a maximum blood volume of 24 liters, whether collected over one or two days. Collections are performed using an automated cell separator according to established procedures. The apheresis facility must have a written procedure(s) for the collection of peripheral blood stem cells by leukapheresis. It is expected that PBSC collections will occur Monday through Friday.

Each PBSC product should have a minimum final volume of 200 ml. For some blood cell separators, additional autologous plasma will need to be collected and added to the PBSC product at the end of the procedure. See the protocol for recommendations on the ratio of anticoagulant and optional use of heparin.

9.31.1. Preparation Prior to the Day of Collection

Prior to the day of the first PBSC collection, the designated parties must ensure that the following activities are performed:

- Make travel arrangements for the donor and companion.
- Make courier arrangements if the donor center is providing the courier. Arrangements should be made two weeks prior to collection. Provide courier with delivery information supplied by the SCU. Inform the SCU if no courier will be provided and immediately forward pick-up instructions
- Receive the filgrastim from the NMDP.
- Make arrangements for filgrastim administration.
- Verify that the apheresis center coordinator has the name of the recipient. This information is required for labeling.
- Review the additional information regarding product labeling, transport and courier procedures. See *Cellular Product Labeling and Transport* chapter (chapter 12) in this manual.
- If the donor is determined to be ineligible, verify that a *Declaration of Urgent Medical Need* has been received.

9.31.2. Day of Collection Responsibilities

On the day(s) of PBSC collection, the designated parties must ensure that the following activities are performed:

Table 9-3: Required Activities for Day 1 vs. Day 2 of PBSC Collection

Activity	Day 1	Day 2
Collect blood sample for IDM and West Nile Virus testing. Note: Chagas testing is not required on Day of Collection.	X	
Collect blood and product samples for CBC/differential testing before and after apheresis procedure. Monitor the platelet count.	X (pre) X (post)	X (pre) X (post)
Collect blood and/or product samples for the transplant center as specified on the workup request.	X	X
Collect a 10 mL blood sample for ABO and Rh typing as indicated on the workup request (send blood with product(s)).	X	X
Prepare the PBSC product for labeling, packaging and transport. See *Cellular Product Labeling and Transport* chapter (chapter 12) of this manual.	X	X
Obtain a copy of *the Interpretation of Infectious Disease Marker (IDM) Test Results* to be included with product.	X	X
Complete product analysis using the Form 770/771, *Peripheral Blood Stem Cell (PBSC) Product Analysis.*	X	X

9.31.3. Donor Safety Considerations

A donor's platelet count will fall 20 to 30% with each apheresis procedure. It is important to monitor a donor's platelet count for thrombocytopenia.

- A platelet count is performed before and after each collection. A pre-apheresis platelet count of <120,000 x 10^9/L, requires NMDP approval to proceed. The protocol defines various actions that may be considered.
- A platelet count of <80 X 10^9/L after the first PBSC collection, requires immediate notification to the SCU.
- A platelet count of <100 X 10^9/L after the second collection, requires that the donor be counseled about the increased risk of bleeding or bruising for approximately seven days after donation.

9.31.4. Central Venous Access

When PBSC products cannot be collected using peripheral veins, a central venous line may be used. NMDP data shows that approximately 18% of female donors and 2.5% of male donors may require a central line. A separate institution-specific consent is required. The physician who places the line is responsible for obtaining consent.

Placement of a central line in the femoral vein is preferred because of the lower incidence of serious adverse effects as compared to lines placed in the subclavian or internal jugular veins. However, the decision about line placement rests with the responsible physician.

Use of a central line falls into two scenarios:

- Inadequate venous access is identified during workup so central line placement is planned.
- Venous access fails during the collection and a central line must be placed to complete the procedure. Should the donor decline, he or she may be asked to consider an urgent marrow collection.

Central line placement occurs in a hospital setting. Donors with a central line shall remain hospitalized between apheresis procedures. A physician must be within reasonable walking distance of the donor whenever a leukapheresis procedure is performed using a central line. If a central line is placed that was not previously anticipated, the SCU must be informed immediately by phone. Follow-up may need to be completed using a Form 701.

9.31.5. CD34+ Enumeration

The apheresis center performs CD34+ testing and reports results using the Form 730/731, *Filgrastim Mobilized PBSC Days Five and Six Donor Assessment /Apheresis Procedure,* and 770/771, *Peripheral Blood Stem Cell (PBSC) Product Analysis.* If the CD34+ results were not reported on these (770/771) forms prior to departure, also fax the forms to the number listed on the *Donor Workup Request* or original TC Donor Request Report.

9.32. Storage and Transport of Cellular Products

For specific details regarding the labeling, packaging, storage, and transport of PBSC and marrow products, along with courier instructions, see *Cellular Product Labeling and Transport* chapter (chapter 12) in this manual.

9.33. Cryopreservation of Products

Occasionally, a product will not be infused immediately and will be cryopreserved. In most cases the cryopreservation will be planned in advance. Examples of such instances include:

- The patient's condition necessitates a delay of the collection date and the donor's schedule would make it difficult if not impossible to collect the product at a later date.

- The donor is unable to provide a product other than that being requested. The requested product may be collected and cryopreserved prior to the patient starting their conditioning regimen, since an alternate method of collection is not an option. Examples include a marrow donor on lithium or PBSC donor who is not medically suitable to donate marrow. As a precaution, the product may be cryopreserved prior to patient prep in the event the donor does not mobilize.

In rare cases the cryopreservation will be unplanned. An example of such a situation would be when the donor is collected, and the patient unexpectedly requires additional treatment prior to the infusion of the product.

In most cases the product is ultimately infused. However, if the patient does not receive the product, the transplant center may dispose of the cryopreserved product. If the transplant center wishes to use the unused product for anonymous research, the donor's prior permission must be obtained. Search and Transplant will inform the donor center of the request. The donor center shall notify Search and Transplant when the donor has given permission for the use of the donated product in anonymous research. For additional information, refer to the *Policy for Disposition of Donor Products, Cord Blood Units and Specimens* available on the NMDP Network Web site.

9.34. Adverse Events

Donor adverse events (AE) must be reported to the NMDP for all stem cell collections. The donor or apheresis center medical director must sign the Form 701, *Stem Cell Donor Adverse Event Form*, to document the serious adverse event to the NMDP and provide any follow-up information requested by the NMDP. All serious adverse events will be followed until resolution or the event is judged to be chronic or stable by the donor center medical director (investigator), apheresis center medical director or collection center medical director.

Life-threatening events must be simultaneously reported to the donor center and the NMDP SCU, within four hours of the onset of the complications. Non-life threatening complications must be reported to the donor center medical director and/or search coordinator within 24 hours of their discovery.

See *Adverse Events* chapter (chapter 15) of this manual for reporting requirements.

9.35. Protocol Deviations

The NMDP anticipates that situations may arise where it is necessary to use a procedure that falls outside of trial specific protocol guidelines. These situations may arise out of medical necessity, ethical concerns or unforeseen events during the donor evaluation, mobilization or collection. Examples of possible protocol deviations include, but are not limited to, the following:

- Variation in dosage of filgrastim
- Technical problem during apheresis procedure
- Problem during transport of product
- Unexpected termination of procedure after filgrastim injections have started

Any deviation from the protocol must be reported using the *Protocol Deviation Form 3000.*

- Planned Deviations:
  - Submission of the *Protocol Deviation Form 3000* to the CIBMTR is for protocol documentation and reporting purposes. Planned deviations must go through the SCU for pre-approval and will be considered on a case-by-case basis upon review by the NMDP medical director or designee.
- Unplanned Deviations:
  - If the deviation is associated with a data collection form then the *Protocol Deviation Form 3000* should accompany the Data Collection Form (DCF).

For further instruction on the completion and submission of protocol deviations, see the Donor Forms Instructions Manual.

9.36. Donor Recovery and Follow-Up

After a PBSC donation, it is critical to contact the donor to monitor recovery and collect specific data. Donor centers should provide the donor with the *Now That You Have Donated* brochure, available in the NMDP Materials Catalog.

The donor center is responsible for collecting and submitting data on the Form 760, *Post Donation – One Month, Six Months and Annual Donor Assessment* and the Form 777, *Stem Cell Donor Follow-Up Evaluation* at specified intervals.

Two Days (48 hours)	Form 777
One Week (and weekly until recovered)	Form 777
One Month	Form 760
Six Months	Form 760
Annually	Form 760

After the donor is completely recovered and released from the search, the donor's status changes to temporarily unavailable (TU) for a period of one year. If the donor has now donated stem cells twice (within the NMDP), the donor is

temporarily unavailable for three years. See *Policy for Subsequent Donations Following Initial Marrow or PBSC Donation by NMDP Donors.*

If no attempt is made to contact the donor for any of the above required contacts, a *Protocol Deviation Form 3000* must be submitted to the NMDP Research Department.

Donor centers may access the *Post Donation Follow-Up* chapter (chapter 11) in this manual for detailed information regarding follow-up requirements.

9.37. Possible Subsequent Donation Request

When a donor is asked to provide an additional stem cell or other product following an initial donation of marrow or PBSC for the original patient, it is considered a subsequent donation request; whereas when a donor is asked to provide marrow or PBSC for a different recipient, this is considered a second donation request. The transplant center may request a subsequent donation from the original donor to treat the following clinical conditions of the recipient:

- Graft failure
- Disease relapse
- Continuation of treatment for the recipient's disease

It is important that the donor understands that a subsequent donation request is a possibility. Approximately ten to 14 days after the original collection, the donor center shall ask the donor if s/he or she would consider a subsequent donation if one were to be requested by the transplant center.

The donor center is responsible for the following:

- Educate the donor about the possibility of a subsequent donation request at the time of the information session.
- Contact the donor 10-14 days after the primary collection to assess his or her willingness to consider a subsequent donation request by sending the donor the letter titled *Willingness to Consider Second Donation* available in the STAR Link application.
- Request that the donor return the questionnaire stating whether he or she is willing to consider providing a subsequent donation. Answering *yes* is not binding and the donor can freely decline at the time of the request.
- Retain documentation of donor contact and response in the donor chart and in the STAR Link application. Inform the SCU of information affecting the donor's availability for a subsequent donation as appropriate. The SCU will inform the transplant center as necessary; however, the transplant center will still be able to submit a subsequent donation request

should it remain the best option for the patient. Any subsequent donation request made will proceed through the standard approval process.

- It is recommended that the donor be instructed not to donate blood for a period of one year after donation. This may help ensure optimum availability for subsequent requests.

If such a request is made, refer to chapter 10, *Subsequent Donation Requests*, of this manual for detailed information.

9.38. Cancellation of Workup Request by Transplant Center

The transplant center may cancel a workup for a variety of reasons. For example, the patient's medical condition deteriorates, another donor is identified as a more compatible match, or the patient decides not to proceed. The transplant center notifies the SCU of the need to cancel a workup. The SCU immediately notifies the donor center so appropriate actions can take place.

The donor center is responsible for the following:

A. Receive the workup cancellation in the STAR Link application.

B. Contact the donor and enter the date of the contact in the STAR Link application.

C. Cancel any future appointments related to the workup or collection and remove any associated dates in the STAR Link application.

D. Cancel courier and/or travel arrangements if applicable.

9.39. Reimbursement

U.S. donor centers receive reimbursement for workup activities. See the *NMDP Fee-For-Service Policies and Reimbursement Procedures* for specific information. Collection centers and international donor centers receive reimbursement through separate mechanisms.

Apheresis centers may access the *Apheresis Center Reimbursement* chapter of this manual for additional information.

9.40. Donor Center Support Services

The NMDP offers support to donor centers with search requests and centralized testing services for infectious disease markers. Donor centers may access the *NMDP Network Support Services* chapter of this manual for detailed information.

Table 9-3: International Donor Infectious Disease Testing Profile

Infectious Disease	Infectious Disease Marker	Approved Screening Test	Approved Confirmatory Test
Hepatitis B	**HBsAg** Hepatitis B surface antigen	Required	Required if positive screening test
	HBcAb (anti-HBc) Total antibody to Hepatitis B Core antigen	Required	Not Available
Hepatitis C	**HCV Ab (anti-HCV)** Antibody to Hepatitis C virus	Required	Required if positive screening test
	HCV NAT Hepatitis C Virus RNA (nucleic acid test)	Required May be performed in combination with HIV NAT test	Not Available
Human Immunodeficiency Virus Types 1 & 2	**HIV-1/HIV-2 (anti-HIV 1/2)** Antibodies to Human Immunodeficiency Virus types 1 & 2	Required	Required, separate HIV-1 and HIV-2 confirmatory tests if positive screening test
	HIV NAT Human Immunodeficiency Virus type 1 RNA (nucleic acid test)	Required May be performed in combination with HCV NAT test	Not Available
Human T-Lymphotropic Virus Type I & II	**HTLV I/II** Antibodies to Human T- Lymphotropic Virus types I & II	Required	Not Available once kit supply is depleted
Syphilis	**STS or RPR** Serologic test for syphilis, rapid plasma reagin	Required	Required if positive screening test
Cytomegalovirus	**CMV Total** Cytomegalovirus immune globulin G and M.	Required	Not Available
West Nile Virus	**WNV NAT** Not required	Not required	Not Available
Chagas	**Chagas** Antibody to *T. cruzi*	Required only at time of workup. (Not required on Day of Collection)	Supplemental testing required if reactive screening test. Administer FD0658 (Follow-up Questions)

Table 9-2: U.S. Donor Infectious Disease Testing Profile

Infectious Disease	Infectious Disease Marker	FDA Approved Screening Test	FDA Approved Confirmatory Test
Hepatitis B	**HBsAg** Hepatitis B surface antigen	Required	Required if positive screening test
	HBcAb (anti-HBc) Total antibody to Hepatitis B Core antigen	Required	Not Available
Hepatitis C	HCV Ab (anti-HCV) Antibody to Hepatitis C virus	Required	Required if positive screening test
	HCV NAT Hepatitis C Virus RNA (nucleic acid test)	Required May be performed in combination with HIV NAT test	Not Available
Human Immunodeficiency Virus Types 1 & 2	HIV-1/HIV-2 (anti-HIV 1/2) Antibodies to Human Immunodeficiency Virus types 1 & 2	Required	Required, separate HIV-1 and HIV-2 confirmatory tests if positive screening test
	HIV NAT Human Immunodeficiency Virus type 1 RNA (nucleic acid test)	Required May be performed in combination with HCV NAT test	Not Available
Human T-Lymphotropic Virus Type I & II	HTLV I/II Antibodies to Human T- Lymphotropic Virus types I & II	Required	Not Available once kit supply is depleted
Syphilis	STS or RPR Serologic test for syphilis, rapid plasma reagin	Required	Required if screening test is positive
Cytomegalovirus	**CMV Total** Cytomegalovirus immune globulin G and M	Required	Not Available
West Nile Virus	**WNV NAT** West Nile Virus RNA (nucleic acid test); Roche and Gen-Probe test kits are under license and no longer require donor consent	Required only on Day of Collection IDM sample for marrow/PBSC using singlet (not pooled) testing	Not Available
Chagas	**Chagas** Antibody to *T. cruzi*	Required only at time of workup. Not required on Day of Collection	Supplemental testing required if reactive screening test. Administer FD0658 (Follow-up Questions)

■細胞数について

＜細胞数と生着、移植成績について＞

1．Poor mobilization の定義は CD34 陽性細胞数いくつか。また、それはどれくらいの頻度で起こるか。

—20　CD34＋/ml 以下。

CD34 陽性細胞の測定法は標準化されていない。細胞数が多い・少ないという判断は移植医と NMDP のメディカルディレクターが話し合い、その後どうするかを決めている。

2．例えば、CD34 陽性細胞が 0.3×10E6 だった場合、このプロダクトをどう扱うか。

—CD34 陽性細胞が少ないケースは稀であるが、起きた場合には NMDP のメディカルディレクターが患者の疾患や体重等を考慮してケースごとに検討する。Day6 の採取を行う、移植して生着するかどうかを確認する、緊急で同一ドナーからの骨髄移植へ移行する（＝これは極めて稀とのこと)、追加の PBSC 採取（別の日に行い、採取量を増やす。＝これも稀ということであった）を行うこともある。

3．細胞数が少なくて移植しなかったケースはあるか。

—移植施設が使用しないことはほとんどないが、このようなケースでは、同ドナーからの BM のセカンドド
ネーションをリクエストすると思われる。この場合、ドナーセンターとドナーへ即座に知らせるが、承認さ
れてもセカンドドネーションは何週間か経過し、生着がないことが確認されてからでないと行われないと思われる。生着しなかった場合、ドナーと採取施設の都合がつき次第すぐに採取を行う（PBSC でも骨髄でも)。最終同意の説明の際にセカンドドネーションの可能性を説明しておき、実際にその必要が出てきたら同意を確認する。

4．その場合の代替手段としての移植ソースはなにか。

①臍帯血　②血縁 BM・PBSC　③非血縁 BM（同一ドナー／別ドナー）

—同ドナーからの BM 提供が多いと思われる。移植医と NMDP のメディカルディレクターが検討して決める。その他の選択肢は、最初の検索時にそれらの選択肢がどのように考えられていたかによる。

5．NMDP に CD34 陽性細胞数と生着および移植成績の関係のデータはあるか。

—Donor, recipient, and transplant characteristics as risk factors after unrelated donor PBSC transplantation: beneficial effects of higher CD34+ cell dose (Michael A. Pulsipher)　(別紙資料 7)

○概要

1999年～2003年のNMDPによるUR-PBSCTの成績に関する前向き試験に登録した932名の患者(AML, ALM, CML, MDS) の結果によると、異なるいくつかの強度のレジメンで移植を行った患者でも同様の生存率であった。移植したCD34陽性細胞数が多いと生着が早く、TRMは低く、3年生存率も高かったが、GVHDのリスクを高めることはなかった。

【資料 7 】

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Donor, recipient, and transplant characteristics as risk factors after unrelated donor PBSC transplantation: beneficial effects of higher CD34 + cell dose

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Donor, recipient, and transplant characteristics as risk factors after unrelated donor PBSC transplantation: beneficial effects of higher $CD34^+$ cell dose

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We report outcomes of 932 recipients of unrelated donor peripheral blood stem cell hematopoietic cell transplantation (URD-PBSC HCT) for acute myeloid leukemia, acute lymphoblastic leukemia, chronic myelogenous leukemia, and myelodysplastic syndrome enrolled on a prospective National Marrow Donor Program trial from 1999 through 2003. Preparative regimens included myeloablative (MA; N = 611), reduced-intensity (RI; N = 160), and nonmyeloablative (NMA; N = 161). For MA recipients, $CD34^+$ counts greater than 3.8×10^6/kg improved neutrophil and platelet engraftment, whereas improved overall survival (OS) and reduced transplant-related mortality (TRM) were seen for all preparative regimens when $CD34^+$ cell doses exceeded 4.5×10^6/kg. Higher infused doses of $CD34^+$ cell dose did not result in increased rates of either acute or chronic graft-versus-host disease (GVHD). Three-year OS and disease-free survival (DFS) of recipients of MA, RI, and NMA approaches were similar (33%, 35%, and 32% OS; 33%, 30%, and 29% DFS, respectively). In summary, recipients of URD-PBSC HCT receiving preparative regimens differing in intensity experienced similar survival. Higher $CD34^+$ cell doses resulted in more rapid engraftment, less TRM, and better 3-year OS (39% versus 25%, MA, $P = .004$; 38% versus 21% RI/NMA, $P = .004$) but did not increase the risk of GVHD. This trial was registered at www.clinicaltrials.gov as #NCT00785525. (Blood. 2009;114:2606-2616)

Introduction

In the early 1990s hematopoietic cell transplantation programs began using cytokine-mobilized peripheral blood stem cells (PBSCs) from sibling donors in lieu of bone marrow (BM) as a primary stem cell source.[1-4] Unrelated donor (URD) transplantation networks followed suit at the end of the 1990s,[5] and the use of URD-PBSC grafts has grown rapidly. In 2007, 59% of National Marrow Donor Program (NMDP)–facilitated URD transplantations involved PBSCs (versus bone marrow and cord blood) and adult recipients of non–cord blood donations received PBSC grafts 80% of the time. The marked increase in the use of URD PBSCs was fueled by early reports showing more rapid engraftment, good survival, and similar rates of graft-versus-host disease (GVHD) compared with URD BM.[6,7] The trend toward the use of URD PBSCs was further influenced by a report of lower rates of rejection and disease progression compared with the use of BM after a nonmyeloablative preparative regimen,[8] resulting in PBSCs being the preferred choice in many reduced toxicity regimen approaches. Finally, ease of acquisition (apheresis versus marrow harvest) and donor choice probably added to the increased use of URD PBSCs. This high rate of URD-PBSC usage continues despite recent studies raising concern about late chronic GVHD-related morbidity.[9-12]

Large studies have defined specific donor, graft, and transplant characteristics that lead to better outcome after URD BM transplantation.[13-17] Aside from a recent analysis of $CD34^+$ cell dose,[18] the effects of other factors such as donor sex, HLA match, preparative regimen intensity, GVHD prophylactic regimen, and so forth, on survival and GVHD outcomes after URD-PBSC transplantation have not been studied in a large cohort.

Since 1999, all NMDP PBSC transplantations have been performed under a US Food and Drug Administration–accepted Investigational New Drug application protocol designed to assess URD-PBSC safety, collection efficacy, and recipient outcomes. To correlate transplant characteristics with URD-PBSC outcomes, we limited our cohort to recipients who received a transplant for the 4 most common hematologic malignancies (acute myeloid leukemia [AML], acute lymphoblastic leukemia [ALL], chronic myelogenous leukemia [CML], and myelodysplastic syndrome [MDS]) enrolled in the NMDP PBSC trial. We included key donor, product, and transplant-related variables.

Methods

Study cohort and data collection

The study cohort consisted of all recipients of primary PBSC transplants for AML, ALL, CML, or MDS facilitated by the NMDP from August 1999 through December 2003. Recipients of products that were manipulated for T-cell depletion or $CD34^+$ cell selection were excluded from the analysis. This analysis was conducted on recipients who gave informed consent for submission of their outcome data to the NMDP for studies, in accordance with the Declaration of Helsinki. This study was approved by the NMDP central Institutional Review Board. This was done prospectively for all recipients since May 2002 but inconsistently for patients who received

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transplants at some centers before then. In 2002, the NMDP asked surviving recipients who received a transplant before May 2002 to document their consent for study participation. To address bias introduced by the inclusion of only a proportion of surviving recipients (those documenting consent) but all deceased recipients of transplants before May 2002, random exclusion of recipients who died before initiation of the corrective action plan was performed to generate a "corrective action plan–corrected" dataset as previously described.[15] The final study population included 932 recipients from 99 transplantation centers. The analysis used the data collected on the NMDP Donor and Recipient Baseline and Follow-up Data Collection Forms and contract laboratory reports.

End points

Transplantation outcomes examined were neutrophil engraftment, platelet engraftment, overall survival, grades II-IV and grades III-IV acute GVHD, chronic GVHD, relapse, and transplant-related mortality (TRM). Neutrophil engraftment was defined as an achievement of an absolute neutrophil count of at least 500 neutrophils/mm^3 sustained for 3 consecutive laboratory measurements on different days. Platelet engraftment was defined as an achievement of a platelet count recovery of at least 50 000 platelets/mm^3 sustained for 3 consecutive laboratory measurements on different days with no platelet transfusions in the previous 7 days. A severity grade for acute GVHD was calculated according to the reported stages of skin, liver, and intestinal involvement with the use of the Glucksberg grading system.[20] Relapse was defined as hematologic recurrence; patients who failed to achieve remission after transplantation were considered to have had a recurrence at day 1. Treatment-related mortality was defined as death in continuous complete remission. Death from any cause was considered an event for overall survival.

Statistical methods

Patient-, disease-, transplant-, product-, and donor-related characteristics were compared for recipients of myeloablative (MA), reduced-intensity (RI), and nonmyeloablative (NMA) regimens with the chi-square test for categorical variables and the Kruskal-Wallis test for continuous variables. A conditioning regimen was considered MA if it included one of the following: total body irradiation (TBI) greater than 500 cGy as a single fraction; TBI greater than 800 cGy regardless of the number of fractions; busulfan 9.5 mg/kg or more; melphalan greater than 150 mg/m^2; any combination of busulfan and melphalan; or any combination of cyclophosphamide, etoposide (VP-16), and TBI. RI conditioning regimens included TBI between 200 and 500 cGy; TBI between 500 and 800 cGy as multiple fractions; busulfan less than 9.5 mg/kg; melphalan no greater than 150 mg/m^2; 1,3-bis(2-chloroethyl)-1-nitrosourea (BCNU), etoposide, cytarabine, and melphalan (BEAM regimens) or cyclophosphamide, BCNU, and VP-16 (CBV regimens); or any combination of VP-16 and cyclophosphamide. NMA conditioning regimens included TBI dose of 200 cGy, fludarabine with 200 cGy TBI, any combination of fludarabine and cyclophosphamide, or any combination of fludarabine and cytarabine. Univariate probabilities of overall survival were calculated with the Kaplan-Meier estimator; the log-rank test was used for univariate comparisons of survival curves; the chi-square test was used for pairwise comparisons.[21] Probabilities of neutrophil and platelet recovery, acute and chronic GVHD, relapse, and TRM were calculated with the cumulative incidence function estimator with a subsequent transplantation as a censoring event.[22,23] For neutrophil and platelet engraftment and acute and chronic GVHD, death without an event is the competing risk. For TRM, relapse was the competing risk for relapse, TRM was the competing risk. The analyses of neutrophil and platelet engraftment were restricted to patients receiving MA regimens.

Assessment of potential risk factors for day 28 neutrophil engraftment and day 60 platelet engraftment was performed with the use of logistic regression. The estimated effects of each significant risk factor were given by odds ratios. Multivariate analyses of acute and chronic GVHD, relapse, TRM, and overall mortality were performed with the use of Cox proportional hazards regression.[24] The estimated effects of each significant risk factor are given as relative risks (RRs). The following risk factors were considered as candidate effects in the model building process of each regression analysis.

Recipient- and disease-related factors. These factors included recipient age, sex, race or ethnicity, body mass index (BMI), Karnofsky/Lansky performance score at conditioning, diagnosis and stage, disease risk, time from diagnosis to transplantation, coexisting disease, and CMV status. Disease risk was classified into 3 categories. Early disease included acute leukemia in first complete remission, chronic leukemia in first chronic phase, refractory anemia, or refractory anemia with ringed sideroblasts. Intermediate diseases included acute leukemia in second or higher complete remission or chronic leukemia in accelerated or second chronic phase. Advanced diseases included acute leukemia in relapse, chronic leukemia in blastic phase, refractory anemia with excess blasts, or refractory anemia with excess blasts in transformation.

Transplantation-related factors. These factors included donor/recipient HLA match, ABO match, sex match, race match, CMV status match, conditioning regimen type, use of TBI, GVHD prophylaxis, use of planned growth factors for engraftment defined as G-CSF or GM-CSF between day −3 and day 7, and year of transplantation. On the basis of the best available typing data at the time of analysis, HLA match was classified into 3 categories: well-matched, partially matched, and mismatched, according to a recently developed algorithm that considers level of typing resolution and matching at HLA-A, -B, -C, and -DRB1 loci as described by Weisdorf et al.[21] Well matched was defined as no known disparity between donor and recipient at HLA-A, -B, -C, and -DRB1, partially matched as one known or one likely disparity, and mismatched as 2 or more disparities.

Product-related factor. This included CD34$^+$ cells per kilogram of recipient weight in infused product.

Donor-related factors. These factors included donor age, sex, race or ethnicity, BMI, CMV status, donor parity, 1-day versus 2-day collection, and the preapheresis day 5 values of donor white blood cell counts, platelet counts, and CD34$^+$ cell counts.

A stepwise selection technique with a significance level of .05 was used in all regression analyses. Separate analyses were performed for MA transplants and RI/NMA transplants. For the Cox regression models, all possible risk factors were checked for proportional hazards with a time-dependent covariate approach, and there were no violations to the proportionality assumption. No significant first-order interactions were observed. For the cell dose variables, the optimal cutpoint was determined by examining the Martingale residual plots. P values are 2-sided. All analyses were done with the use of SAS Version 9.1 (SAS Institute Inc).

Results

Donor and recipient populations

No significant differences were noted between recipients of MA, RI, and NMA conditioning regimens in donor/recipient HLA, ABO, sex, and race matching, as well as CMV status and performance scores (Tables 1 and 2). Age of recipients varied significantly, with a median age of 38 years for patients receiving MA conditioning, compared with 56 and 57 years for recipients of RI and NMA regimens, respectively ($P < .001$). Fifty-two percent of recipients in the entire cohort had at least one coexisting medical comorbidity. The most common conditions included cardiac disease/hypertension (20%), followed by pulmonary, endocrine, and gastrointestinal disorders in 10%, 10%, and 8% of recipients, respectively (supplemental Table 1, available on the *Blood* website; see the Supplemental Materials link at the top of the online article). As would be expected in an older cohort, patients receiving RI and NMA regimens were more likely to have comorbid conditions (61% and 73% vs 45% of recipients of RI, NMA, and MA conditioning had comorbidities, respectively). The donor population in this study was predominantly younger than 40 years of age (69%). Donation for persons older than age 50 was rare (7%). Donor ages, sex, weight, parity, and other characteristics were similar among the 3 preparative regimen cohorts.

Table 1. Recipient and transplantation characteristics according to preparative regimen (N = 932 donor/recipient pairs undergoing harvest/transplantation)

Variable	Myeloablative	Reduced intensity	Nonmyeloablative	P
Recipient characteristics				
No. of patients	611	160	161	
No. of centers	79	52	36	
Median follow-up time among survivors, d (range)	1224 (226-2812)	1133 (364-2200)	1417 (503-2295)	
Male recipients, n (%)	345 (56)	92 (58)	93 (58)	.857
Recipient race/ethnicity				.011*
White, n (%)	525 (86)	142 (89)	153 (95)	
Hispanic, n (%)	39 (6)	6 (4)	4 (2)	
Asian/Pacific Islander, n (%)	19 (3)	6 (4)	1 (< 1)	
Black/African American, n (%)	16 (3)	5 (3)	2 (1)	
Other/declines, n (%)	10 (2)	1 (< 1)	1 (< 1)	
Recipient age, median (range)	38 (< 1 to 65)	56 (1-75)	57 (17-77)	< .001
0-9 y, n (%)	28 (5)	2 (1)	0 (0)	< .001
10-19 y, n (%)	60 (10)	6 (4)	2 (1)	
20-29 y, n (%)	110 (18)	7 (4)	8 (5)	
30-39 y, n (%)	122 (20)	17 (11)	6 (4)	
40-49 y, n (%)	174 (28)	19 (12)	22 (14)	
50-59 y, n (%)	105 (17)	66 (41)	67 (42)	
60 y or older, n (%)	12 (2)	43 (27)	56 (35)	
Karnofsky performance score				.258
90-100, n (%)	371 (61)	91 (57)	87 (54)	
10-80, n (%)	184 (30)	54 (34)	63 (39)	
Unknown, n (%)	56 (9)	15 (9)	11 (7)	
Disease and stage				< .001†
Acute myelogenous leukemia, n (%)	249 (41)	99 (62)	71 (44)	
First CR, n (%)	87 (14)	33 (21)	34 (21)	
Second CR, n (%)	56 (9)	21 (13)	17 (11)	
Third CR, n (%)	4 (1)	2 (1)	2 (1)	
Not in remission, n (%)	102 (17)	43 (27)	18 (11)	
Acute lymphoblastic leukemia, n (%)	159 (26)	10 (6)	16 (10)	
First CR, n (%)	49 (8)	4 (3)	9 (6)	
Second CR, n (%)	46 (8)	3 (2)	4 (2)	
Third CR, n (%)	21 (3)	1 (< 1)	1 (< 1)	
Not in remission, n (%)	43 (7)	2 (1)	2 (1)	
Chronic myelogenous leukemia, n (%)	95 (16)	15 (9)	24 (16)	
First CP, n (%)	40 (7)	7 (4)	13 (8)	
Accelerated phase/second CP, n (%)	44 (7)	5 (3)	10 (6)	
Blast phase, n (%)	11 (2)	3 (2)	1 (< 1)	
Myelodysplastic syndromes (MDS), n (%)	108 (18)	35 (22)	50 (31)	
Refractory anemia, n (%)	31 (5)	9 (6)	6 (4)	
RAEB/RAEB-T, n (%)	35 (6)	14 (9)	13 (8)	
Other MDS, n (%)	42 (7)	12 (8)	31 (19)	
Disease risk				.013
Early, n (%)	207 (34)	53 (33)	62 (39)	
Intermediate, n (%)	213 (35)	45 (28)	63 (40)	
Advanced, n (%)	191 (31)	62 (39)	34 (21)	
Transplantation characteristics				
HLA match				.021
Well-matched, n (%)	359 (59)	88 (55)	103 (67)	
Partially matched, n (%)	173 (28)	53 (33)	46 (29)	
Mismatched, n (%)	79 (13)	19 (12)	7 (4)	
Donor/recipient sex match				.095
Male/male, n (%)	212 (35)	65 (41)	52 (32)	
Male/female, n (%)	143 (23)	42 (26)	46 (29)	
Female/male, n (%)	133 (22)	27 (17)	38 (24)	
Female/female, n (%)	123 (20)	26 (16)	25 (16)	

CR indicates complete remission; CP, chronic phase; RAEB, refractory anemia with excess of blasts; RAEB-T, RAEB in transformation; N/A, not applicable; and MTX, methotrexate.

*White compared with others.

†Comparing broad diseases.

‡CsA compared with FK506.

§Other GVHD prophylaxis included MTX, mycophenolate mofetil, corticosteroids, and G-CSF.

Table 1. Recipient and transplantation characteristics according to preparative regimen (N = 932 donor/recipient pairs undergoing harvest/transplantation)—Continued

Variable	Myeloablative	Reduced intensity	Nonmyeloablative	P
Donor/recipient CMV status				.235
Negative/negative, n (%)	187 (31)	35 (22)	52 (33)	
Negative/positive, n (%)	186 (30)	63 (39)	57 (36)	
Positive/negative, n (%)	68 (11)	20 (13)	21 (13)	
Positive/positive, n (%)	131 (22)	42 (26)	28 (18)	
Unknown, n (%)	6 (N/A)	0 (N/A)	2 (N/A)	
TBI, n (%)	399 (66)	26 (16)	129 (80)	< .001
GVHD prophylaxis				< .001‡
CsA + MTX ± other, n (%)	327 (54)	25 (16)	4 (2)	
CsA ± other (no MTX), n (%)	18 (3)	55 (34)	152 (92)	
FK506 + MTX ± other, n (%)	220 (36)	32 (21)	12 (7)	
FK506 ± other (no MTX), n (%)	40 (7)	46 (29)	8 (5)	
Other, n (%)§	6 (<1)	1 (<1)	5 (3)	
Use of planned growth factors, n (%)	187 (31)	66 (41)	27 (17)	< .001

CR indicates complete remission; CP, chronic phase; RAEB, refractory anemia with excess of blasts; RAEB-T, RAEB in transformation; N/A, not applicable; and MTX, methotrexate.

*White compared with others.

†Comparing broad diseases.

‡CsA compared with FK506.

§Other GVHD prophylaxis included MTX, mycophenolate mofetil, corticosteroids, and G-CSF.

Transplant characteristics, engraftment, and overall survival

Table 1 reviews characteristics of the transplants included in the analysis. Sixty percent of the transplants were from well-matched donors. Most recipients received MA conditioning procedures (66%). Most recipients received cyclosporine-based GVHD prophylaxis, but nearly 40% of the recipients received FK506. Forty-six percent of recipients underwent sex-mismatched procedures, and 56% of recipients were CMV positive.

The median time to neutrophil engraftment for patients receiving MA regimens was 14 days with a 92% and 95% cumulative incidence of engraftment at 25 and 100 days, respectively. The median time for platelets to reach 50 000 mm^3 was 21 days with a cumulative incidence of 70% at 60 days and 77% at 1 year. Data were not available to assess the timing or cumulative incidence of lymphocyte recovery. The probability of overall survival of the entire cohort at 100 days, 1 year, 2 years, and 3 years was 75%, 47%, 39%, and 33%, respectively.

Multivariate analysis of transplantation outcomes in patients receiving MA conditioning

Because the time course of some transplantation outcomes differs after MA versus RI/NMA regimens, multivariate analyses attempting to define key factors contributing to outcomes was performed separately for MA versus RI/NMA approaches. The risk factors considered as candidate effects for the model building process of each regression analysis are described in "Statistical methods."

Neutrophil and platelet engraftment. Table 3 shows logistic regression results for neutrophil engraftment at day 25 and platelet recovery to 50 000 mm^3 at day 60 in the MA cohort. Recipients

Table 2. Donor and product characteristics according to preparative regimen

Variable	Myeloablative	Reduced intensity	Nonmyeloablative	P
Product characteristics				
Median CD34+ cell dose, × 10^6/kg (range)*	6.2 (0.4-58.0)	5.4 (0.7-55.4)	4.3 (0.3-29.0)	.415
Donor characteristics				
Male donors, n (%)	355 (58)	107 (67)	99 (61)	.120
Donor race/ethnicity				.004†
White, n (%)	484 (79)	130 (81)	146 (91)	
Hispanic, n (%)	47 (8)	13 (8)	5 (3)	
Multiple, n (%)	24 (4)	7 (4)	4 (2)	
Asian/Pacific Islander, n (%)	26 (4)	5 (3)	1 (< 1)	
Black/African American, n (%)	16 (3)	3 (2)	1 (< 1)	
Other/unidentified, n (%)	14 (2)	2 (1)	4 (2)	
Median donor age at donation, y (range)	35 (19-60)	37 (19-59)	39 (18-60)	.290
18-30 y, n (%)	213 (35)	42 (26)	51 (32)	.237
31-40 y, n (%)	217 (36)	70 (44)	54 (34)	
41-50 y, n (%)	135 (22)	39 (24)	44 (27)	
51-60 y, n (%)	46 (8)	9 (6)	12 (7)	
Donor parity (female only)				.252
0, n (%)	100 (35)	11 (21)	27 (43)	
1-2, n (%)	77 (30)	21 (40)	17 (27)	
3 or more, n (%)	60 (23)	15 (28)	16 (24)	
Unknown, n (%)	19 (7)	6 (11)	4 (6)	

*CD34+ cell dose is missing in 176 myeloablative cases, 46 reduced-intensity cases, and 39 nonmyeloablative cases.

†White compared with others.

Table 3. Multivariate analysis of factors associated with engraftment in patients undergoing myeloablative unrelated donor PBSC transplantation

Variable	n	Engrafted, n	OR (95% CI)	P
Day 25 neutrophil engraftment				
Karnofsky score				.002
90-100	354	244	1.00	
10-80	178	151	0.37 (0.19-0.84)	< .001
Missing	56	53	1.24 (0.34-4.46)	.738
CD34+ cells dose, ×10⁶/kg				.001
3.8 or less	107	94	1.00	
More than 3.8	319	306	3.70 (1.61-8.47)	.002
Missing	170	148	0.97 (0.45-2.11)	.941
Recipient BMI, kg/m²				.034
Less than 18.5	47	41	0.8 (0.32-2.47)	.730
18.5-24.9	220	198	1.00	
25-29.9	185	175	2.38 (1.07-5.22)	.033
30 or greater	144	136	2.72 (1.14-6.46)	.024
Use of planned growth factors				
No	412	373	1.00	
Yes	184	175	2.37 (1.09-5.17)	.031
Day 60 platelet 50 000 engraftment				
Karnofsky score				.007
90-100	362	272	1.00	
10-80	180	110	0.54 (0.36-0.81)	.003
Missing	52	35	0.61 (0.32-1.17)	.135
CD34+ cell dose, ×10⁶/kg				< .001
3.8 or less	102	55	1.00	
More than 3.8	321	238	2.69 (1.68-4.33)	< .001
Missing	171	125	2.48 (1.48-4.21)	< .001
HLA matching status				.016
Well-matched	352	261	1.00	
Partially matched	168	111	0.74 (0.48-1.12)	.150
Mismatched	76	45	0.47 (0.27-0.83)	.009
Recipient CMV status				
Negative	268	202	1.00	
Positive	336	215	0.68 (0.47-0.99)	.042

were more likely to engraft neutrophils at day 25 and platelets at day 60 if the Karnofsky score at transplantation was at least 90, if they received planned doses of growth factors (filgrastim or sargramostim), or if the CD34+ cell dose exceeded 3.8 × 10⁶/kg recipient weight. Recipients whose BMI was below 25 kg/m² were less likely to engraft neutrophils. Recipients who were CMV positive and those who received HLA-mismatched grafts were less likely to achieve platelet engraftment.

Grades II-IV and grades III-IV acute and chronic GVHD. Table 4 shows Cox proportional hazards regression results for grades II-IV and grades III-IV acute GVHD and chronic GVHD in the MA cohort. As anticipated, HLA mismatching increased the risk of grades III-IV acute GVHD. Of note, higher CD34+ dose was not associated with an increase in acute or chronic GVHD. The risk of grades II-IV acute GVHD was noted to be less in based prophylaxis regimens compared with cyclosporine-based regimens (RR = 0.68, $P < .001$). The risk of chronic GVHD was also less with based GVHD prophylaxis (RR = 0.59, $P < .001$) or when TBI was used (RR = 0.72, $P = .007$).

Relapse and TRM. Recipients in the MA cohort with AML or ALL were more likely to relapse, with markedly lower rates in patients who received transplants for MDS or CML (Table 4). Disease risk was a significant determinant of relapse outcomes in the MA group, with a RR of 3.72 and 2.17 for patients with advanced disease and intermediate disease, respectively, compared with those with early disease ($P < .001$ and $P = .002$, respectively). Of note, TRM in the MA cohort was not associated with advanced disease as it has been in previous URD BM studies; instead, TRM was associated with HLA mismatching, CD34+ dose 4.5 × 10⁶/kg or less, lower Karnofsky scores, and the use of FK506-based GVHD prophylaxis regimens.

Multivariate analysis of transplantation outcomes in patients receiving RI/NMA conditioning

Acute GVHD, relapse, and TRM. Because many recipients of RI/NMA conditioning did not become neutropenic or require platelet transfusions, engraftment was not assessed by multivariate analysis. In addition, insufficient data were available for chimerism analysis in this cohort.

FK506-based prophylaxis was associated with lower risk of acute GVHD in the RI/NMA group (grades II-IV: RR = 0.62, $P = 0.040$; grades III-IV: RR = 0.52, $P = .033$; Table 5). The risk of acute GVHD tended to decrease through the years. The risk of significant acute GVHD (grades III-IV) was also lower in patients receiving NMA versus RI conditioning (RR = 0.37, $P < .001$). The only factor associated with relapse in the RI/NMA cohort was disease risk: patients who received a transplant for advanced disease were twice as likely to recur compared with those who received a transplant for early disease (RR = 2.00, $P = .003$). Advanced disease was also associated with TRM of patients receiving RI/NMA conditioning, with a RR of 1.91 for patients with advanced disease compared with those with early disease ($P = .008$). Finally, TRM was decreased in the RI/NMA group

Table 4. Multivariate analysis of factors associated with GVHD, relapse, and TRM in patients undergoing myeloablative unrelated donor PBSC transplantation

Variable	n	RR (95% CI)	P
Grades II-IV acute GVHD			
GVHD prophylaxis			
CsA-based	337	1.00	
FK506-based	260	0.68 (0.54-0.85)	< .001
Grades III-IV acute GVHD			
HLA matching status			.001
Well-matched	345	1.00	
Partially matched	173	1.57 (1.13-2.19)	.007
Mismatched	79	1.93 (1.29-2.88)	.001
Chronic GVHD			
GVHD prophylaxis			
CsA-based	342	1.00	
FK506-based	260	0.59 (0.48-0.73)	< .001
Conditioning regimen			
Non-TBI	209	1.00	
TBI	393	0.72 (0.57-0.91)	.007
Year of transplantation			
1999-2000	95	1.00	
2001	139	1.28 (0.89-1.87)	.193
2002	153	1.55 (1.08-2.23)	.018
2003	253	1.70 (1.21-2.40)	.002
Relapse			
Disease			< .001
AML	230	1.00	
ALL	157	0.83 (0.56-1.23)	.348
CML	93	0.10 (0.07-0.46)	< .001
MDS	107	0.43 (0.25-0.73)	.002
Disease risk			< .001
Early	203	1.00	
Intermediate	210	2.17 (1.33-3.54)	.002
Advanced	182	3.72 (2.33-5.93)	< .001
Transplant-related mortality			
HLA matching status			< .001
Well-matched	348	1.00	
Partially matched	168	1.47 (1.12-1.92)	.005
Mismatched	78	2.30 (1.63-3.26)	< .001
CD34+ cells dose, $\times 10^6$/kg			.031
4.5 or less	139	1.00	
More than 4.5	287	0.69 (0.50-0.92)	.013
Missing	170	0.89 (0.64-1.23)	.472
Karnofsky score			< .001
90-100	362	1.00	
10-80	177	1.83 (1.41-2.37)	< .001
Missing	56	0.94 (0.57-1.54)	.799
GVHD prophylaxis			
CsA-based	309	1.00	
FK506-based	226	1.51 (1.18-1.93)	.001

Table 5. Multivariate analysis of factors associated with GVHD, relapse, and TRM in patients undergoing reduced-intensity or nonmyeloablative unrelated donor PBSC transplantation

Variable	n	RR (95% CI)	P
Grades II-IV acute GVHD			
GVHD prophylaxis			
CsA-based	215	1.00	
FK506-based	99	0.62 (0.40-0.98)	.040
Year of transplantation			.028
1999-2000	43	1.00	
2001	53	0.74 (0.42-1.31)	.307
2002	93	0.56 (0.33-0.96)	.033
2003	125	0.47 (0.28-0.78)	.004
Grades III-IV acute GVHD			
GVHD prophylaxis			
CsA-based	215	1.00	
FK506-based	99	0.52 (0.36-0.86)	.003
Year of transplantation			.016
1999-2000	43	1.00	
2001	53	1.06 (0.51-2.18)	.877
2002	93	0.56 (0.27-1.15)	.114
2003	125	0.41 (0.20-0.85)	.016
Conditioning intensity			
Reduced intensity	159	1.00	
Nonmyeloablative	155	0.37 (0.22-0.64)	< .001
Relapse			
Disease risk			.005
Early	114	1.00	
Intermediate	107	1.15 (0.71-1.84)	.572
Advanced	86	2.00 (1.27-3.14)	.003
Transplant-related mortality			
CD34+ cells dose, $\times 10^6$/kg			.039
No more than 4.5	79	1.00	
More than 4.5	154	0.56 (0.38-0.86)	.013
Missing	83	0.63 (0.38-1.04)	.073
Disease risk			.029
Early	114	1.00	
Intermediate	107	1.38 (0.87-2.18)	.175
Advanced	93	1.91 (1.19-3.09)	.008

when CD34+ cell doses exceeded 4.5×10^6/kg recipient weight (RR = 0.58, $P = .017$).

Multivariate analysis of mortality of patients receiving MA and RI/NMA conditioning

We analyzed both cohorts for overall mortality and for treatment failure (defined as TRM or relapse). Because extended survival after relapse was rare, outcomes from both analyses were interchangeable, and we present only the mortality analysis. Table 6 outlines key transplant characteristics associated with increased risk of mortality in the study cohorts. For recipients of an MA transplant, intermediate and advanced disease significantly increased a patient's risk of death, as did low Karnofsky score and HLA mismatching. Other important factors increasing risk of mortality included the use of FK506-based regimens (RR = 1.37, $P = .002$) and CD34+ doses less than 4.5×10^6/kg (RR = 0.75, $P = .021$). Finally, there was a statistically significant increase in mortality when both donor and recipient were CMV positive compared with when both were negative (RR = 1.61, $P < .001$).

Only 2 variables reached significance in the regression analysis of mortality in the RI/NMA cohort. As expected, patients with advanced disease did poorly compared with those with early disease (RR = 1.85, $P < .001$). As with recipients of MA conditioning, cell dose was important. CD34+ cell doses exceeding 4.5×10^6/kg recipient weight were associated with a decrease in overall mortality (RR = 0.66, $P = .010$).

Effect of higher CD34+ cell doses on engraftment, GVHD, and survival

We further analyzed the effect of infused CD34+ dose on key outcomes (Figures 1-3). Figure 1 shows the cumulative incidence of neutrophil and platelet engraftment after MA transplantation in recipients who received 3.8×10^6 CD34+ cells/kg recipient weight or less (Low) compared with those who received more than the cutoff value (High; $P = .025$ for neutrophil engraftment at 25 days; $P < .001$ for platelet engraftment at 60 days). The difference in both the rapidity and eventual ability to achieve platelet engraftment with higher doses of CD34+ cells is marked.

Table 6. Multivariate analysis of factors associated with overall mortality in patients undergoing myeloablative or reduced intensity/nonmyeloablative unrelated donor PBSC transplantation

Variable	n	RR (95% CI)	P
Myeloablative			
HLA matching status			< .001
Well-matched	362	1.00	
Partially matched	162	1.11 (0.89-1.40)	.351
Mismatched	73	1.84 (1.38-2.44)	< .001
CD34+ cells dose, × 10⁶/kg			.024
4.5 or less	130	1.00	
More than 4.5	289	0.75 (0.58-0.96)	.021
Missing	172	0.97 (0.74-1.27)	.828
Karnofsky score			< .003
90-100	353	1.00	
10-80	180	1.79 (1.43-2.23)	< .001
Missing	56	0.94 (0.64-1.38)	.775
GVHD prophylaxis			
CsA-based	342	1.00	
FK506-based	257	1.37 (1.12-1.67)	.003
Donor/recipient CMV status			.007
Negative/negative	168	1.00	
Negative/positive	196	1.19 (0.89-1.59)	.173
Positive/negative	87	1.17 (0.84-1.62)	.357
Positive/positive	130	1.61 (1.23-2.12)	< .001
Disease risk			< .001
Early	300	1.00	
Intermediate	210	1.32 (1.03-1.69)	.028
Advanced	186	1.74 (1.35-2.24)	< .001
Reduced intensity/nonmyeloablative			
CD34+ cells dose, × 10⁶/kg			.024
4.5 or less	80	1.00	
More than 4.5	156	0.68 (0.48-0.91)	.010
Missing	85	0.67 (0.47-0.96)	.031
Disease risk			< .001
Early	115	1.00	
Intermediate	160	1.17 (0.84-1.63)	.356
Advanced	96	1.85 (1.33-2.56)	< .001

We explored in more depth whether higher CD34+ cell doses were associated with increased rates of acute or chronic GVHD or both. Figure 2A and B shows the cumulative incidence of grades III-IV acute GVHD based on CD34+ doses by quartiles for recipients of MA and RI/NMA conditioning, respectively. No difference was noted between the quartiles ($P = .599$ and .305 at 180 days for MA and RI/NMA, respectively). For recipients of MA conditioning, the incidence of grades III-IV acute GVHD in the top quartile of CD34+ cells doses (> 9.5 × 10⁶/kg) compared with doses in the second quartile (between 3.8 and 6.3 × 10⁶/kg) had a RR of 0.81 ($P = .393$); doses above the 90th percentile (> 14.9 × 10⁶/kg) had a similarly nonsignificant RR of 1.13 ($P = .696$). For recipients of RI/NMA conditioning, the RR of grades III-IV acute GVHD in the top quartile (> 9.4 × 10⁶/kg) and the top 10% (> 14.6 × 10⁶/kg) compared with the second quartile (between 3.6 and 5.9 × 10⁶/kg) were 0.62 ($P = .301$) and 0.64 ($P = .488$), respectively. An analysis of grades II-IV acute GVHD similarly showed no increase in incidence with higher cell doses (data not shown).

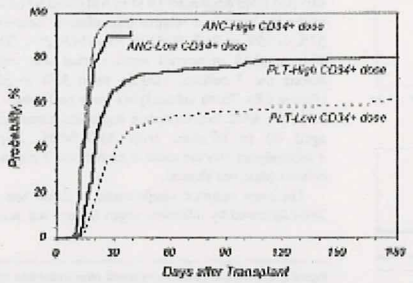


Figure 1. Cumulative incidence of neutrophil and platelet engraftment after MA URD-PBSC transplantation by CD34+ dose. CD34+ cell doses higher than 3.8 × 10⁶/kg recipient weight improved neutrophil and platelet engraftment compared with lower doses ($P = .005$ for neutrophil engraftment at 26 days; $P < .001$ for platelet engraftment > 50 000/μL at 60 days). ANC indicates neutrophil engraftment; PLT, platelet engraftment; Low, no more than 3.8 × 10⁶ CD34+ Ag (n = 107, ANC: n = 106, PLT); High, greater than 3.8 × 10⁶ CD34+/kg (n = 329, ANC: n = 324, PLT).

Figure 2C and D shows the incidence of chronic GVHD by quartiles, demonstrating no increase in incidence with higher cell doses for recipients of MA and RI/NMA conditioning, respectively ($P = .068$ and .189 at 2 years, respectively). Further analysis of patients receiving cell doses above the top quartile and the 90th percentile compared with the second quartile similarly shows no evidence of an increase in chronic GHVD for recipients of MA and RI/NMA conditioning (MA: RR = 1.17, $P = .405$ for top quartile vs second quartile; RR = 1.24, $P = .389$ for top 10% vs second quartile; RI/NMA: RR = 1.35, $P = .262$ for top quartile vs second quartile; RR = 1.24, $P = .508$ for top 10% vs second quartile).

Higher cell doses were independent predictors of better survival regardless of preparative regimen approaches. CD34+ doses between 4.5 and 9.5 × 10⁶/kg recipient weight resulted in a 12% improvement in 3-year survival in recipients of MA conditioning compared with lower doses (37% vs 25%; $P = .020$, Medium vs Low; Figure 3A). However, doses greater than 9.5 × 10⁶/kg did not further improve the survival rate ($P = .489$ at 3 years, Medium vs High). Three-year survival after RI/NMA preparative regimens also significantly improved in patients with CD34+ doses between 4.5 and 9.5 × 10⁶/kg recipient weight compared with patients with lower doses (34% vs 21%; $P = .045$, Medium vs Low; Figure 3B). Similar to the MA cohort, CD34+ cell doses greater than 9.5 × 10⁶/kg did not further improve outcome in this cohort ($P = .157$ at 3 years; Medium vs High).

We also analyzed CD34 doses based on ideal body weight as opposed to actual body weight. This analysis was restricted to adults only because of the differences in computing ideal body weight for children. Compared with CD34+ cells/kg based on actual body weight, CD34+ cells/kg based on ideal body weight was similarly associated with neutrophil and platelet engraftment, but it was not significantly associated with TRM or survival in MA transplantations. Among NMA/RI transplants, CD34 dose based on ideal body weight was only significantly associated with survival but not TRM (data not shown). This indicates that cell dose based on ideal body weight may be a less sensitive predictor of transplantation outcomes in URD-PBSC transplantations, compared with cell dose based on actual body weight.

Comparison of outcomes between preparative regimen cohorts

Although the preparative regimen cohorts differed by age and the presence of coexisting conditions, these variables did not come out as significant in multivariate outcome analysis; therefore, comparisons of the cohorts may be instructive. NMA regimens resulted in significantly less severe (grades III-IV)

acute GVHD compared with RI or MA regimens (cumulative incidence at 180 days: 16% vs 26% vs 30%, NMA vs RI vs MA, $P < .001$; Figure 4A), but chronic GVHD was statistically identical between the regimens, with an incidence just above

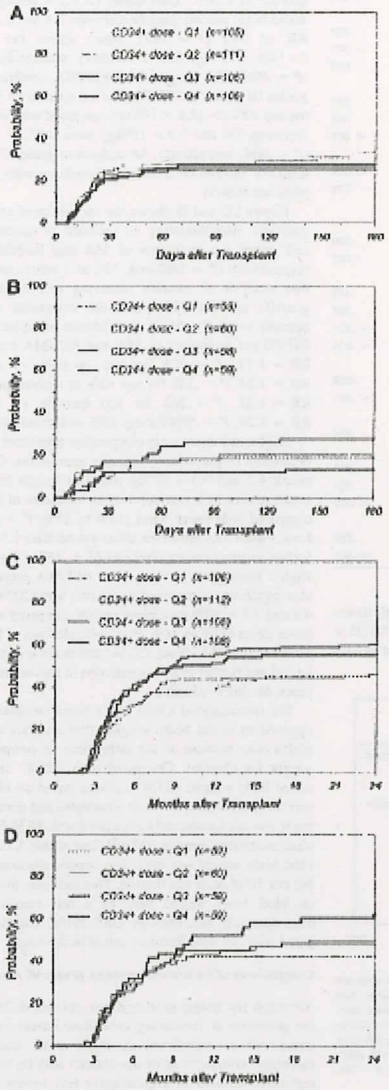


Figure 2. Cumulative incidense of GVHD after URD-PBSC transplantation by quartile (Q) of CD34+ dose. Higher CD34+ cell doses did not increase the incidence of GVHD. (A) Grades III-IV acute GVHD after MA transplantation ($P = .699$ at 100 days); (B) grades III-IV acute GVHD after RiNMA transplantation ($P = .305$ at 100 days); (C) chronic GVHD after MA transplantation ($P = .068$ at 2 years); (D) chronic GVHD after RiNMA transplantation ($P = .180$ at 2 years). MA: Q1 indicates no greater than 3.8; Q2, 3.8 to 6.2; Q3,6.2 to 9.5; Q4, greater than 9.5; RiNMA: Q1, no greater than 3.8; Q, 3.8 to 5.9; Q3, 5.9 to 9.4; Q4, greater than 9.4 (× 10^6 CD34+/kg).

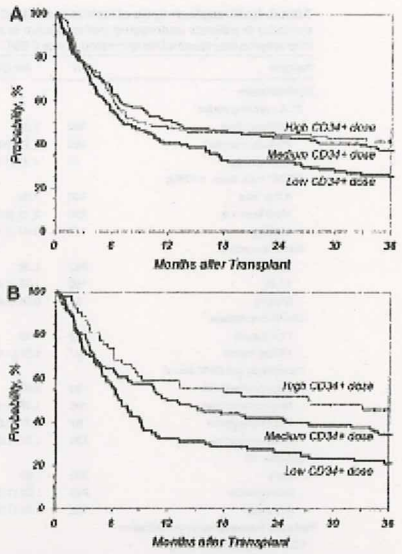
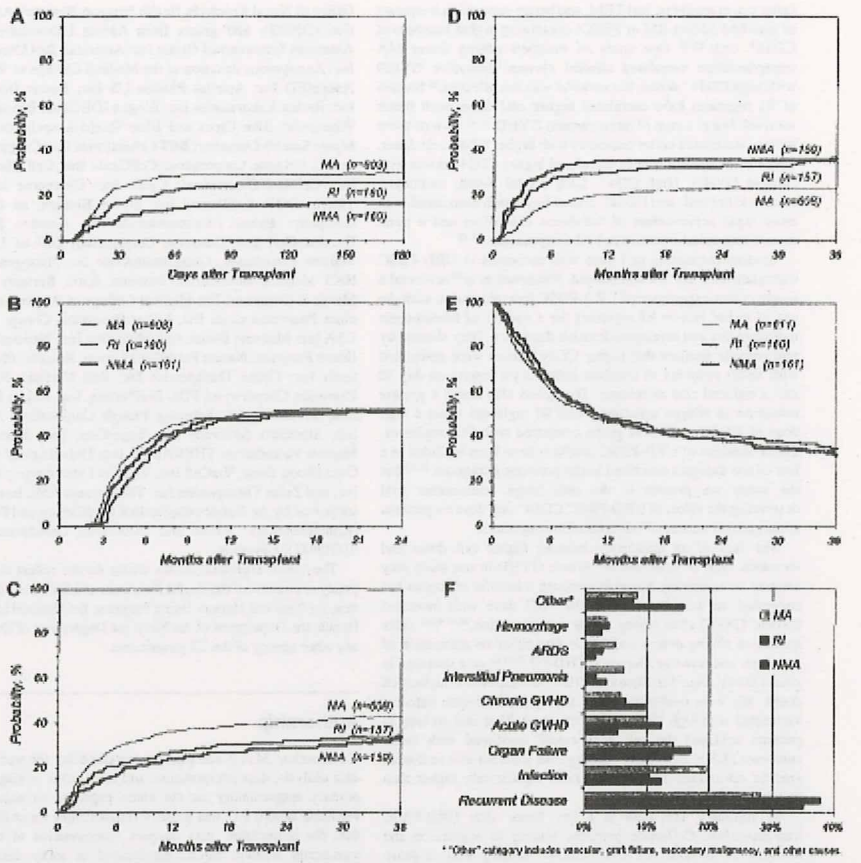


Figure 3. Overall survival after URD-PBSC transplantation by CD34+ dose. CD34+ cell doses higher than 4.5 × 10^6/kg recipient weight improved overall survival compared with lower doses. However, doses much higher than 4.5 × 10^6/kg did not further improve the survival rate compared with doses just above 4.5 × 10^6/kg. (A) Overall survival after MA transplantation ($P = .025$ at 3 years for Medium vs Low; $P = .499$ at 3 years for Medium vs High). (B) Overall survival after RiNMA transplantation ($P = .845$ at 3 years for Medium vs Low; $P = .157$ at 3 years for Medium vs High). Low indicates no greater than 4.5 (n = 142, MA; n = 80, RiNMA); Medium, 4.5 to 9.5 (n = 183, MA; n = 102, RiNMA); High, greater than 9.5 (n = 110, MA; n = 84, RiNMA) (× 10^6 CD34+/kg).

50% at 2 years (Figure 4B). TRM was higher after MA procedures (cumulative incidence at 3 years: 34% vs 34% vs 43%, NMA vs RI vs MA, $P = .027$; Figure 4C), but any gains in survival from decreased TRM in NMA and RI conditioning were offset by increased relapse (cumulative incidence at 3 years: 37% vs 35% vs 24%, NMA vs RI vs MA, $P < .001$; Figure 4D). This resulted in overall survival that was indistinguishable among the 3 cohorts, ranging from 32% to 35% at 3 years (Figure 4E). Three subanalyses were performed: (1) excluding ALL, (2) AML first complete remission alone, and (3) patients aged 40 to 60 years with AML/MDS. Survival in the 3 subanalyses was the same in each of the 3 preparative regimen cohorts (data not shown).

The most common single cause of death was relapse (28%-38%) followed by infection, organ failure, and acute and chronic



* "Other" category includes vascular, graft failure, secondary malignancy, and other causes.

Figure 4. Key outcomes after URD-PBSC transplantation by preparative regimen. (A) Grades III-IV acute GVHD, (B) chronic GVHD, (C) TRM, (D) relapse, (E) overall survival, and (F) primary cause of death. ARDS indicates acute respiratory distress syndrome.

GVHD (Figure 4F). Recipients receiving MA procedures died more frequently of infection, acute respiratory distress syndrome, and interstitial pneumonia compared with patients who received RI/NMA conditioning, whereas patients who received RI/NMA conditioning died more frequently of recurrent disease, chronic GVHD (recipients of NMA conditioning), and other causes (recipients of NMA conditioning). Causes of death did not vary by $CD34^+$ cell dose.

Discussion

We have shown in this large, multi-institutional prospective study that transplantation with NMDP-facilitated URD PBSCs results in rapid engraftment and survival comparable to published transplantation experiences with URD BM.[17,28] Because PBSCs from URDs has become the most commonly used URD stem cell source, the *multivariate risk factor analysis presented here is useful in defining* prognosis and identifying populations at risk to design strategies aimed at improving outcome.

One of the key findings of this study is the independent predictive value of higher $CD34^+$ dose for improvements in major transplantation outcomes. Cell dose has long been recognized to be important in allogeneic transplantation. Early studies showed less rejection and better survival in patients undergoing transplantation for severe aplastic anemia who received higher mononuclear cell doses in their BM grafts.[27,28] More recent studies involving MA approaches have shown

faster count recovery, less TRM, and better survival in recipients of matched sibling BM or PBSCs containing higher numbers of $CD34^+$ cells.[29-35] One study of matched sibling donor MA transplantation correlated clinical chronic extensive GVHD with high $CD34^+$ doses, but survival was not affected.[36] Studies of RI regimens have correlated higher cell doses with better survival, but at a cost of more chronic GVHD.[37-40] Two of these studies associated better outcomes with higher $CD8^+$ cell doses, whereas the other 2 studies correlated higher $CD34^+$ doses with chronic GVHD. High $CD4^+$, $CD8^+$, total T-cell, monocyte, natural killer cell, and $CD34^+$ counts have been associated with more rapid achievement of full-donor chimerism and a trend toward decreased rejection in NMA approaches.[41-43]

Studies correlating cell dose with outcomes in URD-PBSC transplantation are few and limited. Nakamura et al[18] reviewed a single center experience of URD-PBSC transplantation with the use of either MA or RI regimens for a variety of hematologic malignancies and myeloproliferative disorders. They showed by multivariate analysis that higher $CD34^+$ doses were associated with faster recovery of absolute lymphocyte counts on day 30 and a reduced rate of relapse. The group also noted a greater reduction in relapse associated with RI regimens when a high dose of $CD34^+$ cells was given compared with MA regimens. Small numbers of URD-PBSC products have been included in a few of the analyses described in the previous paragraph,[35,41] but the study we present is the only large, multicenter trial describing the effect of URD-PBSC $CD34^+$ cell dose on patients undergoing a variety of transplantation regimens.

The lack of an association between higher cell doses and increased rates of acute and/or chronic GVHD in our study may seem to be surprising; however, although a handful of studies has suggested an association of $CD34^+$ cell dose with increased chronic GVHD after sibling donor transplantation,[36,39,40,42] other studies of sibling donors and URDs find either no association of cell dose and acute or chronic GVHD[29,35,38,41,44] or a decrease in grades III-IV acute[34] or chronic GVHD[45] in recipients of higher cell doses. We were unable to define any specific adverse outcome associated with high URD-PBSC cell doses. That said, as long as patients achieved the cell dose cutoff associated with better outcomes (4.5×10^6 $CD34^+$ cells/kg), we were not able to discern specific advantages to receiving doses significantly higher than that threshold.

In summary, cell dose is a key factor after URD-PBSC transplantation. Collection practices leading to acquisition and infusion of at least 4.5×10^6 $CD34^+$ cells/kg may improve survival and decrease morbidity in patients receiving this stem cell source for transplantation, regardless of regimen intensity. Other factors identified in this study may help individual patients understand risk and may assist investigators in targeting high-risk populations for studies aimed at improving outcome.

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Authorship

Contribution: M.A.P. had primary responsibility for study design, data analysis, data interpretation, and manuscript writing and had primary responsibility for the entire paper as an accurate and verifiable report; P.C. had primary responsibility for study design, data file preparation, data analysis, interpretation of data, and manuscript writing; B.R.L. participated in study design, data analysis, interpretation of data, and manuscript writing; S.F.L. and P.A. participated in interpretation of data and manuscript writing; J.P.K. participated in study design, data analysis, and interpretation of data; M.M.H. participated in study design, interpretation of data, and manuscript writing; J.P.M. and R.J.K. participated in data file preparation, interpretation of data, and manuscript writing; and D.L.C. had responsibility for study design, data file preparation, data analysis, data interpretation, and manuscript writing and had responsibility for the entire paper as an accurate and verifiable report.

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