Growth factors prior to stem cell donation

Efficiency, precautions, long term side effects

November 19th 2014 Dr S. Servais and Prof. F. Baron, University of Liège

Before starting…

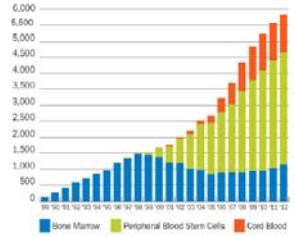
Topic of this presentation:

- **Healthy donors** (allogeneic transplantation)
- **G-CSF**

Introduction | G-CSF-mobilized PBSCs

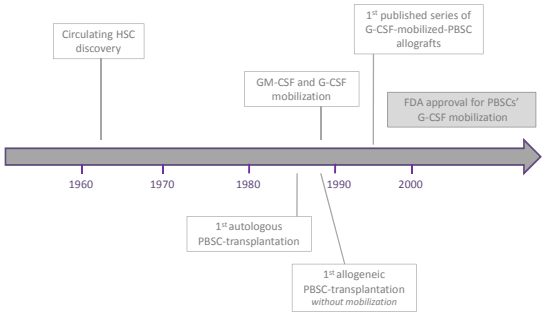
Granulocyte colony-stimulating factor (G-CSF)-mobilized peripheral blood stem cells (PBSCs)

- Alternative graft source to bone marrow (BM) and cord blood
- Increasingly used over the past two decades



Number of transplants by stem cell source
from the *NMDP registry (USA)*

Introduction — History of G-CSF mobilized PBSCs



reviewed in Korbling and Freireich , Blood 2011

Introduction — PBSC collection

- **Recombinant human G-CSF**
- Subcutaneous injections for +/- **4 – 5 days** (up to the last day of apheresis)
- **10 µg/kg/day** standard dose

  Higher doses (10-12µg/kg/12h)
  → ↑ CD34+ cell yield, ↓ Nb of apheresis sessions
  But ↑ toxicity, ↑costs

  Engelhardt et al. JCO 1999; Martinez et al. BMT 1999; Kroger et al. Leuk Lymphoma 2002

- **Apheresis** from day 5
  - 2 x 10-15 L on days 5-6
  - 1 x 20-25 L on day 5

Introduction — PBSC collection

- **filgrastim, Neupogen® or lenograstim, Granocyte®**
- Biosimilars?

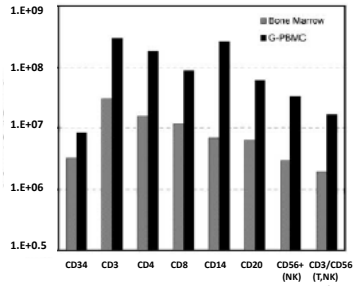
WMDA and EBMT recommandations:

They **should not** be used for PBSCs mobilization in healthy donors
unless in **clinical trials** examining theses issues
(after both the recipient and the donor have provided informed consent)

Shaw et al. Haematologica 2011

Introduction — PBSC graft composition

- PBSCs *versus* BM grafts



from Heimfeld Leukemia2003

Efficiency — Targeted PBSCs doses for transplantation

Minimum = 1-2 x 10^6 CD34+ cells/kg recipient

Optimum = 4-6 x 10^6 CD34+ cells/kg recipient

Efficiency — Factors influencing HPSCs yield

- **Filgrastim *versus* lenograstim?**

Filgrastim = non-glycosylated >< Lenograstim = glycosylated

G-CSF glycosylation:

In vitro: - ↑ stability to T°, PH
- ↓ degradation by proteases
- ↑ CFU potency of BM progenitor cells (greater than no-gly G-CSF)

In vivo: - No impact on G-CSF half-life in circulation
- **Impact on PBSCs mobilization in clinics remains uncertain** (conflicting results) *

Better mobilization with lenogastrim in male (but not female) unrelated donors? **

** Hoglund et al. EJH 1997; Watts et al. BJH 1997; Martino et al. J Clin Aph 2005*
***Fischer et al. BJH 2005*

Efficiency | Factors influencing HPSCs yield

- **Donor body weight**
  High > Low
- **Donor age**
  Young > Old

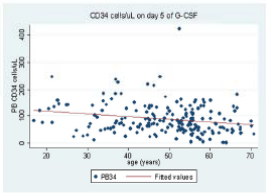


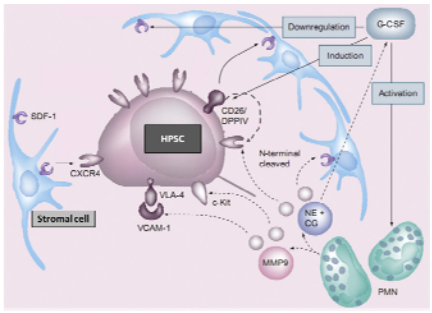
Figure 1. Impact of Donor Age on Progenitor Cell Mobilization.
Richa et al. BBMT 2009

- **Donor sex**
  Male > Female

* Factors impacting mostly on the blood volume for apheresis rather than on the biological effects of G-CSF

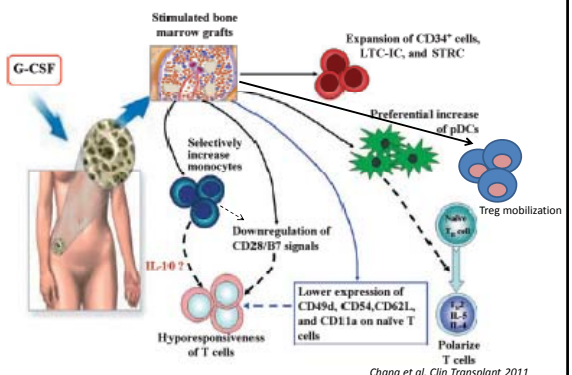
Efficiency | Biological effects of G-SCF

Hematopoietic progenitor stem cells (HPSCs) mobilisation



adapted from Fruehauf and Tricot BBMT 2010

Efficiency | Biological effects of G-SCF



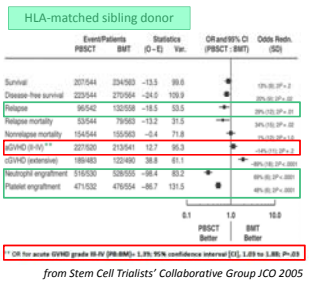
Chang et al. Clin Transplant 2011

⇒Impact of G-CSF on graft composition and properties

Efficiency — From the recipient's point of view

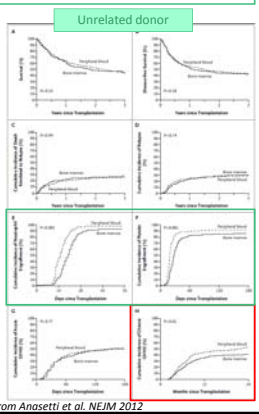
- PBSC- *versus* BM- transplantation

HLA-matched sibling donor



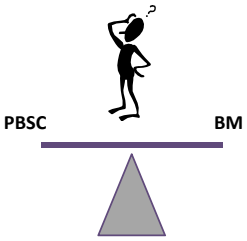
from Stem Cell Trialists' Collaborative Group JCO 2005

Unrelated donor



from Anasetti et al. NEJM 2012

Efficiency — From the recipient's point of view

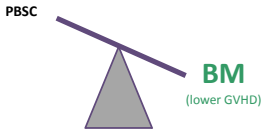


Efficiency — From the recipient's point of view

Risk of graft failure
(i.e. non myeloablative conditioning)

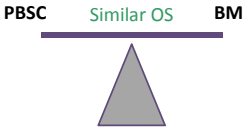
Efficiency | From the recipient's point of view

Non-malignant hematological disease
Pediatric population



Efficiency | From the recipient's point of view

Other indications



Efficiency | From the donor's point of view

Advantages compared to BM:

- No bone punctures
- No anesthesia
- No hospitalization
- No blood transfusions
- No anemia (no need for martial support)
- Avoidance of some rare side effects associated with BM harvest: bleeding complications, local infections, TVE
- **Globally less morbidity (mortality)???**

Side effects | Acute side effects

-Bone pain, headache, fatigue, insomnia, nausea, anorexia

-Fever

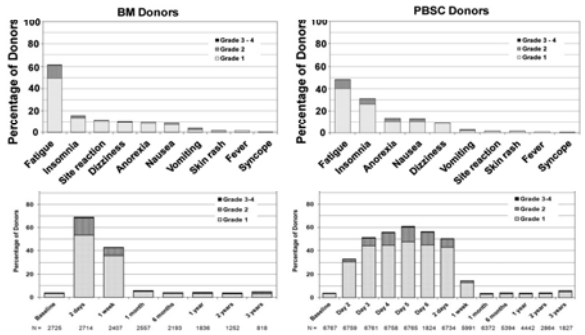
-Reversible changes in lab parameters: thrombocytopenia, ↑LDH, ↑ALP

-Gout

Side effects | Acute side effects

PBSCs *versus* BM donation

NMDP : 6768 PBSC donors and 2728 BM donors, 2004-2009



Pulsipher et al. Blood 2013

Side effects | Severe adverse events and fatalities

PBSCs *versus* BM donation

EBMT study: 23254 PBSC donors and 27770 BM donors, between 1993-2005

Risk of fatal complication: +/- 1 in 10,000

Risk of severe complication (needing hospitalization) : +/- 1 in 1500

Table 1. Characteristics of donors who died within 30 days after stem cell donation.

Donor number	Age (years)	Sex	Mode of harvest	Mobilization	Number of harvest days	Died on day	Donor-recipient relationship	Cause of death
1	38	Male	BM	n.a.	1	15	Related	Massive pulmonary embolism after diagnosis of deep vein thrombosis and pulmonary embolism on day 7. Antithrombin III deficiency was later diagnosed in the family but was unknown at the time of donation
2	67	Male	PB	G-CSF	2	29	Related	Subarachnoid hematoma on day 1. Died on day 29.
3	43	Male	PB	G-CSF	2	15	Related	Cardiac arrest (no autopsy). Risk factors: arterial hypertension, heavy smoker
4	52	Male	PB	G-CSF	2	17	Related	Cardiac arrest Risk factor: smoker
5	27	Male	PB	G-CSF	1	0	Related	Cardiac arrest after human error (see text). Resuscitation unsuccessful

Halter et al. Haematologica 2009

Side effects | Severe adverse events and fatalities

Fatalities in PBSC donors reported in the litterature:

-Thrombotic events (MI, stroke)

-Cardiac arrest

- Tension hemo/pneumothorax

Besinger et al. BMT 1996
Horowitz et al. Hematology Am Soc Hematol Educ Program 2005
Martino et al. Expert Opin Biol Ther 2012

Side effects | Severe adverse events and fatalities

PBSCs *versus* BM donation

EBMT study: 23254 PBSC donors and 27770 BM donors, 1993-2005

Table 2. Severe adverse events among 51,024 stem cell donations.

Stem cell source	Bone marrow		Peripheral blood	
event	N.	Comment	N.	Comment
Cardiovascular				
Myocardial infarction			2	
Cardiac arrest	4	All during or shortly after harvest		
Supraventricular arrhythmia			1	Probably related to catheter. Needed transesophageal stimulation
Severe hypertension	2	Former normotensive donors	1	Required treatment for 1 month post-donation in a former normotensive donor
Thromboembolic				
PE/DVT			7	Between day –2 and day 30 of harvest. Three events occurred before day 0
Stroke	1	Due to HIT antibodies		
Pulmonary complications				
TRALI			1	Due to priming the cell separator with erythrocyte concentrates (pediatric donor)
Lung edema	1	At the end of anesthesia after two donations within 1 month. Needed mechanical ventilation for 24h.		
Hemorrhage				
Subdural hematoma			1	Day 21 after donation
Unspecified	1	Recovered after transfusion of four units of red blood cells	1	Hemorrhage from femoral artery after insertion of central venous catheter
Seizures			1	Due to severe electrolyte disorder during apheresis
Splenic rupture			5	
Unspecified	3		3	
Total	12		25	

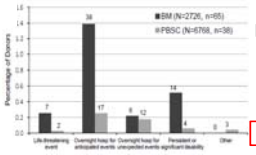
→ +/- 1 in 2500 → +/- 1 in 1000

Halter et al. Haemotologica 2009

Side effects | Severe adverse events and fatalities

PBSCs *versus* BM donation

NMDP : 6768 PBSC donors and 2728 BM donors, 2004-2009



Event	BM	PBSC
Life-threatening Events	7	2
Major hypotension with EKG changes/ hypokalemia	1	
Abdominal thrombosis, E coli septicemia	1	
Severe laryngospasm after extubation requiring extensive resuscitation	1	
Post-op hypotension, pulmonary edema	1	
Laryngospasm, non-cardiogenic pulmonary edema	1	
Asystole x 30 seconds, arrhythmias, desaturation	1	
Severe pain and anemia (hematocrit 15%)	1	
Intracranial hemorrhage not requiring surgery		1
After apheresis, fainted, pulseless requiring resuscitation, pericarditis		1

Pulsipher et al. Blood 2014

Side effects | **Thrombotic events**

Effect of G-CSF on hemostasis

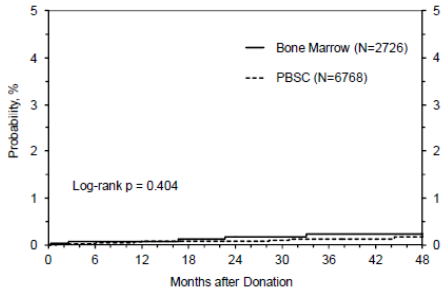
- Platelets: G-CSF receptors on platelets*: ↑ activity, ↑aggregation
- Coagulation**:
  - activation of endothelial cells
  - activation of the coagulation system

** Shimoda et al. J Clin Invest 1993*
*** Falanga et al. Blood 1999*

?

Side effects | **Thrombotic events**

NMDP study, prospective, 2004-2009



Pulsipher et al. Blood 2014

Side effects | **Splenic rupture**

- Enlargement of the spleen during mobilization:
  Universal (Ultrasounds study*)
  Regress after discountinuing G-CSF
- Splenic ruptures**:
  Rare
  High dose G-CSF

** Stroncek et al. Transfusion 2003*
*** Becker et al. BBMT 1997; Falzetti et al. Lancet 1999; Halter et al. Haematologica 2009*

Side effects | Autoimmune disease

Cases reports:

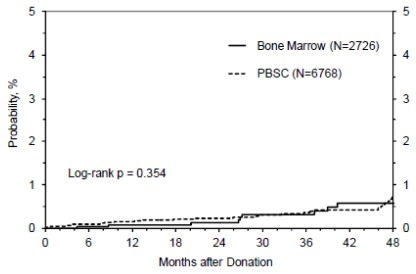
New onset or flare of autoimmune disorders

(systemic lupus erythematosus with serositis, rheumatoid arthritis, multiple sclerosis)

?

Side effects | Autoimmune disease

NMDP study, prospective, 2004-2009



Pulsipher et al. Blood 2014

Precautions | Population at risk for complications

- History of cardiovascular disease or high risk profile *(!)*
- History of TVE *(!)*
- Splenomegaly *(!!)*
- Autoimmune disease *(!)*

➔ **Caution**

i.e. In CHU of Liège:
- *Absolute CI (!!)*
- *Relative CI (need for transplant committee approval) (!)*

Side effects | Catheter-related

Catheter-related (CVC)

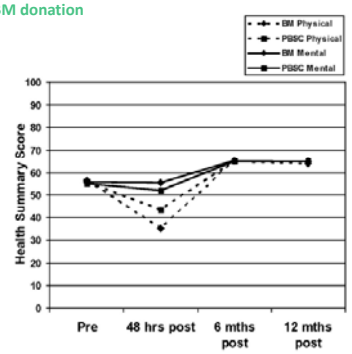
- Infections
- Pneumothorax
- Hemorrage

Several groups prohibit the use of CVC in (unrelated) donors (WMDA: CVC is only used in exceptional circumstances).

**Martino et al. Exp Opin Biol Ther 2012*

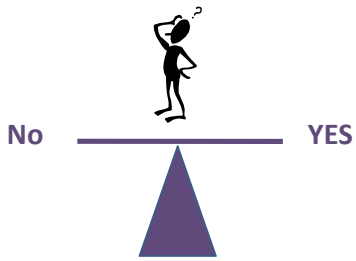
Side effects | Long-term side effects

PBSCs *versus* BM donation



Switzer et al. BBMT 2014

Side effects | Malignancies ?



Side effects | Malignancies ?

Long-term data in healthy donors are **insufficient** to make a firm conclusion…

⇒ Informations from

- **preclinical studies**
- **clinical data in patients with malignancies** treated with G-CSF (neutropenia, autologous stem cell mobilization)
- **limited data in healthy donors**

Side effects | Malignancies ?

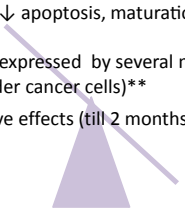
Preclinical data

Side effects | Malignancies ?

Preclinical data

G-CSF:

- - ↑ proliferation, ↓ apoptosis, maturation troubles in HPSCs and AML cells*
  - G-CSF receptors expressed by several malignant cells (AML, lung and bladder cancer cells)**
- Immunosuppressive effects (till 2 months) → ↓ anti-tumoral surveillance



*Brodsky et al. Leukemia 1996; Rutella et al. Exp Hematol 2000
**White at al. Leukemia 1998

Side effects | Malignancies ?

Preclinical data

G-CSF:

- - ↑ proliferation, ↓ apoptosis, maturation troubles in HPSCs and AML cells*
  - G-CSF receptors expressed by several malignant cells (AML, lung and bladder cancer cells)**
- Immunosuppressive effects (till 2 months) → ↓ anti-tumoral surveillance
- Not leukemogenic in mice (antileukemic effect?) ¶
- No long-term DNA instability ¶¶

**Brodsky et al. Leukemia 1996; Rutella et al. Exp Hematol 2000*
***White at al. Leukemia 1998*
¶ reviewed in Metcalf et al. Cancer 1990
¶¶ Shapira et al. Am J Hematol 2003

Side effects | Malignancies ?

Clinical data from leukemic patients

- Randomized trials in AML patients*:
  - No impact on PFS
  - No impact incidence of secondary therapy-related leukemia

**Dombret et al. NEJM 1995; Heil et al. Blood 1997*

Side effects | Malignancies ?

Clinical data from aplastic anemia (AA) patients:

- ↑ incidence of AML/MDS in patients receiving G-CSF*

Side effects | Malignancies ?

Clinical data from autologous transplantation

- Cases of secondary malignant disease (AML, MDS)

  Previous cytotoxic therapy >< G-CSF ?

=> Similar risks after PBSC- and BM- autologous transplantation*:

*Milligan et al. BJH 1999; Metayer et al. Blood 2003

Long term side effects | Malignancies ?

Clinical data from patients (large populations): conclusion

- Reassuring
- Chronic administration = safe ? (except disease associated with genetic abnormalities)

« It is unlikely that the short-term administration of G-CSF may lead to development of malignancies in healthy donors »

Cited from Martino et al. Expert Opin Biol Ther 2012

Long term side effects | Malignancies ?

Clinical data in healthy donors: biological events

- FISH from healthy donors*:
  G-CSF → loss of synchrony in allelic replication timing
  aneuploidy
  → Cancer-characteristic DNA modifications
- Prospective study of the genotoxic effects (22 donors)**
  G-CSF → No alteration in replication kinetics
  → No ↑ in aneuploidy
- Microarray : no persistant differences in gene expression***

*Nagler et al. Exp Hematol 2004
** Hirsch et al. Blood 2011
*** Hernandez et al. BMT 2006

Long term side effects | Malignancies ?

Clinical data in healthy donors

Table 2. Incidence of malignancies among healthy donors of peripheral blood hematopoietic progenitor stem cells mobilized with granulocyte colony-stimulating factor (G-CSF).

Authors, year	Study design	Country	Relationship	No. of donors	Follow-up	G-CSF type	AML	Other HMs	Non-HMs
Lavalaru, 2000	Retrospective	US/Italy	Related	95	3.6 (2.9 – 6.2)	Filgrastim	0	0	2
Anderlini, 2002	Retrospective	US	Related	281	3.3 (0.6 – 6.7)	Filgrastim and Lenograstim	0	0	NA
Lapi, 2005	Prospective	Italy	Related	94	2.5 (0.5 – 7)	Lenograstim	0	0	0
MMTP Registry, 2007	Prospective	US	Related/Unrelated	4.015	NA (1 – 9)	Filgrastim	0	0	30
de la Tuba, 2008	Prospective	Spain	Related/Unrelated	1.436	3 (1 – 5)	Filgrastim and Lenograstim	0	0	5
Holig, 2009	Prospective	Germany	Unrelated	3.928	NA (0.1 – 5)	Filgrastim and Lenograstim	1	3	7
Halter, 2009	Retrospective	Europe	Related/Unrelated	22.354	Up to 12	Lenograstim	1	11	NA
Pulsipher, 2009	Prospective	US	Unrelated	2.408	4 (0.7 – 8)	Filgrastim	0	1	25
Martino, 2009	Prospective	Italy	Related	184	5 (0.2 – 13)	Lenograstim	0	0	1
Schmidt, 2010	Retrospective	Germany	Unrelated	8.730	3.3 (NA)	Unknown	1	5	44
Jeger, 2010	Retrospective	Switzerland	Related	291	13,8 (5 – 22)	Unknown	NA	NA	18

Follow-up: Years, median, range; HMs: Hematological malignancies; NA: Not available; Other HMs: Non-Hodgkin lymphoma, Hodgkin's disease, multiple myeloma, chronic lymphocytic leukemia, acute lymphoblastic leukemia.

Reviewed in Martino et al. Exp ert Opin Biol Ther 2012

Largest prospective studies:
Similar incidence as in the age-adjusted population(except higher incidence of Hodgkin's lymphoma in one of them *[Holig et al. Blood 2009]*)

Conclusion | G-CSF mobilized PB

G-CSF mobilization appears to have a favourable risk-benefit profile.

Acute side effects:
- Mild/moderate
- Severe events= rare, probably mostly if preexisting risk

⇒ **Carefull donor evaluation before PBSC donation**

Long-term effects:
- No clearly identified
- Long-term FU of donors is needed for confirmation.
  To detect an improbable 10-fold increase in risk of malignancies
  →+/- 2000 donors would need to be followed up for ≥ 10 years!

⇒**Encourage donor participation in carefully designed studies for long-term monitoring**

REVIEW ARTICLES

- Navarro et al. BBMT 2013, 19, S15-S19
- Martino et al. Expert Opin Biol Ther 2012, 12 (5); 609-621
- Horowitz and Confer. Am Soc Hematol Educ Program 2005;469-75
- Avalos et al. BBBMT 2011, 17; 739-1746
- Anderlini and Champlin. Blood 2008 111; 1767-1772

Thank you for your attention

Growth factors prior to stem cell donation

Efficiency, precautions, long term side effects