Subsequent Donations: **One More Time**

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Financial Disclosures – None

Conflict of Interest Disclosure

We attest that we have no relevant financial, professional, or personal relationship with a commercial interest producing health care goods/services related to this educational activity.

We will not discuss off-label use of commercial products.
Objectives

1. State common patient situations that warrant a subsequent donation & the rationale for certain product requests.

2. Describe the NMDP approval process of subsequent donation request.

3. Review case studies of complicated subsequent donation requests and ethical issues that may be encountered with these requests.
Subsequent Donation Request Situations

- Relapse / Recurrence of Disease
- Immune Reconstitution
- Graft Failure
- Post-Transplant Lymphoproliferative Disorder (PTLD)
- Insufficient Cell Dose

Product Request Rationale

- **TC, Apheresis**
  - Relapse
  - Mixed chimerism
  - Immune Reconstitution

- **HPC, Apheresis**
  - Graft Failure
  - Relapse
  - Insufficient Cell Dose

- **HPC, Marrow**
  - Graft Failure
  - Relapse
  - Insufficient Cell Dose

Note: Common terms “T-Cells”, “Marrow” & “PBSC” will also be used within presentation.
### Number of Requests by Product per CIBMTR

<table>
<thead>
<tr>
<th>Original Product</th>
<th>Requested Product</th>
<th>Number 1/1/12 - 12/31/12</th>
<th>Number** 1/1/13 - 6/14/13 Actual / Projected</th>
</tr>
</thead>
<tbody>
<tr>
<td>HPC, Marrow</td>
<td>HPC, Marrow</td>
<td>5</td>
<td>7 / 11</td>
</tr>
<tr>
<td>HPC, Marrow</td>
<td>HPC, Apheresis</td>
<td>39</td>
<td>33 / 53</td>
</tr>
<tr>
<td>HPC, Marrow</td>
<td>TC, Apheresis</td>
<td>77</td>
<td>66 / 106</td>
</tr>
<tr>
<td>HPC, Apheresis</td>
<td>HPC, Marrow</td>
<td>9</td>
<td>3 / 5</td>
</tr>
<tr>
<td>HPC, Apheresis</td>
<td>HPC, Apheresis</td>
<td>43</td>
<td>66 / 106</td>
</tr>
<tr>
<td>HPC, Apheresis</td>
<td>TC, Apheresis</td>
<td>154</td>
<td>143 / 229</td>
</tr>
</tbody>
</table>

**Mean = 343 days**  
**Median = 175 days**

### Number that actually Donated by product type per CIBMTR

<table>
<thead>
<tr>
<th>Original Product</th>
<th>Second Product</th>
<th>Number 1/1/12 - 12/31/12</th>
<th>Number** 1/1/13 - 9/9/13 Actual / Projected</th>
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<tbody>
<tr>
<td>HPC, Marrow</td>
<td>Tubes</td>
<td>1</td>
<td>0 / 0</td>
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<tr>
<td>HPC, Marrow</td>
<td>HPC, Marrow</td>
<td>4</td>
<td>4 / 6</td>
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<td>HPC, Marrow</td>
<td>HPC, Apheresis</td>
<td>31</td>
<td>23 / 35</td>
</tr>
<tr>
<td>HPC, Marrow</td>
<td>TC, Apheresis</td>
<td>65</td>
<td>45 / 68</td>
</tr>
<tr>
<td>HPC, Apheresis</td>
<td>HPC, Marrow</td>
<td>8</td>
<td>0 / 0</td>
</tr>
<tr>
<td>HPC, Apheresis</td>
<td>HPC, Apheresis</td>
<td>36</td>
<td>34 / 51</td>
</tr>
<tr>
<td>HPC, Apheresis</td>
<td>TC, Apheresis</td>
<td>147</td>
<td>95 / 143</td>
</tr>
</tbody>
</table>

**Mean = 407 days**  
**Median = 222 days**

**Mean = 343 days**  
**Median = 175 days**
Emergency Subsequent Request?

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

<table>
<thead>
<tr>
<th>Dose</th>
<th>NMDP MD Action</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt;2 x10^6 for PBSC x10^6 for Marrow</td>
<td>Monitor for engraftment x4 wks</td>
</tr>
<tr>
<td>1 – &lt;2</td>
<td>Evaluate request</td>
</tr>
<tr>
<td>&lt;1</td>
<td>Approve request</td>
</tr>
</tbody>
</table>

Incidence Rate of Subsequent Donation Request For Inadequate Collections*

Marrow 1 in 500

PBSC 1 in 1000

* Wide statistical confidence intervals given the low frequency of these events; based on review of Quality Incidents 4/16/12 – 6/30/13 by TMS
Will this work?
What is Success of Subsequent Transplant?

*A chance with but no chance without*
No single general statistic
Many variables affect outcome
Reasonable for TC to request subsequent

NMDP Review & Approval Process
NMDP Request & Approval of Subsequent Donation Request

- Submits request & paperwork to Case Management (CM)
- Reviews donor recovery status
- Discusses request with TMS if not recovered

NMDP Request & Approval of Subsequent Donation Request

- Evaluates
  - diagnosis
  - disease status
  - indications shared for rationale of subsequent donation request
  - last transplant date
  - previous product cell dose
  - reported donor recovery status
TC Request for Subsequent Donation

Pg 1 Data Reviewed
1. Diagnosis
2. Current Disease Status
3. Reason for Request
4. Date of Last Infusion
5. Cell Dose Administered
6. Conditioning Type
7. Rescue / Cryo available?
8. Engraftment / Chimerism

Pg 2 Data Reviewed
1. Clinical Condition
2. Hgb / Platelets
3. Red Cell Dependent?
4. Platelet Dependent?
5. Is a new HCT planned?
6. Reason for preferred product
Donor Considerations

NMDP Request & Approval of Subsequent Donation Request

- Receives request when NMDP MD does
- Evaluates donor status & discusses concerns with DC MD
- Approaches donor re: subsequent donation request
- Informs CM of donor’s decision

Why at the same time?
Time is of the essence for this decision. Rarely is a request denied.
# NMDP Subsequent Donation Policy

<table>
<thead>
<tr>
<th>Product</th>
<th>Recipient 1</th>
<th>Recipient 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>HPC</td>
<td>1-2</td>
<td>1-2</td>
</tr>
<tr>
<td>• Marrow</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• PBSC</td>
<td></td>
<td></td>
</tr>
<tr>
<td>T-Cells</td>
<td>1-2</td>
<td>1-2</td>
</tr>
<tr>
<td>Total Donations</td>
<td>3 Max 2 HPC</td>
<td>3 Max 2 HPC</td>
</tr>
</tbody>
</table>

**Lifetime max for HPC, Marrow donations = 2**

Non-conforming request may be submitted to NMDP MD for consideration

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## NMDP Subsequent Donation Policy

- Every subsequent donation requires consent
- Donor suitability and eligibility guidelines must be met
- Donor should not be available for a second recipient until at least 1 yr since first HPC or at least 3 yrs since a subsequent HPC
- Donors shouldn’t donate HPC for second recipient unless no equally compatible donor is available for second recipient
- Donations for a 3<sup>rd</sup> recipient not permitted
- Donor must have reported full recovery
- Second PBSC shouldn’t be undertaken if donor was a non-mobilizer
- Non-conforming request may be submitted to NMDP MD for consideration

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Subsequent Donation Considerations

Current Process

- Info Session includes discussion of possibility of Subsequent donation
- DC sends "Willingness to Consider" Letter to donor post donation
- Varying use of "Willingness to Consider" letter; some DC absolute if donor said no & some DC not

Future Process under consideration

- Info Session includes discussion of possibility of Subsequent donation
- Donor is approached if TC requests Subsequent Donation

Issues to Consider
- Medical Concerns
- Non-Medical Issues

Issues that Impact Approaching Donor

- Tolerated initial donation process poorly
- Non-medical issues
- Caretaking behaviors of DC staff usurping donor decision
- Donor/Recipient relationship
- Medically unsuitable
- Central line placement
- Multiple requests of same donor
### Suitability Assessment

<table>
<thead>
<tr>
<th>Original PE &lt;6 months from proposed PBSC/marrow collection</th>
<th>Original PE &gt;6 months from proposed PBSC/marrow collection</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. New Form 700</td>
<td>1. New Form 700</td>
</tr>
<tr>
<td>2. All PE blood work - except Hgb S</td>
<td>2. New PE and Addendum to Physical Examination (F00806)</td>
</tr>
<tr>
<td>3. CXR, EKG, &amp; UA not required</td>
<td>3. All PE testing (including CXR, EKG, &amp; UA) and all blood work - except Hgb S</td>
</tr>
<tr>
<td>4. Repeat HHSQ</td>
<td>4. Enter PE date in STAR Link</td>
</tr>
<tr>
<td>5. Use date of earliest signature on HHSQ as “date of medical evaluation” on Form 700</td>
<td>5. Repeat HHSQ</td>
</tr>
<tr>
<td>6. Repeat IDMs if &gt;30 days</td>
<td>6. Repeat IDMs</td>
</tr>
</tbody>
</table>

**NOTE:**
NMDP MD may deviate from described suitability assessment plan in the event of an inadequate initial product collection. Appropriate documentation should be retained in the work-up chart.

### T-Cells Suitability Assessment
- HHSQ, IDMs, venous assessment & any tests requested by MDs

Eligibility determination & documentation must still be performed for the new product.

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**CASE STUDIES**
Case Study #1

Recipient: 42 yo F NHL at International TC
Donor: 38 yo F 5’4” 249 lbs

Total CD34 cells requested 336 x 10⁶
Cell dose administered 12.5 x 10⁶ / kg

June 13 PBSC collected
Did not tolerate initial collection well.
Required Vicodin to control pain; four wks to recover & still had some pain off/on

July 2 Subsequent Product Request Received
“The patient did NOT engraft”

Case Study #1

What product would you request?

0% 1. PBSC
0% 2. Marrow
0% 3. T-Cells
Case Study #1

Would you approach this donor?

0% 1. Yes
0% 2. No

WHAT HAPPENED?

July 5  Donor approached & immediately said “Yes, I’ll do it!”
        Discussed options to improve pain management
        Cancelled her vacation plans to donate!

July 10  Cleared for PBSC

July 18  PBSC #2 collected; tolerated collection well
        Total CD34 cells collected 1410.6 x 10^6

Sept  Donor recovered 1 wk; waiting for pt update 10/15/13

Case Study #2

Recipient:  55 yo M Myelofibrosis, 80 kg at Domestic TC
Donor:     24 yo F

Total CD34 cells requested  401 x 10^6
Cell dose administered     1.94 x 10^6 / kg

Sept 12  Day 1 Filgrastim
        Reports scratchy throat & fever; MDs believe viral; TC informed

Oct 2  PBSC collected & cryopreserved
       24 L over 6.5 hours

Oct 5  Product infused

Oct 17  Subsequent Product Request Received
        “No engraftment; clinical status good; red cell/platelet dependent”
        Alternative suitable URD identified
Case Study #2

What product would you request?

0% 1. PBSC
0% 2. Marrow
0% 3. T-Cells

Case Study #2

Would you approach this donor?

0% 1. Yes
0% 2. No

WHAT HAPPENED?

Oct 18  Donor approached; agrees to donate
Oct 29  Filgrastim starts with minimal symptoms
Nov 2   PBSC #2 collected; CD34 cells collected 285.1 x 10^6
Dec 12  Recipient engrafted; doing well; to be discharged soon
Feb 17  Recipient death reported d/t treatment-related complications
Case Study #3

Recipient: 10 yo M with Fanconi anemia
Donor: 44 yo F

May 2011 PBSC collected
May 2012 Donor and Recipient meet & establish close relationship
Aug 2013 Donor reports she had tick bite; contracted Lyme’s and Babesiosis; recovered w/o complications

Babesiosis is medical deferral due to possible transmission of disease.

Case Study #3

Would you approach this donor, if needed?

0% 1. Yes
0% 2. No

WHAT HAPPENED?

Aug 2013
DC asks input from NMDP MD who recommends that donor be removed from Registry but remain available for evaluation of subsequent donation should her recipient require one.

✓ Primary vs Subsequent Donation
✓ Donor and Recipient Relationship
Case Study #4

Recipient: F b 1986 CML
Donor: F b 1979

May 2003 Marrow
Long recovery; hematoma w/ pain & numbness requiring ongoing pain meds; doesn’t report recovery until spring 2004

June 2006 Whole Blood collected
Donor knew of pending request; had been in touch with recipient

May 2012 T-Cells requested for mid-July
Donor is very willing but is currently being treated for ectopic pregnancy
& has received 2 doses of methotrexate; may eventually need surgery

DC contacts NMDP MDs to ask
-Should she be TU’d? How long? Can she ever donate?

WHAT HAPPENED?

May 2012
NMDP MD recommends
• TU until condition resolved
• Monitor HCG levels
• Inform TC of medical issue requiring assessment

Jun 2012
Donor notifies the DC that HCG is now normal;
NMDP MD says donor is acceptable to proceed

Jul 2012
T-Cells collected

Sep 2013
10 yr recipient report – complete remission
Case Study #5

Recipient:  
#1 M  b 1951  CLL  
#2 F  b 1978  NHL at International TC  
Donor:  
M  b 1955  

Apr 2004  Donated PBSC #1 for Recipient #1  
Feb 2006  Donated T-cell for Recipient #1  
Aug 2007  Recipient #1 death reported  
Nov 2012  Donated PBSC #2 for Recipient #2  

Day 4 dose reduced d/t severe HA  
Total CD34 cells requested  \(220 \times 10^6\)  
Cell dose administered  \(4.8 \times 10^6 / \text{kg}\)  

Mar 2013  Subsequent product request received  
Engrafted; 100% donor; acute GVHD resolved; WBC 1.5; Neut 0.8; Lymph 0.2; platelet & RBC dependent  

What product would you request?  

0%  1. PBSC  
0%  2. Marrow  
0%  3. T-Cells
**Case Study #5**

**Would you approach this donor?**

0%

1. Yes

0%

2. No

<table>
<thead>
<tr>
<th>Product</th>
<th>Recipient 1</th>
<th>Recipient 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>HPC Marrow or PBSC</td>
<td>1-2</td>
<td>1-2</td>
</tr>
<tr>
<td>T-Cells</td>
<td>1-2</td>
<td>1-2</td>
</tr>
<tr>
<td>Total Donations HPC &amp; T-Cells</td>
<td>3 Max 2 HPC</td>
<td>3 Max 2 HPC</td>
</tr>
</tbody>
</table>

Lifetime max for HPC, Marrow donations = 2

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**WHAT HAPPENED?**

**Mar 14** NMDP MD approves to approach

**Mar 28** Cleared for PBSC

**Apr 4** **PBSC #3 collected**

First collection ends at 16L w/ interface problems; new machine primed; NMDP MD approves to cont (if platelets >60K) to collect additional 6L over original 18L to try to obtain cells; donor tolerating collection well.

- **Bag #1** CD34 cells collected $157.7 \times 10^6$
- **Bag #2** CD34 cells collected $224.9 \times 10^6$

**May 4** Donor reports full recovery; HA resolved
Case Study #6

Recipient: F b 1954 AML
Donor: M b 1985 5’4” 135lb

Cell Dose Requested: 293.5 x 10^6
Cell Dose Administered: <1 x 10^6 / kg

Pre-apheresis WBC 28.7 x 10^9; pre-apheresis CD34+ 0.11%; abs CD34+ 31.57

Oct 19 Cleared for both products
Hgb 12.6; Hct 39.6; MCV 72; MCH 22.8; RDW 17.6 MD notes “frequent blood donor; most recent donation 1 mo ago; likely Fe deficient”

Nov 15 PBSC collection 24L collection
Post-collection platelets 65K; AC MD recommends to wait until platelets >100K before considering subsequent collection

Dec 5 Recipient update
Recipient is +15 day, clinically well; afebrile, transfusion dependent; WBC 0.3; TC wants to wait and watch

Dec 29 Subsequent product request received
“Persistent disease”

Dec 31 Donor reports full recovery

What product would you request?

0% 1. PBSC
0% 2. Marrow
0% 3. T-Cells
Case Study #6

Would you approach this donor?

0% 1. Yes
0% 2. No

WHAT HAPPENED?

Jan 2013  Consented to donate but Medically Deferred
  • Donor labs repeated: WBC 3.3; Hgb 12.9; MCV 72.6; MCH 22.2; Neu Abs 1.90; Iron 39; Fe Binding Capacity 452; % Sat 9
  • Donor deferred by AC d/t iron deficiency and abn labs

Mar 2013
Donor #2 identified through co-op registry; PBSC collected

May 2013
TC reports recipient is disease-free and doing well

Case Study #7

Recipient:  F  b 1974  MDS
Donor:  M  b 1961

Cell Dose Requested  288 x 10⁸ / kg
Cell Dose Administered  0.65 x 10⁸ / kg

Nov 23  PE for PBSC reveals sickle cell pos & platelets 144K; cleared as marrow-only; TC accepts marrow
Dec 19  Donor notifies DC of Dengue fever diagnosis
Dec 29  Marrow collection following donor’s recovery
Apr 19  Subsequent product request received
  "disease progression; chimerism 60% donor & 40% recipient"
Case Study #7

What product would you request?

0%  1. PBSC
0%  2. Marrow
0%  3. T-Cells

Case Study #7

Would you approach this donor?

0%  1. Yes
0%  2. No

WHAT HAPPENED?
May 8  Cleared for T-Cells; plts 137K
May 10  T-Cells collected w/ femoral central line
         AC collects 18L; not 23L as requested by TC
May 17  Donor fully recovered; central line site healing
Dec 2012 Recipient death reported d/t disease relapse
Case Study #8

Recipient: M b 1945 AML
Donor: M b 1995

Cell Dose Requested: 1,106 x 10^6
Cell Dose Administered: 5.2 x 10^6 / kg

Mar 12: Declines PBSC; consents to marrow only; TC accepts product change
Misses PE appt twice; difficult to contact

Apr 8: Marrow collection
Reports hip pain 3 wks post collection with bruising

Jul 21: Subsequent product request received
“Marrow with cytogenetic relapsed disease”

Case Study #8

What product would you request?

1. PBSC
2. Marrow
3. T-Cells
Case Study #8
Would you approach this donor?

0% 1. Yes
0% 2. No

WHAT HAPPENED?
Jul  DC attempts to contact donor multiple times. Finally he returns call - he is not interested in donation. He never told his parents that he donated marrow. He is living at home now during summer break. He is sure his family will not be supportive.
Sep  Recipient death reported

Case Study #9

Recipient: M b 1963 MM
Donor: F b 1962

Cell Dose Requested 620 x 10^6
Total CD34+ cells collected 845 x 10^6 / kg

June 14  PBSC collection
Required central line; very poor venous access
July 2  TC submits research request to participate in study to create cell line for possible treatment of post-transplant viral infections BUT this requires T-Cells collection

Cells may never be used by this recipient.
Would you approach this donor?

0%  1. Yes
0%  2. No

WHAT HAPPENED?
DC discusses request with NMDP MD who determines that donor risk of central line is too great to allow collection with low potential of recipient use; donor is withdrawn from study

Aug 12
Donor informed recipient engrafted & has been discharged; donor states she would be “happy to donate any product needed in the future…”

Summary

- Stem cell transplantation is a multifaceted medical treatment.
- A subsequent donation request may present complex practical, logistical, and ethical considerations.
- A subsequent donation may be an integral component in providing the optimal treatment regimen.