Donor safety including minors as donors

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Continuous change:
- Increasing numbers of alloHCT
- Increasing proportion of HCT recipients >60y
- URD > 50%, currently increasing use of haplo-protocols
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No change:
- For allogeneic HSCT, a donor is a prerequisite
  - pretreatment with G-CSF/plerixafor
  - maybe CVC (gen.anaesth. In 26% of ped.donors
  - anticoagulation during apheresis
  - Extracorporeal circuit
  - general-(spinal-) anaesthesia
  - multiple punctures from both iliac crest
acute toxicity of HPC donation frequent, unpleasant but rarely serious

comparable for related and unrelated donors:

- pain
- fever in the absence of signs of infection
- fatigue
- skin rash
- local reactions
- nausea, vomiting
- anorexia
- insomnia
- dizziness and syncope
Pain by donation in 2726 unrelated BM and 6768 PBSC donors

A

BM Donors

PBSC Donors

B

BM Donors

PBSC Donors

Pulsipher MA et al., Blood 2013;121(1):197-206
Higher risk for discomfort in unrelated BM and PBSC donors:
- Obesity (BMI ≥ 30kg/m2)
- Increasing age
- Female sex
- for BM collection: low volume BM collection centers (≤ 1 BM collection every 2 months)

Inconsistent/minimum impact:
- Race
- Socioeconomic status

Serious adverse events in PBSC vs BM donation prospective NMDP-study 2004-2009 in URD

**Graph:**
- **BM (N=2726, n=65):**
  - Life-threatening event: 7 (2.6%)
  - Overnight hosp for anticipated events: 38 (14.0%)
  - Overnight hosp for unexpected events: 17 (6.3%)
  - Persistent or significant disability: 14 (5.2%)
  - Other: 2 (0.7%)

- **PBSC (N=6768, n=38):**
  - Life-threatening event: 2 (0.3%
  - Overnight hosp for anticipated events: 6 (0.9%
  - Overnight hosp for unexpected events: 12 (1.8%
  - Persistent or significant disability: 4 (0.6%
  - Other: 3 (0.4%

**Pie charts:**
- **BM (N=2726, n=65):**
  - Multifactorial/Other: 23 (35%)
  - Anesthesia: 17 (26%)
  - Mechanical: 25 (38%)

- **PBSC (N=6768, n=38):**
  - Multifactorial/Other: 9 (24%)
  - Apheresis: 11 (29%)
  - G-CSF: 18 (47%)

**Table 3. Logistic regression model for SAEs after donation**

<table>
<thead>
<tr>
<th>Category</th>
<th>BM (N=2726, n=65)</th>
<th>PBSC (N=6768, n=38)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Life-threatening event</td>
<td>7 (2.6%)</td>
<td>2 (0.3%)</td>
<td></td>
</tr>
<tr>
<td>Overnight hosp for anticipated events</td>
<td>38 (14.0%)</td>
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<td>14 (5.2%)</td>
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<td></td>
</tr>
<tr>
<td>Other</td>
<td>2 (0.7%)</td>
<td>3 (0.4%)</td>
<td></td>
</tr>
</tbody>
</table>

**Discussion:**

An analysis of the BMT CTN 0201 trial comparing the health-related quality of life experiences of 332 BM and PBSC donors was also conducted. This analysis found an incidence of SAEs that was comparable with published retrospective data. Further analysis also showed that the risk of developing an autoimmune disease was significantly lower in the PBSC donor population compared to the BM donor population. This finding highlights the importance of understanding the long-term effects of different donor types on recipients.
Serious adverse events in PBSC vs BM donation prospective NMDP-study 2004-2009 in URD

<table>
<thead>
<tr>
<th>7 life-threatening events in 2726 BM donations: 0.26%</th>
<th>BM</th>
<th>TTR</th>
</tr>
</thead>
<tbody>
<tr>
<td>major hypotension with ECG changes/hypo-K⁺</td>
<td>1</td>
<td>&lt;1d</td>
</tr>
<tr>
<td>postop. hypotension, pulm.edema</td>
<td>1</td>
<td>&lt;1d</td>
</tr>
<tr>
<td>asystole x 30s, arrhythmias, desaturation</td>
<td>1</td>
<td>&lt;1d</td>
</tr>
<tr>
<td>laryngospasm after extubation, extensive resuscitation</td>
<td>1</td>
<td>&lt;1d</td>
</tr>
<tr>
<td>laryngospasm, noncardiogenic pulm.edema</td>
<td>1</td>
<td>&lt;1d</td>
</tr>
<tr>
<td>severe pain and anemia (hct 15%)</td>
<td>1</td>
<td>&lt;2d</td>
</tr>
<tr>
<td>abdominal thrombosis, E.coli septicemia</td>
<td>1</td>
<td>&gt;3m</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>2 life-threatening events in 6768 PBSC donations: 0.03%</th>
<th>PBSC</th>
<th>TTR</th>
</tr>
</thead>
<tbody>
<tr>
<td>intracranial hemorrhage, no surgery</td>
<td>1</td>
<td>&gt;3m</td>
</tr>
<tr>
<td>after apheresis fainted, pulsless requiring resuscitation, pericarditis</td>
<td>1</td>
<td>&gt;3m</td>
</tr>
</tbody>
</table>

In this series:
- life-threatening events in 1:385 BM- and 1:3333 PBSC-donations
- no deaths

TTR: Time to resolution

Pulsipher MA et al. Blood 2014;123;3655
serious adverse events associated with the donation process

With bone marrow donation:
• Associated with risks of anaesthesia: Arrhythmias with/without cardiac arrest, myocardial infarction, stroke, pulmonary edema, PE, malignant hyperthermia, anaphylaxis
• Local complications: wound infection (local, systemic), fractures, nerve, bone or tissue injury, severe pain, chronic pain
• (blood loss: need for allogeneic transfusion)

With PBSC donation:
• Catheter-related: Bleeding, thrombosis, pneumo-/hematothorax
• Related to apheresis procedure: Hypocalcemia, thrombocytopenia/ anticoagulation, bleeding, need for priming with allogeneic blood
• Associated with biologic actions of G-CSF: Allergic reactions/ anaphylaxis, splenic rupture, respiratory distress/acute lung injury, triggering of inflammatory diseases, thrombosis (arterial, venous), Sickle cell crisis

⇒ Causality vs. Coincidence? Risk factors today only incompletely understood: age?, higher dose of G-CSF?, concurrent health disorders?

## Incidence of SAE in prospective studies

<table>
<thead>
<tr>
<th></th>
<th>DKMS</th>
<th>JSHCT</th>
<th>NMDP</th>
<th>NMDP</th>
<th>EBMT ped</th>
</tr>
</thead>
<tbody>
<tr>
<td>n BM</td>
<td>--</td>
<td>5921</td>
<td>9245</td>
<td>2726</td>
<td>313</td>
</tr>
<tr>
<td>n PB</td>
<td>3928</td>
<td>3264</td>
<td>7850</td>
<td>6768</td>
<td>140</td>
</tr>
<tr>
<td>BM</td>
<td>--</td>
<td>0.37%</td>
<td>1.35%</td>
<td>2.38%</td>
<td></td>
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<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>(0.99%)*</td>
</tr>
<tr>
<td>PB</td>
<td>&lt;0.1%</td>
<td>0.61%</td>
<td>0.5-0.6%</td>
<td>0.56%</td>
<td></td>
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<tr>
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<td></td>
<td></td>
<td>(0.31%)*</td>
</tr>
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</table>

*life-threatening, unexpected or chronic/disabling

15-29% of RD beyond suitability criteria for URD

**NL 1996-2006**
268 related PBSC donors
- 40 (15%) didn’t fulfill URD suitability criteria:
  - age
  - art.Hypertension
  - BMI>40kg/m2
  - other
- no correlation between donor’s eligibility status and the occurrence of short-term procedure-related SAEs.
Median FU 4.5y (0-13.6y)
- Incidence rates for cardiovascular events and malignancies higher in deferrable donors but for both groups within range of general population

**UK 2004-2013**
216 donations in 208 RD (37BM, 179 PBSC)
- 28.6% didn’t meet URS suitability criteria:
  - age
  - art. hypertension
  - diabetes
  - others
  - more likely to develop SAE (8% vs 0.7%)

Anthias C et al. BMT 2015

**CH 2007-2013**
578 donors (448RD (83%PBSC, 130URD 75%PBSC)
Preexisting health disorders:
- Related donors: 27%
- Unrelated donors: 9%
- and: more severe in related donors (cardiovascular, endocrine/autoimmune)

Rueesch M et al. presented at SGH-SSH 2015

Wiersum-Osselton JC et al. Transfusion 2013
Donors with comorbidities, donors >60 years and pediatric donors: more vulnerable?
Donors older than > 60y

- Experience of URD registries is limited to upper age limit of 60y
- Since health disorders increase with age, more comorbidities are expected
  - eg. Cardiovascular diseases, pulmonary diseases, CKD, neoplasias....but also M-proteins, MBL, clonal hematopoiesis of indeterminate potential
- Donor medical check more time consuming? (and more extensive?)
- Higher risk for deferral (and delay of URD/alternative donor search)?
HR-QoL in related PBSC-donors >60 years
RDSafety Study

104 PBSC donors 61-76 years, mean age 65.55y (SD 3.87)
selected by HSCT centers able to undergo donation
compared with 59 PBSC donors age 18-60y, mean age 41.07y (12.33)

Donors >60y vs younger donors:
- before donation: significantly poorer general physical health, better mental health
At 4 wks:
- No difference in overall physical/mental health or current symptom levels or number of days until they felt completely well after donation
- less donation-related pain, fewer family/work concerns, less perceived responsibility if the HCT was not successful
At 1y:
- similar pattern, no difference in recovery periods after donation

→ Current donor selection and suitability criteria seem to allow safe PBSC-donation for donors above the age of 60y
→ numbers are still too small for definite conclusions for:
  - SAE
  - Donors 70+ years of age

Switzer GE et al. Biol Blood Marrow Transpl 2017;23:165
Pediatric HSC donors

Donate for relatives only; BM preferred but PBSC donations also regularly used

Potential risk factors:
BM need for general anaesthesia
  high need for allotransfusions, risk factor collection vol >15-20ml/kg BW
PBSC CVC more frequently needed, i.e. need for general anaesthesia
  higher need for allotransfusions, 92% for donors with <20kg

• Medically safe
• Donor is not yet in a status for offering independent informed consent
  ➔ Independent donor advocate

Open questions:
– Long term FU after G-CSF exposure
– Health-related quality of life (physical/psychosocial)

Significant decreased HRQoL in large proportion of pediatric stem cell donors: because of donation or sick sib?

- Mean age 11.1y (18: 5-7y; 43: 8-12y; 39: 13-17y; 5:?)
- N=105: 98 BM (93%), incl. 5 GCS-F-primed BM, 7 PBSC (7%)
- Participating parent/guardian: donor’s mother in 74%

10/15 parents with donors of age 5-7y think that age has an impact on the experience of the donation. 70% believe that the young age made donation easier ➔ Psychosocial intervention beneficial?

Late effects after BM- or PBSC donation

- Hematological or other neoplasias: not confirmed, lack of evidence
- Autoimmune disorders: not confirmed, lack of evidence
- HRQoL-impairment in pediatric donors: to be followed
- Prolonged time to full recovery: rare (suitability criteria!)

→ Long term follow up is challenging!
Areas for further research on donor safety

- HRQoL-impairment in pediatric (and adult) donors in different populations
- SAE: incidence, nature, risk factors and preventive measures
- Impact of new mobilizing agents on donor safety
- Multiple donations of HPC and TC
Increasing donor safety by adequate suitability criteria


WMDA donor medical suitability recommendations

https://www.wmda.info/professionals/tools
donor outcome registration and accreditation: ways to further increase donor safety?

SPECIAL REPORT
Allogeneic hematopoietic stem cell donation—standardized assessment of donor outcome data: A consensus statement from the Worldwide Network for Blood and Marrow Transplantation (WBMT)

JP Halter¹, SM van Walraven², N Worel³, M Bengtsson⁴, H Hägglund⁵, G Nicoloso de Faveri⁶, BE Shaw⁷, AH Schmidt⁸, M Fechter⁹, A Madrigal¹⁰, J Szer¹¹, MD Aljurf¹², D Weisdorf¹³, MM Horowitz¹⁴, H Greinix¹⁵, D Niederwieser¹⁶, A Gratwohl¹, Y Kodera¹⁷ and D Confer¹⁸

Bone Marrow Transplant 2013;48:220-225
Donor data:
• Age at donation, sex, relationship to recipient

Harvest data
• Was the product collection completed? → yes/no
• Were hematopoietic growth factors and/or cell binding inhibitors used → yes/no
• Was erythropoietin used? → yes/no

Product:
BM (including harvest of MSC), PBSC, both, unstimulated leucapheresis (eg. DLI), others

Complications in temporal association with the donation procedure:
• only serious adverse reactions (SAR) between start and day 30 after end
  definition of SAE is the same as in WMDA and includes:
    • Death (ICD code)
    • Life-threatening event (ICD code)
    • Require in-patient hospitalization or prolongation of existing hospitalization
      due to WHO grade 3 or 4 toxicity (ICD code)
    • Persistent or significant disability/incapacity (ICD code)

LTFU
- minimal reporting after 1 year, 5 years and 10 years, biannual recommended

Donor survival status
- if no: cause of death (ICD code)

Malignancy & autoimmune disease
  if yes: was diagnosis confirmed by medical data (ICD code)
donor outcome registration and accreditation: way to further increase donor safety?

Involvement of donor's provider in care of recipient before/after FACT 5th ed.

Compliance with RD care standards in JACIE accred. EBMT centers

conclusions

- Donor outcome follow up is part of HCT
- Consensus on minimum donor follow up
- Due to the rarity of SAE only reporting to large international donor outcome registries and periodical data analysis will assure that signals with impact on donor's (and recipient's) health & safety will be detected (e.g. EBMT donor outcome database, WMDA SEAR/SPEAR registry)
- Young related donors with less comorbidities may resemble more closely URD
- Increasing use of haploHCT may lead to an increase in older donors (parent ➔ child) and young donors (child ➔ sibling/parent) where experience in donor safety issues is less
- High motivation among professionals involved in HPC donation to perform outcome follow up – involving their know-how (e.g. clinical/medical committees) is essential
Roundtable discussion
Donor selection and donor safety

Panelists:
Ali Alahmari (KSA)
Feras Alfraih (KSA)
Mohammed Al-Hunieni (Oman)
Mohsen Alzahrani (KSA)
Dennis Confer (USA)
Dennis Gastineau (USA)
Yoshihisa Kodera (Japan)
Navneet Majhail (USA)
Claudia Rutt (NL)

Moderator: Jörg Halter (Switzerland)
Donor selection

Minimal requirements for donor selection and eligibility testing
- Compatibility testing
- Health status, comorbidities, IDM
- Affordability: what needs to be done in the center, what can be done externally?

Role of haploidentical donors, unrelated donors and cord blood

Does a new center need a collection unit?

Donor safety

Suitability criteria and donor outcome follow up

The role of individuals and families in the EMBMT region
Donor advocate for pediatric donors