G-CSF use in healthy hematopoietic stem cell donors

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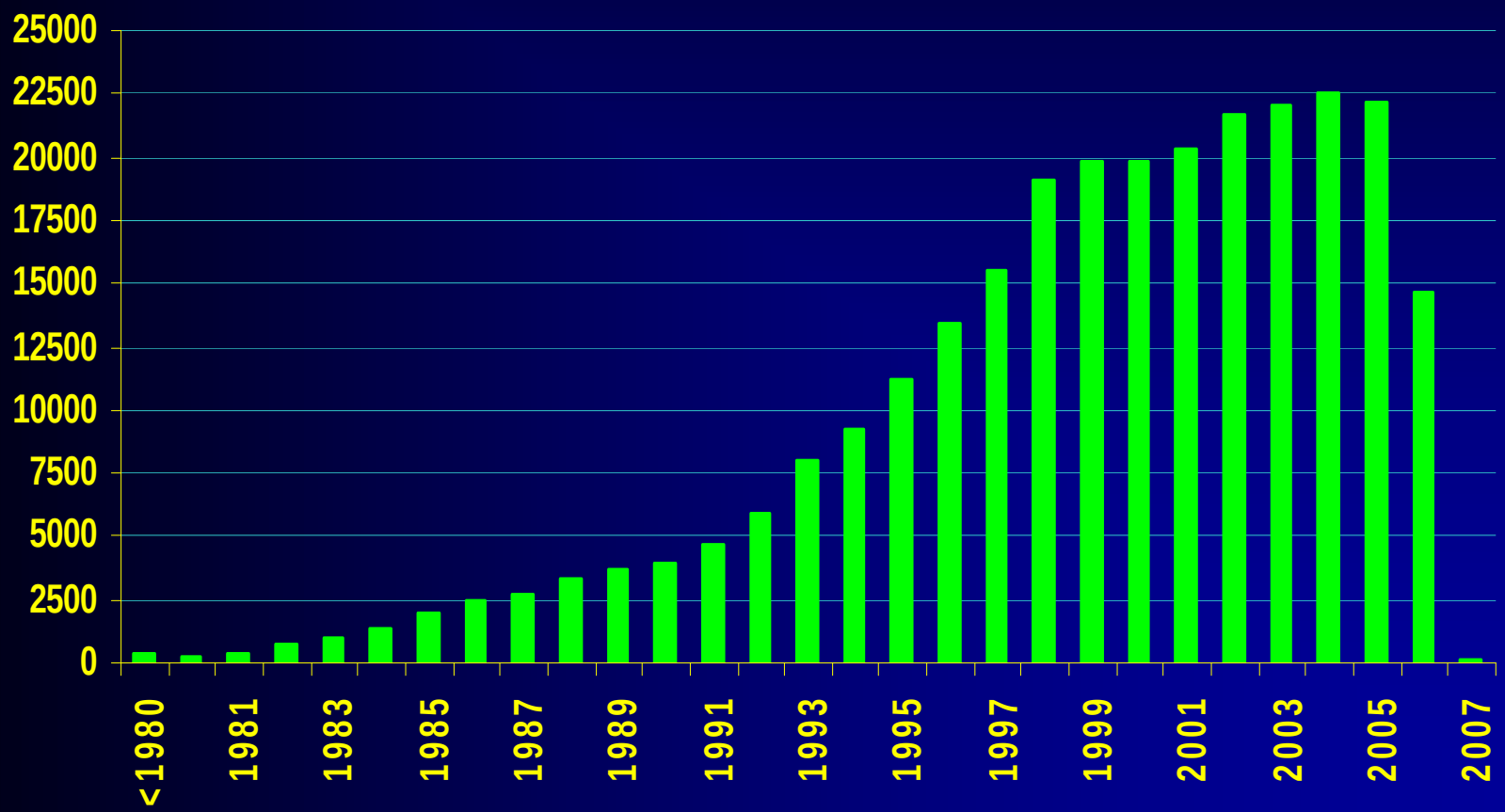
Haematopoietic Stem Cell Donation

- 30 years experience
- > 200,000 donations have been performed worldwide
- Family (usually siblings) or volunteer unrelated donors
- Various stem cell sources
  - Bone marrow
  - Peripheral blood
  - Cord blood
  - Mesenchymal (bone marrow derived)
  - Fetal

History – G-CSF mobilized peripheral blood HSCs in stem cell transplantation

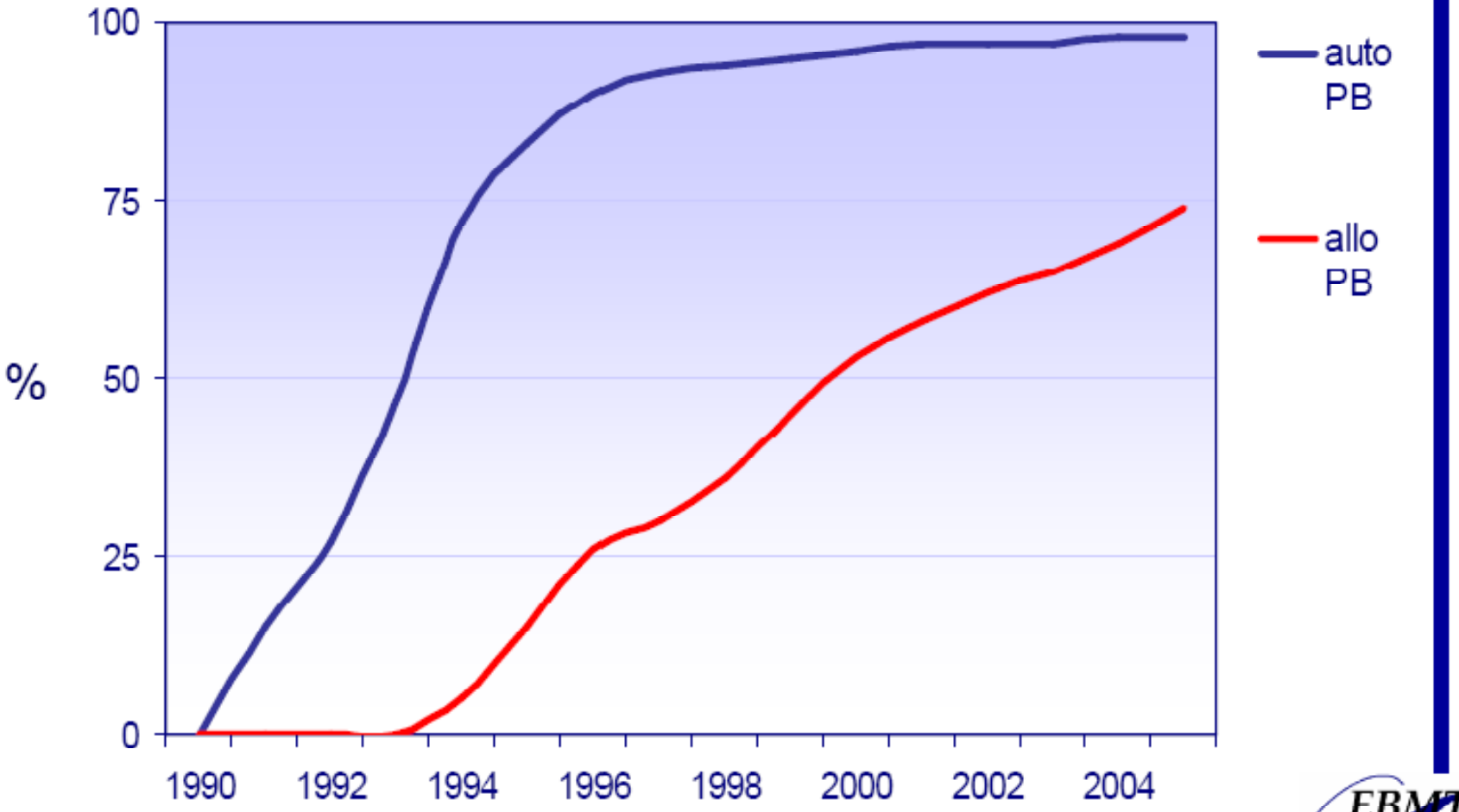
- **Early 1990´s**
  - Autologous HSCT
- **1995 (Houston, Seattle, Kiel)**
  - Pilot studies of allogeneic PBSCT´s

EBMT Database
Number of transplants by year



Note: Data reporting is incomplete, in particular for the most recent years

EBMT Activity survey on HSCT 1990 - 2005: changes in stem cell source



PB vs BM in allogeneic HSCT; patient perspective

- **8 randomized trials 1998-2002**

- **PB vs. BM**
  - aGHVD - increased risk (1/8)
  - cGVHD - increased risk (2/8), trend in all
  - Decreased TRM day 100 - trend (2/8)
  - Relapse - decreased risk (2/8)
  - Survival - better in advanced disease (2/8)

Ethical issues

- Separate the interests of the patient from the interests of the donor; complex within a family especially with a pediatric donor
- Confidentiality issues both before and after the transplantation
- Psychological effects in the donor if the transplant goes badly
- Genetic similarities; knowledge about genetic traits within families
- What if a disease is first noted in the patient that might have been transferred by the donation?
- What are the risks for the donor from the donation

Evaluating risks from the donation

- What do we do / have we done?
- 1) Retrospective surveys
- 2) Prospective studies - donor registries
- 3) Volontary reporting

Complications from PB donation

- Early – during mobilization / harvest
- Late – during long-term follow-up

Filgrastim associated alterations in serum chemistries and blood cell count

- LDH, AP and ALT increases
- Potassium, BUN and magnesium minimal declines
- WBC (ANC) may reach 70-80 x 10^9/l
- Platelets minimal decline

Leukapheresis and alterations in serum chemistries and blood cell counts

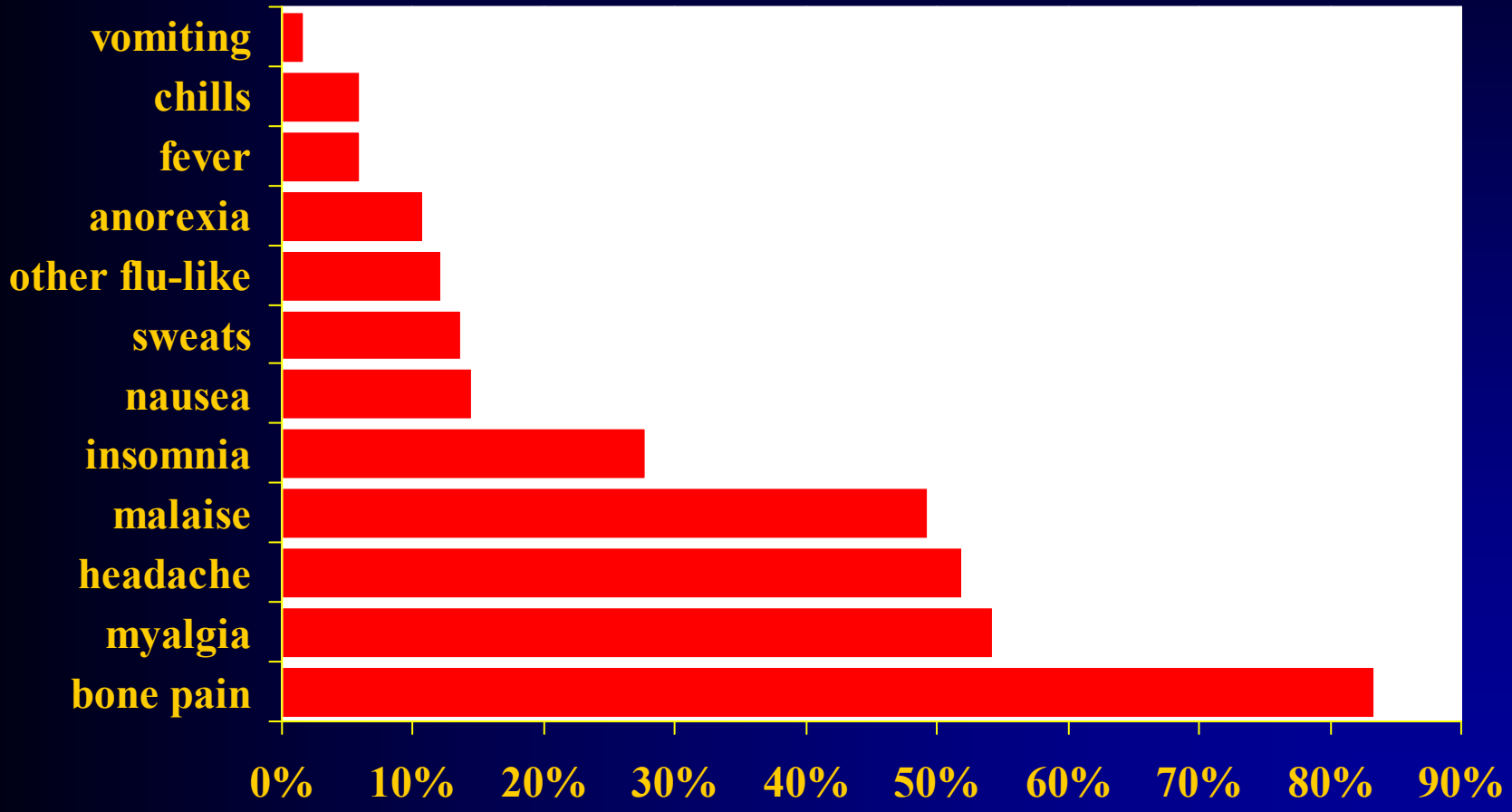
Thrombocytopenia common

Low risk for severe bleeding episodes

Mild neutropenia for weeks up to years

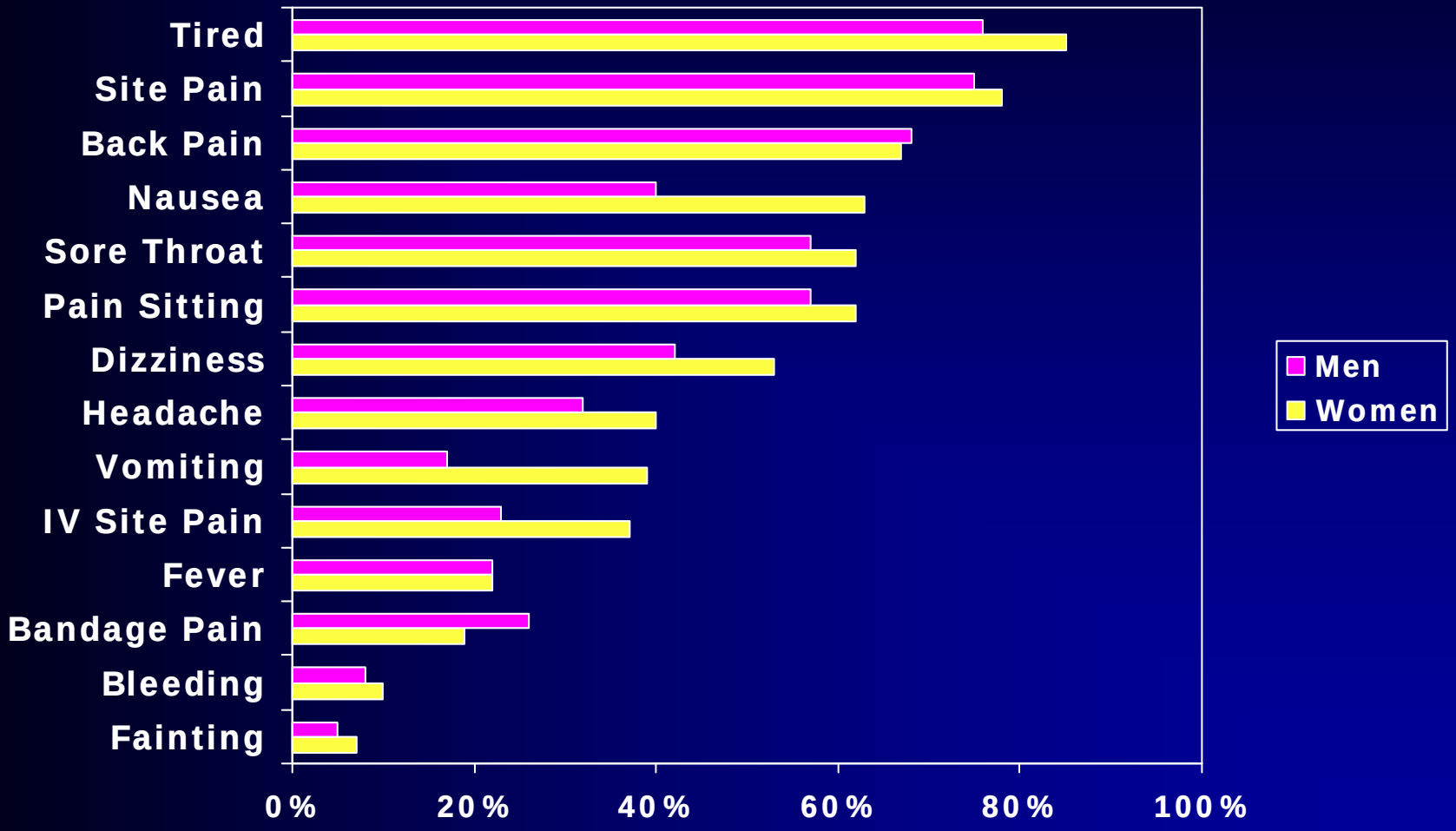
Mild lymphocytopenia for 8-10 weeks

PBSC Donor Symptoms during filgrastim administration, n = 1080



CIBMTR

Symptoms after marrow donations



CIBMTR

Severe donor events after hematopoietic stem cell donation - a retrospective EBMT survey

J. Halter, Y. Kodera, H. Baldomero, G. Favre, A. Urbano-Ispizua, N. Schmitz, J. Apperley, D. Niederwieser, A. Gratwohl

and 338 EBMT centers

Lyon 2007

Design and definitions

In 2003 teams with allogeneic HSCT were asked to report:

- If they had an active donor follow-up procedure

- donor deaths: any death within 30 day from donation
- severe adverse events: occurring within 30 days of donation and necessitating hospitalisation
- hematological malignancies in donors
  - any hematological malignancy (lymphoid/ myeloid)
  - any time post donation
  - not detected at donor workup

In 2006 the responding teams were asked again the same questions

Results: Response rates

2003 (period 1993-2002):

338 teams contacted / 262 teams (77.5%) responded

39210 alloHSCT (78%)

24099 BM (77%) / 15111 PB (78%)

2006 (2003-2005)

262 teams contacted / 169 (64.5%) responded

11814 alloHSCT

3671 BM (50%) / 8143 PB (52%)

Donor deaths within 30 days from harvest

PBSC using G-CSF	4	BM	1
67y male, subdural hematoma/after sudden fall?	d29	38y male, pulmonary embolism	d15
52y male, pulmonary edema/sudden cardiac arrest?	d17		
43y male, cardiac arrest	d15		
27y male, cardiac arrest due to human error	d0		

Incidence of donor death within 30 d 1993-2005

	allo 1993-2005	n	per 10.000
BM	27770	1	0.36
PB	23254	4	1.72
total	51024	5	0.98

Severe Adverse Reactions

PBSC	24	BM	12
MI	2	cardiac arrest	4
PE/DVT	7	stroke	1
subdural hematoma	1	pulmonary edema	1
hypertension	1	hypertension	2
supraventr. arrhythmia	1	hypotension	1
TRALI	1	unknown	3
splenic rupture	3		
hemorrhage	1		
seizures/resp.distress after apheresis	1		
unknown	6		

Incidence SAR

	Allo 1993-2005	n	per 10,000	95% CI
BM	27770	12	4.32	2.24-7.75
PB	23254	24	10.32	6.62-15.32
total	51024	37	7.25	p<0.02

Rare events after G-CSF mobilization

- **Precipitation of sickle crisis – sickle cell anemia or complex sickle cell hemoglobinopathies**
  - Sickle trait assoc with higher symptom scores but not severe reactions in small study
- **Splenic rupture – 5 cases; 1:5-10,000**
- **Flare of autoimmune disorders: RA, ankylosing spondylitis, inflammatory eye disorders**
- **G-CSF induced pulmonary hemorrhage (n=1)**

Kopp, JCO;25:21,2007

Possible conclusions

- Severe complications are rare
- G-CSF stimulated donations might be associated with higher rates of severe adverse events

- PB donors are frequently older than BM donors. More frail?

- PB donations are performed more recently; under reporting of SAEs in BM donations?

G-CSF and malignancies

G-CSF driven MDS or leukemia

Reported in children with congenital granulocyte production defects and in patients with severe aplastic anemia

Mutated G-CSF receptors or cytogenetic abnormalities

High doses of G-CSF over long time

Both these groups have a baseline increased risk for myelodysplastic syndromes / AML

Is the detected risks only due to that these patients now survive longer or is there a real effect of G-CSF?

Hematological malignancies

2/200 G-CSF (healthy donors)

AML 4 and 5 years after G-CSF mobilisation

Bennet L, BJH,135;642:2006

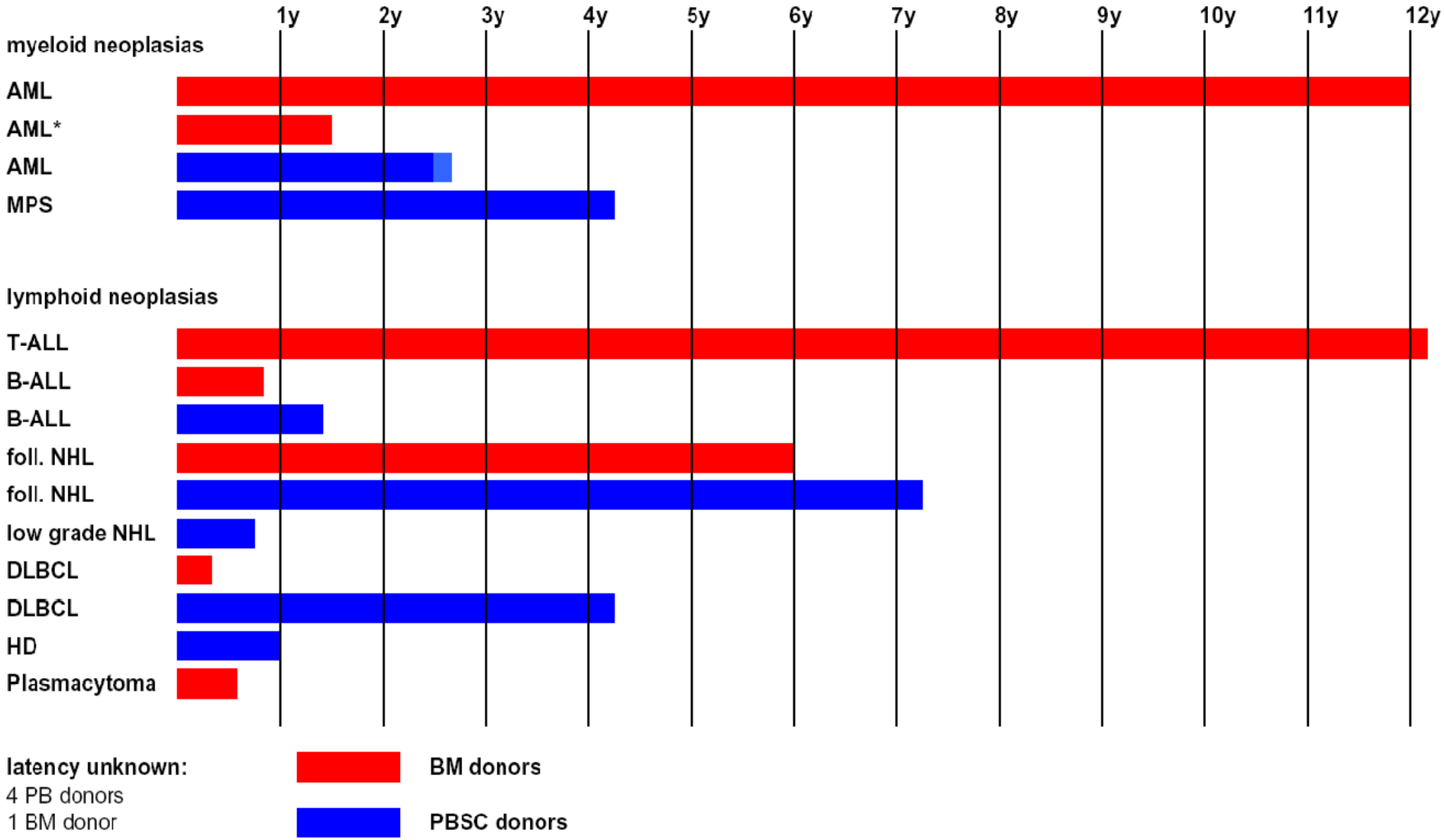
Hematological malignancies EBMT survey 1993-2005

	PBSC: 11	BM: 8
AML	1	2
ALL	1	2
MPS	1	
CLL	1	
NHL low grade	2	1
DLBCL	1	1
Other lymphoma		1
HD	1	
Plasmacytoma		1
Not specified	3	

Incidence of hematological malignancies in donors 1993-2005

	Allo 1993-2005	n	per 10,000	95% CI
BM	27770	8	2.88	1.24-5.68
PB	23254	11	4.73	2.36-8.44
total	51024	19	3.72	

Time from donation to diagnosis of hematological malignancy



Long-term Follow-up of Unrelated Donors after Bone Marrow and PBSC Donation: The National Marrow Donor Program Experience

Thanks to:

Dennis L. Confer, M.D.

Chief Medical Officer, NMDP

Annual Follow-up of PBSC Donors as of November 2006

- 4,015 Donors with at least one year of follow-up
- 9,785 total years of follow-up
- Range 1 – 9 years with 897 ≥ 4 years
- 20 reported cases of all sites cancer
- No reported cases of leukemia, lymphoma or MDS

Brit J Haematol (2007) **137**: 76-7

Annual Follow-up of Marrow Donors as of March 2007

- 1,160 Donors with at least one year of follow-up
- 1,685 total years of follow-up
- Range 1 – 3 years
- 2 reported cases of cancer – Colon, Testicle
- No reported cases of leukemia, lymphoma or MDS

Hematological malignancies (DKMS, reported at EBMT 2007)

- **3713 BM and 7236 PB**

- **PB follow up 5 years**
  - Blood samples 4 w, 6 mos and annually to 5 years post donation
  - 8 cancer in the PB group (1 HD, 7 others)
  - 4 cancer in the BM group (1 CLL, 3 others)

Hematological malignancies (Japan, reported at EBMT 2007)

- April 2000- March 2005
- 3264 donors
- Reports from 1673 donors
- Max 5 years
- 2 hematological malignancies (1 AML and 1 MPD)

Problems; the numbers' game

- **To detect a 10-fold increase in risk of hematologic malignancy with G-CSF would require following ~2000 donors over a 8-10 year period**

- **Certain populations understudied**
  - Most data comes from studies of unrelated donors (adults 18-50)
  - Limited data on children and older donors

Pediatric donors

- **Limited data available since G-CSF mobilization is more uncommon in pediatric patients**

- **Life-threatening complication rate similar to adults (?)**
  - Increased risk of allogeneic blood exposure for both BM and PB collection
  - More likely to require central venous catheter placement for leukapheresis

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

Ongoing initiatives

- The field is very aware of the need for donor follow-up. A lot of studies and research is needed.
- Donor follow-ups by unrelated donor registries
- Voluntary reporting of donor events through the WMDA system (unrelated donors).
- Scandinavian prospective donor registry since 1998 (sibling and unrelated donors)
- Care must be taken in designing regulatory activites so that resources are concentrated on the most important activities.

The Nordic registry of stem cell donors

- Started in 1998
- Sweden, Finland, Norway and Denmark
- Reports short-term complications
- Long-term complications will be studied by linking the registry to the national diagnoses, cancer, and causes of death registries
- Approx. 1300 donors included

Conclusions G-CSF stimulated donors

- Donation is reasonable safe procedure
- Serious adverse events are uncommon and deaths are rare
- Most donors report symptoms
- Many donors and the medical community prefer to work with PB donation for adult patients
- Incidence of hematological malignancies not different from what would have been expected in a normal non G-CSF exposed population
- Based on information available G-CSF for donation continues to have a favorable risk-benefit profile

Thanks to

- J Halter - Basel (EBMT)
- D Confer - Minneapolis (NMDP)
- M Horowitz - Milwaukee (CIBMTR)
- H Hägglund - Stockholm (Nordic registry)