Global Perspective on Donor and Recipient Safety: Biovigilance in Hematopoietic Cell Transplantation

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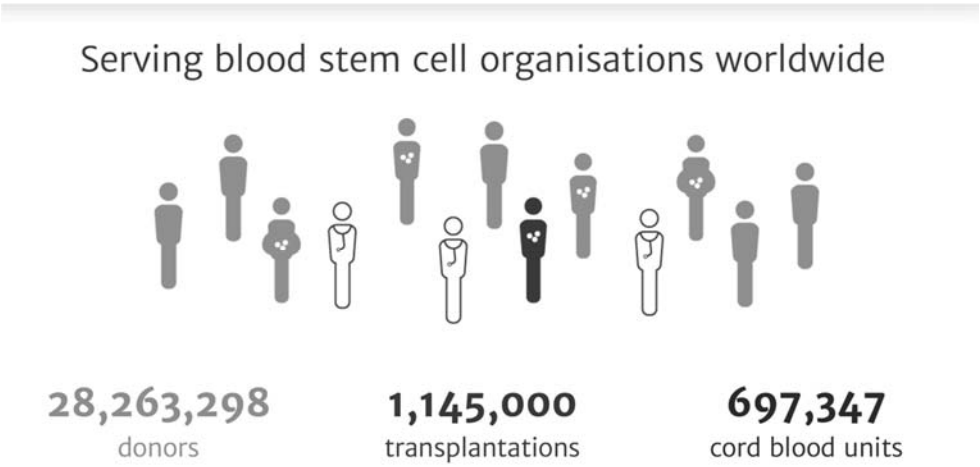
Public Forum of the Quebec Biovigilance Committee
November 16, 2016

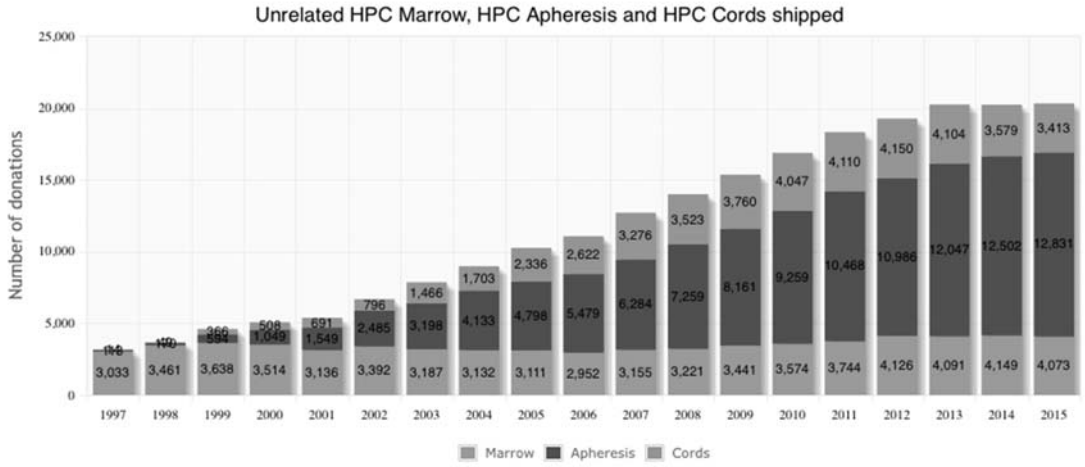
Learning Objectives

- Understand the nature and goals of the NMDP biovigilance system for donors and recipients of hematopoietic progenitor cells (HPC)
  - Global trends in transplantation
  - How are HPC donors different from blood, organ and other tissue donors?
- Describe the NMDP operational processes that support biovigilance
  - Reporting requirements for donor centers and transplant centers
  - NMDP reporting requirements domestically and internationally
- Share incidence data on NMDP biovigilance for donors
  - Common adverse events
  - Serious adverse events
  - Marrow compared to PBSC donors
- Share best practices moving forward: Emerging cellular therapies

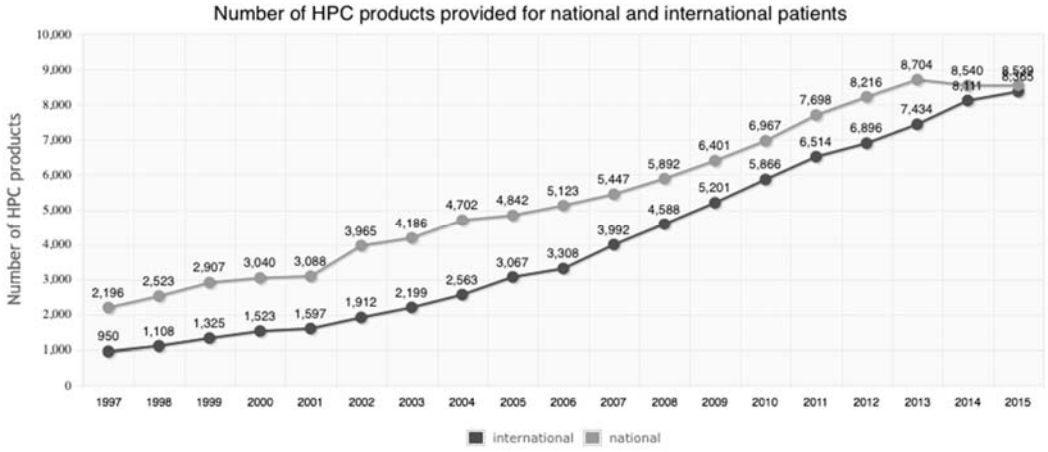
World Marrow Donor Association



Transplants by Cell Source Over Time (WMDA)



International Donor and Transplant Sharing (WMDA)



Differences Between HPC and Blood Donors

	Blood	**HPCT**
Annual # of Events	More than 20,000,000 in the US alone	30,000 alloHPCT/yr worldwide
Donor → Patient	1:1, 1:2, 1:3 whole blood	Usually 1:1
Donor Testing	Day of Collection, strict release criteria	Up to 30 days prior to donation, flexible release criteria
Donor Assessment	HHQ, limited physical assessment	HHQ, complete H&P, labs and EKG, CXR and extended testing possible
Matching	ABO/Rh +/- RBC Ag	**HLA**, gender, ABO, KIR, CCR5 etc. Only/best match

Differences Between HPC and Solid Organ and Tissue Transplantation

	Tissue / Solid Organ	**HPCT**
Annual # of Events	More than 1,000,000 in the US alone	30,000 alloHPCT/yr worldwide
Donor → Patient	1:many (dozen to 100s)	Usually 1:1
Donor Testing	Often cadaveric: no retesting possible	Alive and well; retesting can be done
Donor Assessment	Often very time limited (as little as hours)	Not severely time limited
Matching	HLA, lower resolution	HLA, allele level 8 loci
Product Release/Expiration	ASAP/Hours	ASAP/Hours or days or cryopreservation

Differences Between HPC and Organ, Tissue and Blood Donors

- HPC donors may be the best or only match for a patient
- While transplantation may be urgent clinically, there is time to do a complete donor health assessment
- The emergence of new blood-borne infectious diseases will most likely occur in the setting of the blood and tissue world given the sheer number of transfusion/transplant events
- Therefore, vigilance efforts should focus on donor and recipient adverse events and product quality issues to enhance donor and recipient safety

Key Elements in Donor AE Biovigilance

- Reported via FormsNet Form 701
- Medical Quality Assurance Nurses are notified
  - Investigation ensues if appropriate
  - Donor cared for by DC/AC/CC and NMDP
  - NMDP RN staff (TMS/DMS) follow donor to AE resolution
  - Donor advocacy RN involved if prolonged AE
- Reporting for serious and unexpected AEs plus serious and expected events of interest as determined by medical director review
  - vast majority of events reported are non-serious

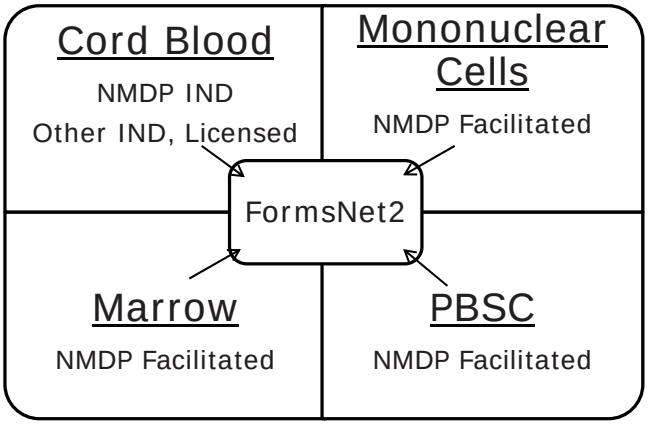
Key Elements in Recipient AE Biovigilance

- AE Reporting
  - TC education regarding what to report, timelines
    - AE training associated with protocols (e.g. 10-CBA)
    - National mtgs (Tandem, NMDP Council, CB Symp)
    - Web resources at marrow.org
- Event Processing
  - Reporting via FormsNet2 (phone or email permitted)
  - Events investigated (NMDP or other stakeholder)
  - Confirmed events entered into IMS
- Tracking and Trending
  - MasterControl tools, reports; staff review

Recipient Serious Adverse Event (SAE) Reporting for the NMDP Network

- SAEs associated with PBSC, marrow and cord blood must be reported promptly to NMDP
  - Report using FormsNet Form 3001
    - **Rationale** for seriousness (death, life-threatening, hospitalization, birth defect, permanent impairment or disability)
    - **Event type / severity** using CTCAE Terms and Grading
    - **Attribution**
- Some events are not NMDP regulatory responsibility and info will be passed to the appropriate IND holder

All Recipient AE and Product Complaint Reporting via FormsNet™2 Effective 4/15/12



Benefits of Recipient AE Reporting System

- Single source of event entry in a system (FormsNet 2) with which the Network is familiar
- Once event is entered, the NMDP provides event notification to the stakeholders (CBBs, IND holders, etc)
  - Enhances ability to comply with all reporting obligations
  - Single source of event submission allows tracking & trending of events producing more timely
  - Network notification
  - Root cause investigation and remedial / corrective interventions

What Happens to AE Reports?

- Investigation by Medical Services RNs and MDs
- Dissemination of Information: Regulatory reporting by NMDP
  - DPSM (the NMDP's DSMB) and IRB
  - FDA when NMDP is the IND holder
    - Otherwise, NMDP passes through the report to the IND holder
  - HRSA and other US government stakeholders
  - Other stakeholders: Network announcements and PI letters
  - Pharma as applicable (e.g. for mobilizing agents)
- International Reporting
  - Reporting to World Marrow Donor Association (WMDA) when donor or product-related: S(P)EAR

Incident Management

- IMS: MasterControl™
  - Maintained/administered by NMDP Quality Systems
  - FDA-compliant, configurable software used to report, resolve, monitor, track and trend QIs
  - Multiple quality management functions
    - Incident capture
    - Remedial action
    - Investigation
    - Risk assessment
    - Corrective Action/Preventative Action (CAPA)
- NMDP SOPs guide actions
  - Definitions of events
  - Process for incident management

International Efforts in Biovigilance in HPCT

- WMDA: S(P)EAR reporting for donor AEs and product-related issues
  - Consolidates data from independent registries: increases power to detect sentinel AE (Shaw, et al, BMT 2013)
  - Mandatory reporting for accredited registries, standard AE definitions and likely *attribution*

WMDA SEAR Reporting

- Serious/unexpected/medically relevant/previously unknown
- Any serious event or reaction during anesthesia should be reported.
- Any serious cardiac complication should be reported.
- Any serious infection should be reported.
- Any serious mechanical injury should be reported.
- Any serious incident in hemostasis should be reported
- Any serious (late) effect of marrow or PBSC donation should be reported (e.g. autoimmune, malignancy)
- Any donor death (from 30 post donation; or at any time if the donation is implicated)

WMDA S(P)EAR Reporting

- Processing, labeling, handling and transport errors/problems
  - Wrong stem cell product transfused
  - Wrong stem cell product received
  - Serious problems in transportation
  - Damage to bag
  - Inadequate cell dose in the stem cell product
  - Clotting or other loss of product viability
  - Contamination leading to serious infection in recipient
- Any serious unpredicted transmissible infection
  - HIV, Hepatitis B, Hepatitis C
  - Any serious unpredicted non-infectious transmissible disease (e.g. malignant)

WMDA S(P)EAR Committee Review

- Reporting requirement for accredited WMDA registries
- Committee has international representation with primary review by non-reporting peers
- Annual reports to community by category
- Almost 300 Cases reported and reviewed in 2016 with determination:
  - Donor or product/patient affected
  - Additional information required
  - Attribution: both that reported and as determined by committee
  - Educational value for the transplant community…

The Case that Sparked GRID

Inadvertent completely HLA-mismatched allogeneic unrelated bone marrow transplant: lessons learned

Bone Marrow Transplantation advance online publication, 14 March 2016; doi:10.1038/bmt.2016.59

We here report a serious adverse event in which a patient was transplanted with stem cells from an incorrect donor due in large part to the inappropriate use of a supposedly unique donor identifier. The purpose of this report is to make the international transplant community aware of this severe adverse event, which has the potential to occur anywhere, and to emphasize the importance of a global unique donor identifier.

GRID will replace the many different methods of identification used across the world today with a standard, consistent format

Biovigilance Reseach: What Have We Learned and Will Learn About Adverse Events

What have we learned:

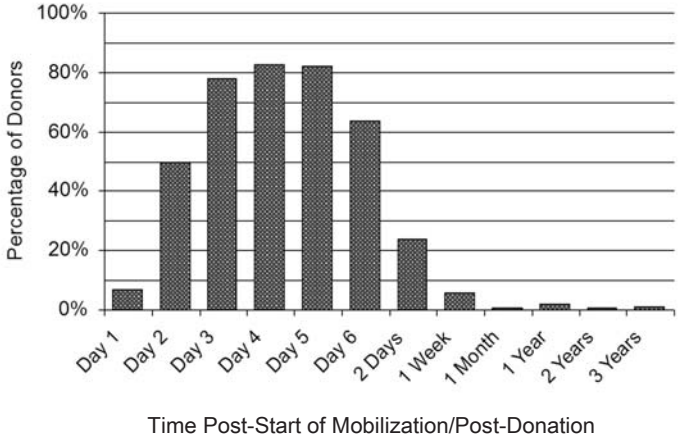
- Common Adverse Events (AEs)
- Marrow vs PBSC donors
- Serious adverse events (SAE)
- Related vs. unrelated donors

What we will learn:

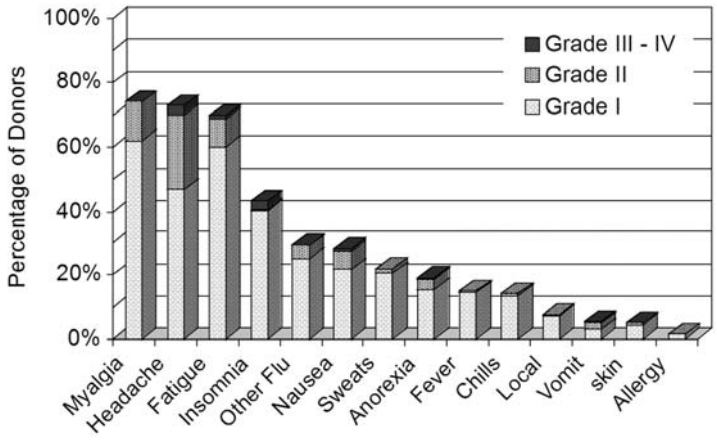
- Long term donor follow-up study
  - Malignant, thrombotic and autoimmune diseases
- Emerging Cellular Therapies

Pulsipher: Blood 2008, 2009 and 2014. CIBMTR Donor Health and Safety Cmte

Common Adverse Events: Frequency of Bone Pain in PBSC Donors



Common Adverse Events: Symptom Score During Mobilization



The Donor Experience Marrow vs PBSC -1

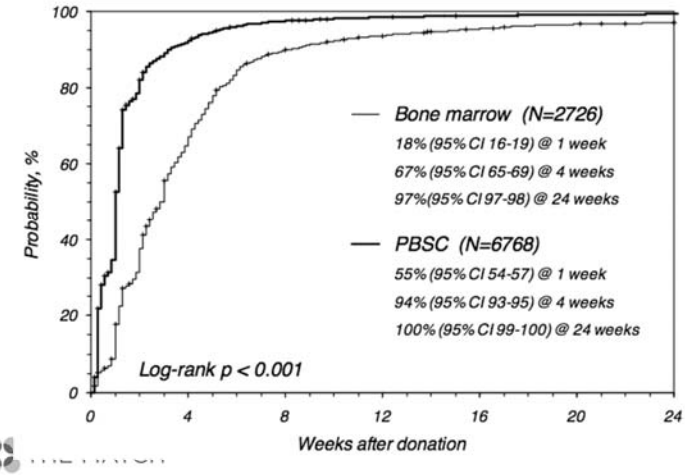
- Bone Pain occurred in 80%, irrespective of donation type
- Timing of bone pain different, mobilization vs. post-collect
- Most pain was rated as mild or moderate
- Other symptoms were similar in both groups
- Bone marrow donors have more prolonged recovery and lower rates of complete recovery

The Donor Experience Marrow vs PBSC -2

- Overweight and obese PBSC donors have higher rates of grade 2-4 pain in the peri-collection period
- Female donors are more likely to report pain and other symptoms and are less likely to experience full recovery, regardless of donation type
- Older marrow donors are less likely to experience grades 2-4 skeletal pain in peri-collection period, but they are more likely to have pain at 1 week and 1 month

Pulsipher, Blood 2013

Probability of Complete Recovery: Marrow vs. PBSC



What About Serious Adverse Events?

FDA Criteria

- Life-threatening or fatal event
- Inpatient hospitalization or prolongation of existing hospitalization
- Persistent or significant disability / incapacity
- Required intervention to prevent permanent impairment/damage
- Congenital anomaly / birth defect
- Other at physician discretion

Serious Adverse Events in Marrow and PBSC Donors

Methods

- 5 Physician panel reviewed all events
  - Probable, possible or not AE
  - Classification as serious or not serious (FDA criteria)
  - Attribution as expected or unexpected
  - Marrow attribution to anesthesia, harvest or unrelated
  - PBSC attribution to GCSF, apheresis or unrelated

Pulsipher M A et al. Blood 2014;123:3655-3663

Serious Adverse Events in Marrow and PBSC Donors

Results: Physician review of Adverse Event Reports

- 457 AE forms associated with 328 events in 296/2726 marrow donors (10.9%)
- 1178 AE forms associated with 972 events in 854 PBSC donors (12.6%)
- Most events were acute and of short duration

Pulsipher M A et al. Blood 2014;123:3655-3663

Serious Adverse Events (SAE): NMDP Experience with Unrelated Donors

- Rates of SAE were 4x higher with bone marrow donation (2.38%) compared to PBSC donation (0.56%)
- Rates of *unexpected* SAE were 3x higher with bone marrow donation (0.99%) compared to PBSC donation (0.22%)
- Life threatening events are rare in both marrow (0.26%) and PBSC donors (0.03%)
- More life-threatening events, hospitalizations and long term disability with marrow donation
- The frequency of SAE are two-fold higher in female donors (Odds ratio for men = 0.5)

Pulsipher M A et al. Blood 2014;123:3655-3663

Classification of SAEs experienced by BM and PBSC donors.

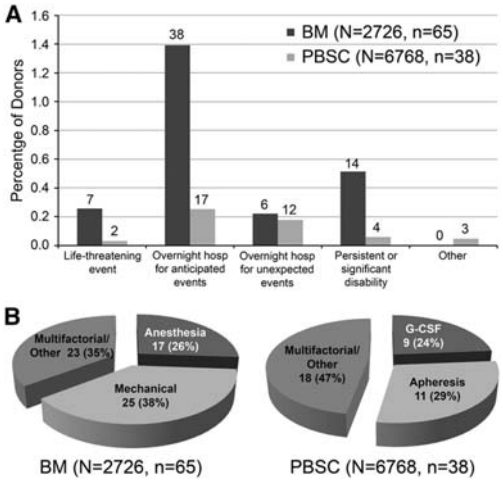


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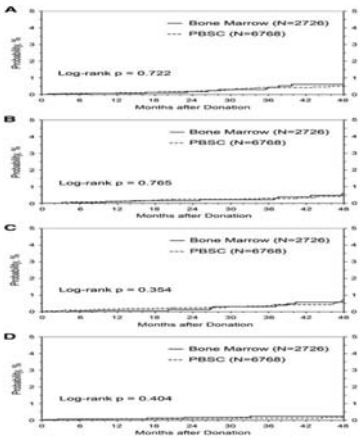
Table 2. Specific SAEs in BM vs PBSC donors

Event	BM	PBSC	Time to resolution
Life-threatening events	7	2	
Major hypotension with electrocardiogram change/ hypokalemia	1		<1 d
Abdominal thrombosis, *Escherichia coli* septicemia	1		>3 mo
Severe laryngospasm after extubation requiring extensive resuscitation	1		<1 d
Postoperative hypotension, pulmonary edema	1		<1 d
Laryngospasm, noncardiogenic pulmonary edema	1		<1 d
Asystole ×30 s, arrhythmias, desaturation	1		<1 d
Severe pain and anemia (hematocrit 15%)	1		<2 d
Intracranial hemorrhage not requiring surgery		1	>3 mo
After apheresis, fainted, pulseless requiring resuscitation, pericarditis		1	>3 mo

Risk of cancer, autoimmunity, and thrombosis in G-CSF–treated PBSC donors vs BM donors.



A = Cancer, excluding basal cell
B = Non-melanoma skin
C = Autoimmunity
D = Thrombosis

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Pulsipher M A et al. Blood 2014;123:3655-3663

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Risk of Cancer Compared to the General Population

	Bone Marrow	**PBSC**
Observed Cancer	11	29
Expected Cancer	19.89	47.95
Ratio (obs/exp)	0.55	0.60
P value	0.045	0.004*

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Long Term Donor Follow-up Study

Primary Objective:

To describe the long-term incidence of malignant myeloid hematologic disorders in donors who received and in those who did not receive filgrastim

Secondary Objectives:

To describe the long-term incidence in donors receiving or not receiving filgrastim:

- Malignant hematologic disorders
- Non-hematologic malignant disorders
- Thrombotic events
- Autoimmune disorders

Long Term Donor Follow-up Study

- Retrospective and Prospective cohorts
  - 1999-2015
- Expected Enrollment:
  - 10,956 unstimulated marrow donors
  - 21,172 filgrastim mobilized PBSC donors
- Enrollment began Oct 2010, now complete
- Collecting data through 2020 to maximize person-years of follow-up

New Frontier in Biovigilance: Emerging Cellular Therapies

- Cytotoxic T cells: leukemic-antigen or virus-specific (e.g. CMV, EBV, adenovirus)
- Tumor vaccines
- Induced pluripotent cells (iPC): regenerate different cell lines
- Regenerative medicine: cell layers (2-D), tissues and organs 3-D
- Genomics: screening, diagnosis and treatment
- Chimeric antigen receptor (CAR) T cells

Summary

- Serious adverse events are rare, but efforts need to be made to minimize the risk of such events
- Adverse events are more common in bone marrow than PBSC donors
- Adverse events are more common in female donors and recovery times are longer
- There appears to be little or no increased risk of malignancies, autoimmune disorders or thrombosis in hematopoietic progenitor cell donors


THANK
You