Donor work up, follow up and ethical issues

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The donor has been identified as a match and agrees to donate hematopoietic stem cells…

- Background
- Inclusion criteria in donor programs
- Care before and during the collection procedure
- Follow up
- Ethical aspects
Indications for allogeneic stem cell transplantation, worldwide, 2005
Stem cell donors

• Related (siblings) to 1/3 of the patients
• Unrelated
• Cord blood
Number of unrelated donors in registries (BMDW)

Approaching 13 million donors
Inclusion criteria in donor programs

The primary goal is to determine if the donor is in good health in order to:

1. Protect the donor from the risk of damage to his/her own health
2. Protect the recipient from transmissible diseases
Donor Selection Criteria*

– HLA compatibility – many (most) patients have a single best donor
– Gender
– Age
– Results of infectious disease testing (CMV)
– Previous antigen exposure
– Weight
– Type of stem cell donation

*When there is a choice of more than one donor!
Care before the collection procedure

- One doctor for the donor and another for the patient
- Health questionnaire
- Careful medical history and physical exam focusing on conditions that might increase risk of known adverse events
- Laboratory tests
- Not a comprehensive health screening!
Physical exam

• Focus on neurologic, respiratory, cardiovascular systems
• Bone marrow harvest: oral airway, musculoskeletal
• Leukapheresis: venous access, splenomegaly
Laboratory evaluation

- CBC
- Electrolytes
- ALT, Bilirubin, alk phosphatase, LDH
- Creatinine, BUN
- Other as indicated by history, physical exam (e.g. x-rays, EKG)
Evaluating the donor for risks to the recipient

• Transmissable infections
  – Absolute contraindication to donate: HIV
  – Relative contraindication to donate: Hepatitis B, C
  – Not a contraindication but may modify treatment: HSV, VZV, CMV, West Nile virus

• Genetic diseases
Care during the collection procedure

• Bone marrow harvest
  – Type of anesthesia
  – Autologous blood transfusion
  – Need for intravenous fluids
  – Postoperative management
Care during the mobilization and collection procedure

• Peripheral blood stem cell harvest
  – G-CSF treatment and complications
  – Apheresis and complications
  – Need for central venous access (0-10%, F>M)
  – No need for blood transfusion or iv fluids
The risk and adverse events associated with donation

- Donation is a reasonably safe procedure but adverse events do occur
  - Life-threatening adverse events occur in 0.3-0.4% of donors
  - Odds of dying – <1/10,000
- Most donors report symptoms – important that donors have reasonable expectations
  - Types of symptoms depend on mode of collection (BM vs PB)
Bone marrow harvest

75% of marrow harvests done under general anesthesia, 25% with spinal or epidural anesthesia (CIBMTR)
### Bone marrow harvest
- events and adverse events

<table>
<thead>
<tr>
<th>Category</th>
<th>Adverse Events</th>
</tr>
</thead>
<tbody>
<tr>
<td>Common (20-85%)</td>
<td>fatigue, collection site pain, back pain, nausea, sore throat, headache, emesis, IV site pain</td>
</tr>
<tr>
<td>Less Common (&lt;20%)</td>
<td>fever, bleeding, syncope, unexpected hospitalization, minor infections, hypotension, chipped teeth, urinary retention, post-spinal headache</td>
</tr>
</tbody>
</table>
## Bone marrow harvest - events and adverse events

<table>
<thead>
<tr>
<th>Serious (1%)</th>
<th>seizure, bacteremia, abscess, prolonged pain, neuropathy, prolonged hospitalization</th>
</tr>
</thead>
<tbody>
<tr>
<td>Life-threatening/Incapacitating (0.3%)</td>
<td>myocardial infarction, anaphylaxis, prolonged paralysis after anesthesia, pulmonary embolus, transfusion events (anaphylaxis, acute renal failure, hepatitis), malignant hyperthermia, pulmonary edema, arrhythmias, stroke, severe pain</td>
</tr>
</tbody>
</table>
Symptoms after bone marrow donation

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Recovery after bone marrow donation

- <2 weeks: 63%
- 2-4 weeks: 24%
- >4 weeks: 13%

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Serious adverse events
1987 – December, 1999

9,345 Total Donations

125 Serious Events
1.34%

CIBMTR
114 Events Related to Collection

- Mechanical: 59%
- Anesthesia: 39%
- Seizure: 1%
- Infection: 1%
Risk Factors for Serious Complications

Multivariate Analysis of Risk Factors:

<table>
<thead>
<tr>
<th>Factor</th>
<th>Significance</th>
<th>Higher Risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>Collection Duration</td>
<td>&lt;0.0001</td>
<td>Longer Collection</td>
</tr>
<tr>
<td>Anesthesia Type</td>
<td>&lt;0.0001</td>
<td>Spinal or Epidural</td>
</tr>
<tr>
<td>Donor Sex</td>
<td>0.003</td>
<td>Female Donors</td>
</tr>
<tr>
<td>Donor Age</td>
<td>0.03</td>
<td>Older Donors</td>
</tr>
</tbody>
</table>

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PBSC collection – G-CSF mobilization and leukapheresis
History – unmanipulated peripheral blood HSCs

• 1909 (Alexander Maximov)
  – Existence of HSCs in PB

• 1962 (Goodman and Hodgson)
  – HSC in PB capable of restoring irradiation-induced marrow aplasia in mice

• 1980 (Abrams)
  – First syngeneic transplant, Ewing’s sarcoma

• 1985/86 (Four different teams)
  – First successful autologous HSCT for hematological malignancies
History –
G-CSF mobilized peripheral blood HSCs in stem cell transplantation

• Early 1990´s
  – autologous HSCT

• 1995 (Houston, Seattle, Kiel)
  – Pilot studies of allogeneic PBSCT´s published in Blood
EBMT activity 1990-2005: changes in stem cell source
Mobilization and collection procedures

• G-CSF (Filgrastim)
  – 5 – 16 µg/kg/day (usually 10 µg/kg/day)
  – A single sc dose or divided into twice daily
  – For 4(-7) days

• Collection (leukapheresis)
  – Starts after the 4th to 5th day of G-CSF
  – Usually peripheral veins
  – 3-4 hours procedure (9-12 l of blood processed)
  – Targets 4-8x10⁶ CD 34+ cells/kg recipient
Characteristics of the grafts

• Mobilized PB vs BM
  – x 2-5 times more CD 34+ cells
  – x 10 times more T-cells
  – x 5-10 more NK-cells
  – x 50 times more CD14+ cells
PBSC Donor Symptoms during filgrastim administration, n = 1080

- Vomiting
- Chills
- Fever
- Anorexia
- Other flu-like
- Sweats
- Nausea
- Insomnia
- Malaise
- Headache
- Myalgia
- Bone pain

CIBMTR
Donors Experiencing Bone Pain

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Symptoms after blood stem cell donation

- Myalgia
- Headache
- Malaise
- Insomnia
- Nausea
- Sweats
- Other Flu Sxs
- Anorexia
- Fever
- Chills
- Vomiting

CIBMTR
Unexpected Serious Adverse Events

- 5,334 healthy unrelated donors reporting to the NMDP between 1999-2005 were reviewed for serious unexpected events.
- These events occurred in 30/5334 (0.6%).

<table>
<thead>
<tr>
<th>Event</th>
<th>Nausea, Vomiting, Headache</th>
<th>Bleeding/Thrombocytopenia</th>
<th>Citrate Toxicity</th>
<th>Severe chest/back pain</th>
<th>Other: hypotension/syncope/rash/viral illness</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>12</td>
<td>3/3</td>
<td>4</td>
<td>3/1</td>
<td>1/1/1/1</td>
</tr>
</tbody>
</table>

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Rare events with G-CSF mobilization

- Precipitation of sickle crisis – sickle cell anemia or complex sickle cell hemoglobinopathies
- Splenic rupture – 5 cases; 1:5-10,000
- Flare of autoimmune disorders: RA, ankylosing spondylitis, inflammatory eye disorders
Long term effects of G-CSF

• Theoretical concern for development of hematologic malignancy
  – In SCN (Kostmann) patients, after 12 years of G-CSF treatment 8% risk of progression to MDS/AML
• No increased risk of hematological malignancies after G-CSF mobilization (EBMT/NMDP)
• Long-term follow-up warranted
Follow up

• Short-term follow up – well known risks
• Long-term follow up - registries/studies needed
• One example is the Nordic Registry for Hematopoietic Stem Cell Donors (NRHSD)
Ethical issues

• Sibling donors
• Older donors
• Younger donors
• Donor health
• Studies
Transmission of CLL from the donor to the recipient

- 64-year old women with AML 2005
- SCT with RIC, HLA-id brother march 2006
- 3 mos follow showed CR, but a CLL infiltrate
- 12 mos 16% CLL cells in the bone marrow
- 18 mos 19% CLL cells and AML relaps
- FISH showed trisomy 12 in a chromosome Y-positive cell population
The donor

- 62 year old healthy brother
- No lymphocytosis
- Retrospective FISH from the time at donation, March 2006, showed trisomy 12 in 15% of the BM cells
- The donor was healthy without lymphocytosis in January 2007
- In March 2008 CLL, lymphocytosis 7.8 and 33% CLL cells in the none marrow. No symptoms.
Sibling donors

- Potential donors unwillingness to donate
- Important to ask the sibling (if a match) before you inform the patient, not suitable may include HLA, health, etc
Older donors

- Increasing use of transplantation in older recipients means increasing use of older (related) donors
- Limited data available on safety
- Careful consideration of co-morbidities necessary
- Need for further follow-up
  - Risk of complications for the donor, increased risk for malignancies and transmission of malignant cells
Pediatric donors

• Parental consent
  – Conflict of interest
  – Independent advocate required in some states/countries/centers

• Consideration of psychosocial issues

• Limited data available

• Life-threatening complication rate similar to adults
Donor health

• Weigh the chance to cure the patient against the risk for the donor
Studies

• Donors as research subjects
  – On donor cells, donor genes etc
  – Expansion of donor cells
  – Experimental transplantations (new indications)
Summary

• HSC donation is safe
• Serious adverse events are uncommon
• All donors must be carefully evaluated and fully informed prior to HSC donation
• PBSC donation have increased dramatically
• Long term follow up after HSC donation is necessary
Additional sources of information

• World Marrow Donor Association - www.worldmarrow.org
• National Marrow Donor Program – www.marrow.org
• Center for International Blood and Marrow Transplant Research – www.cibmtr.org