LA RACCOLTA DI PROGENITORI EMOPOIETICI DA SANGUE PERIFERICO (HPC-A)

Dr Giuseppe Milone

PROGRAMMA DI TRAPIANTO EMOPOIETICO
CIC 792
OSPEDALE FERRAROTTO- CATANIA

- RACCOLTE DI HPC-A in Italia:
- RILEVANZA:

ogni anno:

Trapianti autologhi 3.000 x 1.5 = 4.500 HPC-A autologhe

Trapianti allogenici: (1.200) il 60% PBSC (700) di cui il 50% (350)
da donatori italiani
=350 x 1.25= 425 HPC-A allogeniche.

Totale HPC-A: 4.925 anno

SCELTA FONTE

(MO OPPURE PBSC IN AMBITO ALLOGENICO / AUTOLOGO)

DOSE CD34/KG:

(SOTTOPOPOLAZIONI CD34 /
PESO ATTUALE O IDEALE)

POVERI MOBILIZZATORI

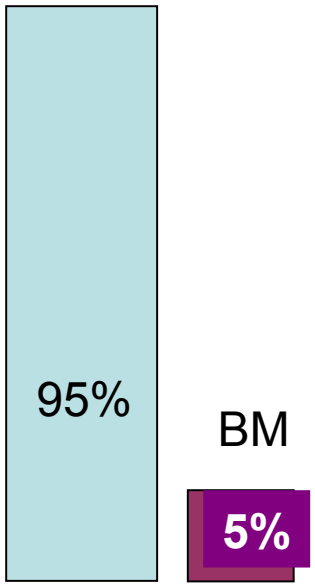
(PLERIXAFOR)

IMPIEGO G-CSF

EVENTI AVVERSI MOBILIZZAZIONE E RACCOLTA

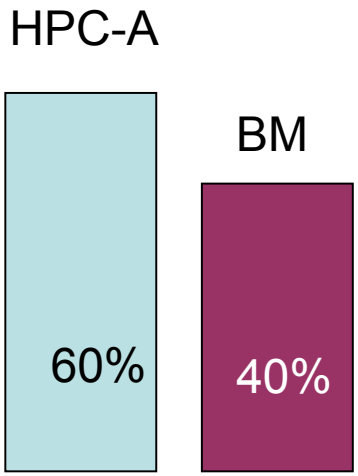
UTILIZZO “ PBSC VERSUS ESPIANTO” MIDOLLO

AUTOLOGO



FONTE
PBSC vs MO

ALLOGENICO



FONTE
PBSC vs MO

Vantaggi PBSC

Vantaggi BM

AUTO

Piu' rapida ripresa Emopoietica

Programmi di terapia multi-cicli di alte dosi

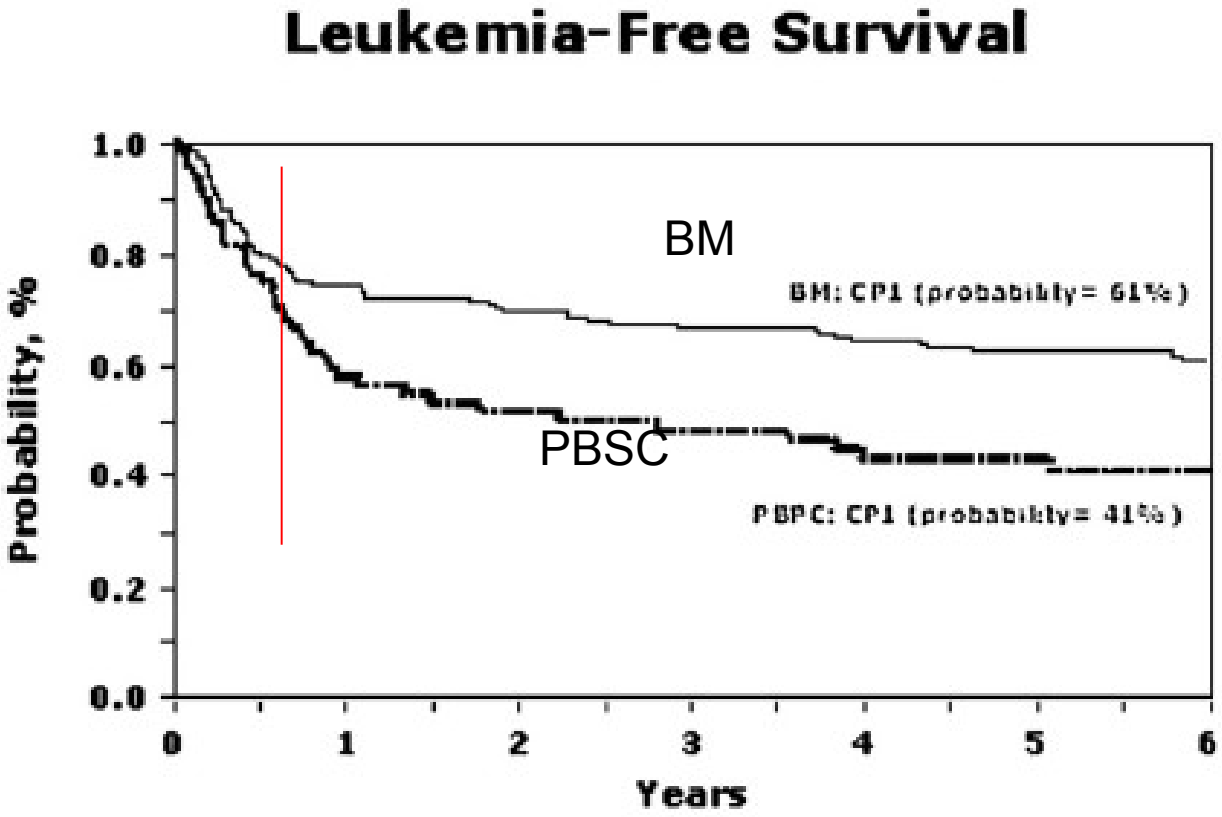
ALLO

Ridotto rischio di GVHD acuta

Ridotto rischio di GVHD cronica

Piu' facile chimerismo completo rilevante se condizionamento non mieloablativo

L'UTILIZZO DI MIDOLLO IN TRAPIANTO ALLOGENICO E' ASSOCIATO A MIGLIORE SOVRAVVIVENZA IN EMOPATIE NEOPLASTICHE EARLY



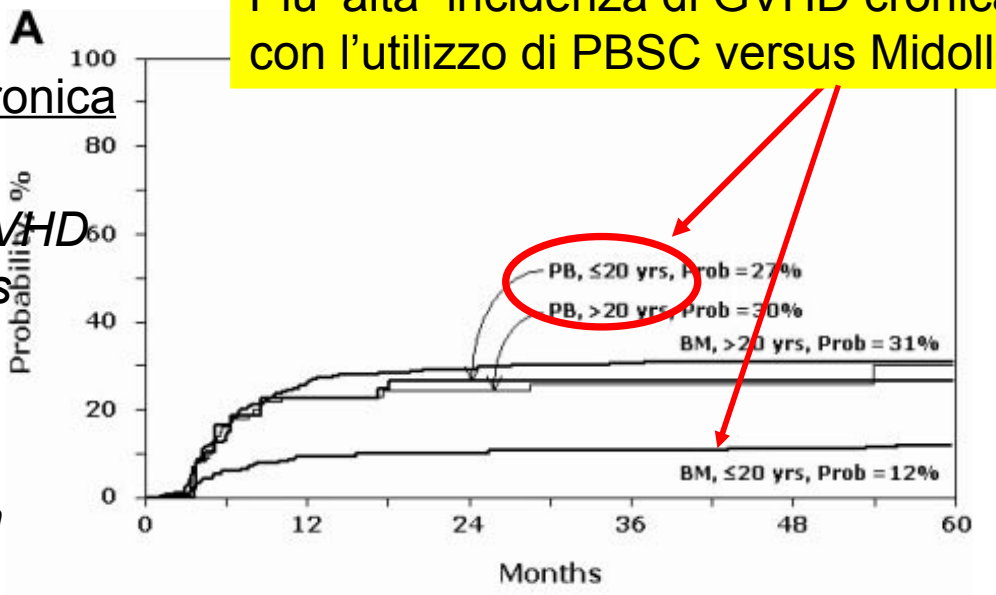
Schmitz N, Eapen M, Horowitz MM, et al.
Long-term outcome
of patients given transplants of mobilized blood or bone marrow: a report from the International Bone Marrow Transplant Registry and the European Group for Blood and Marrow Transplantation. Blood. 2006;108:4288-4290.

Piu' alta incidenza di GVHD cronica con l'utilizzo di PBSC versus Midollo

% GVHD cronica

H. Schrezenmeie

Worse outcome and more chronic GVHD with peripheral blood progenitor cells than bone marrow in HLA-matched sibling donor transplants for young patients with severe acquired aplastic anemia
BLOOD 2006



Overall survival

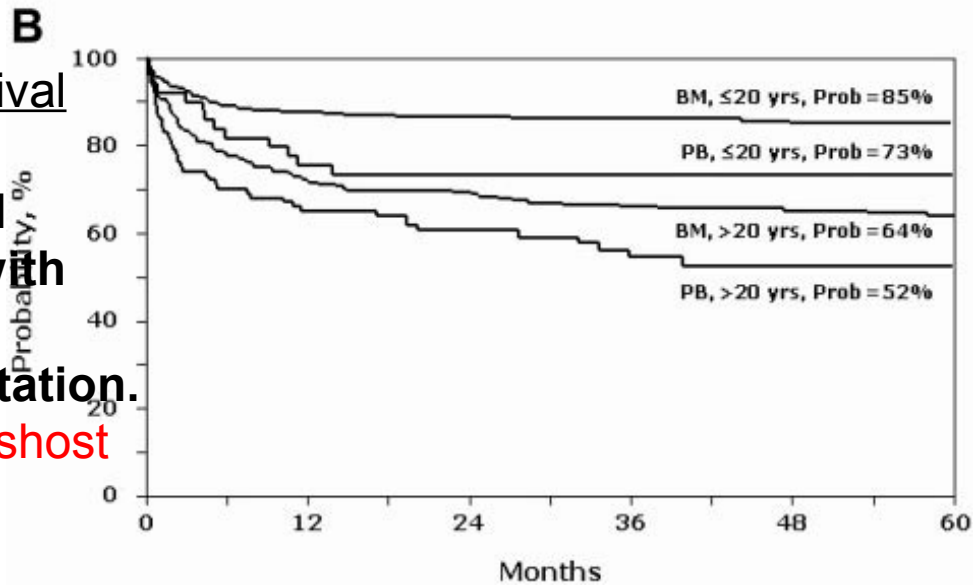


Figure 1. Patients 20 years old and younger and older than 20 years with SAA after PBPC (PB) and BM transplantation.
(A) Probability of chronic graft-versushost disease.
(B) Probability of overall survival

VOLUME 26 · NUMBER 35 · DECEMBER 10 2008

JOURNAL OF CLINICAL ONCOLOGY

ORIGINAL REPORT

From the Roswell Park Cancer Institute, Buffalo, NY; Medical College of Wisconsin, Milwaukee, WI; University of Minnesota, Minneapolis; Mayo Clinic, Rochester, MN; Vanderbilt University, Nashville; St Jude Children's Research Hospital, Memphis, TN; Emory University, Atlanta, GA; Mount Sinai Medical Center, New York, NY; Oregon Health & Science University, Portland, OR; Leiden University Medical Center, Leiden, the Netherlands; Princess Margaret Hospital, Toronto, Ontario, Canada; University Hospital

Risk Factors for Acute Graft-Versus-Host Disease After Human Leukocyte Antigen–Identical Sibling Transplants for Adults With Leukemia

Theresa Hahn, Philip L. McCarthy Jr, Mei-Jie Zhang, Dan Wang, Mukta Arora, Haydar Frangoul, Robert Peter Gale, Gregory A. Hale, John Horan, Luis Isola, Richard T. Maziarz, Jon J. van Rood, Vikas Gupta, Joerg Halter, Vijay Reddy, Pierre Tiberghien, Mark Litzow, Claudio Anasetti, Stephen Pavletic, and Olle Ringdén

Table 2. Multivariable Analysis of Risk Factors for Grade 2-4 Acute Graft-Versus-Host Disease

Variable	RR	95% CI	*P*
For recipients age 18-39 years			
Bone marrow graft	1.0		
Peripheral blood stem-cell graft	1.43	1.14 to 1.79	.0023
For recipients age 40+ years			
Bone marrow graft	1.0		
Peripheral blood stem-cell graft	0.98	0.78 to 1.23	.8528

Vantaggi PBSC

Vantaggi BM

AUTO

Piu' rapida ripresa Emopoietica

Programmi di terapia multi-cicli di alte dosi

LEUCEMIA MIELOIDE ACUTA
È una eccezione ?

ALLO

Ridotto rischio di GVHD acuta

Ridotto rischio di GVHD cronica

Piu' facile chimerismo Completo Se condizionamento non mieloablativo

L'UTILIZZO DI MIDOLLO AUTOLOGO POTREBBE ESSERE VANTAGGIOSO RISPETTO ALLLE PBSC NELLA LMA IN QUANTO ASSOCIATO A INFERIORE RISCHIO DI RELAPSE

Higher Incidence of Relapse With Peripheral Blood Rather Than Marrow As a Source of Stem Cells in Adults With Acute Myelocytic Leukemia Autografted During the First Remission

Norbert-Claude Gorin, Myriam Labopin, Didier Blaise, Josy Reiffers, Giovanna Meloni, Mauricette Michallet, Theo de Witte, Michel Attal, Bernard Rio, Francois Witz, Loic Fouillard, Roel Willemze, and Vanderson Rocha

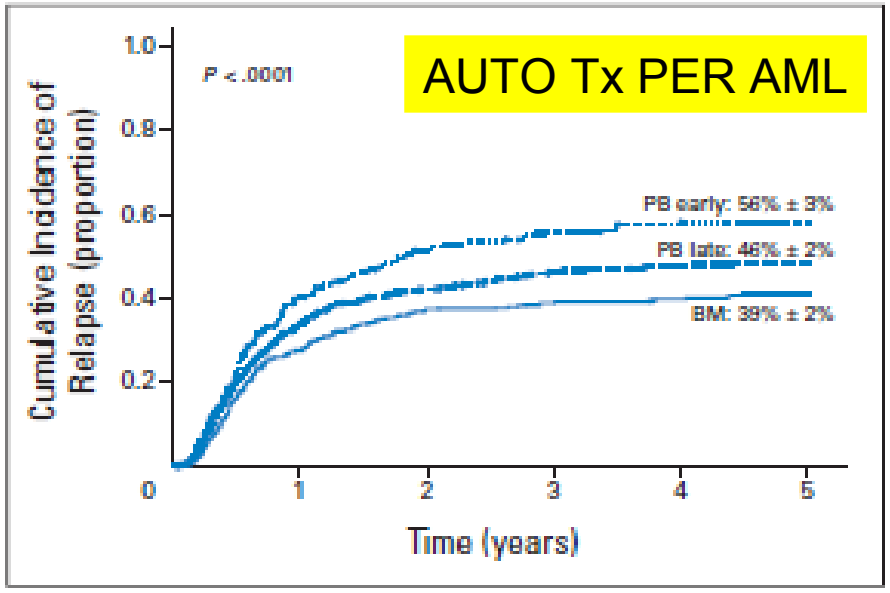


Fig 1. Cumulative incidence of relapse in patients receiving bone marrow (BM), peripheral blood (PB) more than 80 days after the first complete remission (PB late), or PB 80 days or less after the first complete remission (PB early).

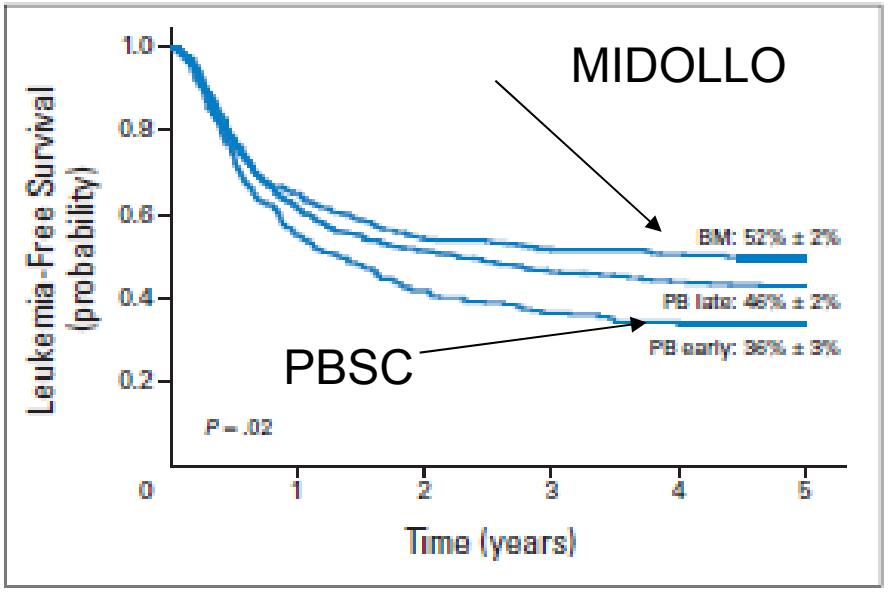


Fig 2. Estimated leukemia-free survival in patients receiving bone marrow (BM), peripheral blood (PB) more than 80 days after the first complete remission (PB late), or PB 80 days or less after the first complete remission (PB early).

L'OTTIMIZZAZIONE DELLA DOSE COSTITUISCE UN OBIETTIVO RILEVANTE SIA IN AMBITO ALLOGENICO CHE AUTOLOGO

Quale dose di CD34 minima e ottimale

Quando iniziare l'aferesi sulla base di WBC o di CD34

Quanti litri processare

Accesso vascolare

Donor, recipient, and transplant characteristics as risk factors after unrelated donor PBSC transplantation: beneficial effects of higher CD34$^+$ cell dose

Michael A. Pulsipher,[1] Pintip Chitphakdithai,[2] Brent R. Logan,[3] Susan F. Leitman,[4] Paolo Anderlini,[5] John P. Klein,[3] Mary M. Horowitz,[3] John P. Miller,[6] Roberta J. King,[2] and Dennis L. Confer[6]

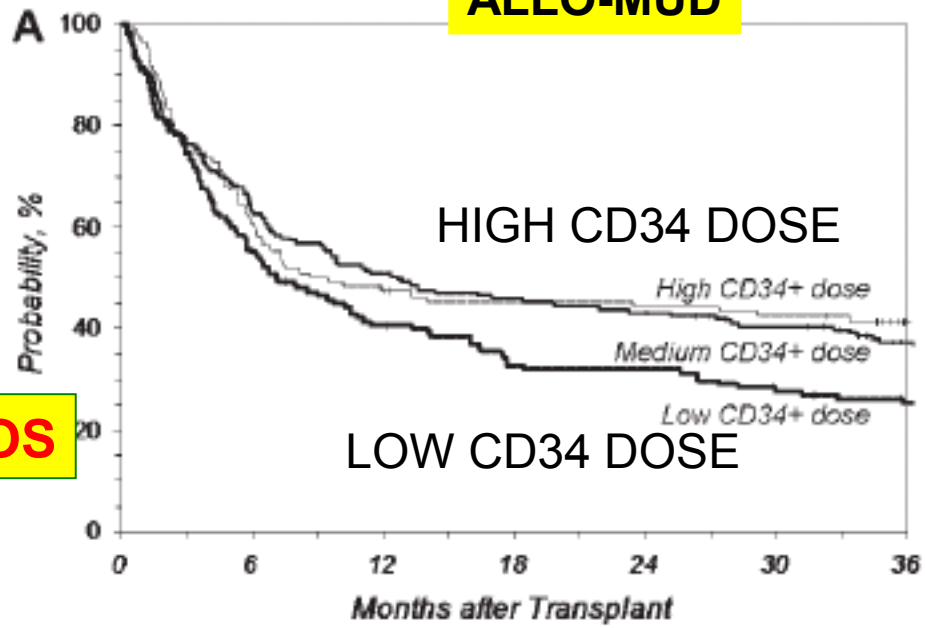
BLOOD, 24 SEPTEMBER 2009 • VOLUME 114, NUMBER 13

MUD Tx PBSC

Collection practices leading to acquisition and **infusion of at least 4.5 x 10e6 CD34 cells/kg may improve survival** and decrease morbidity in patients receiving this stem cell source for transplantation, regardless of regimen intensity

Low < 4.5
Medium 4,5-9.5
High > 9.5

ALLO-MUD



OS

UNA DOSE DI CD34 SUPERIORE A CD34+ >10.0 X10E6/KG IN ALCUNI STUDI SEMBRA ASSOCIATA A UNA MAGGIORE INCIDENZA DI GVHD CRONICA

CD34 INFUSE E GVHD CRONICA

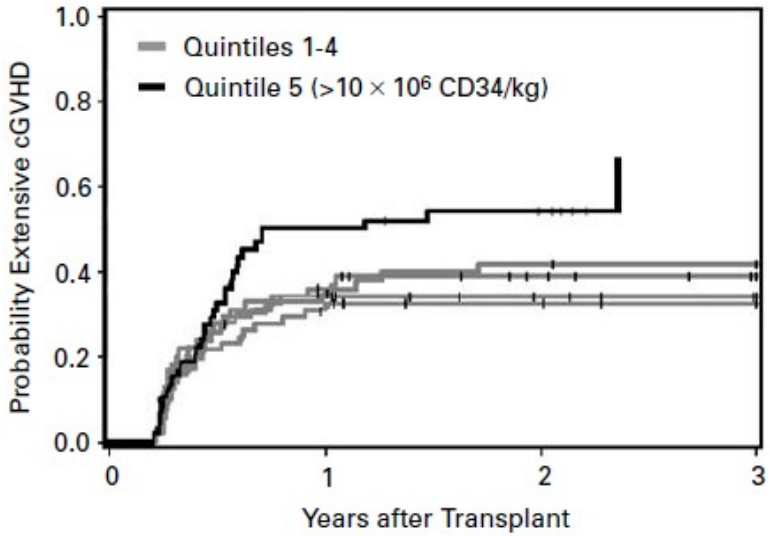
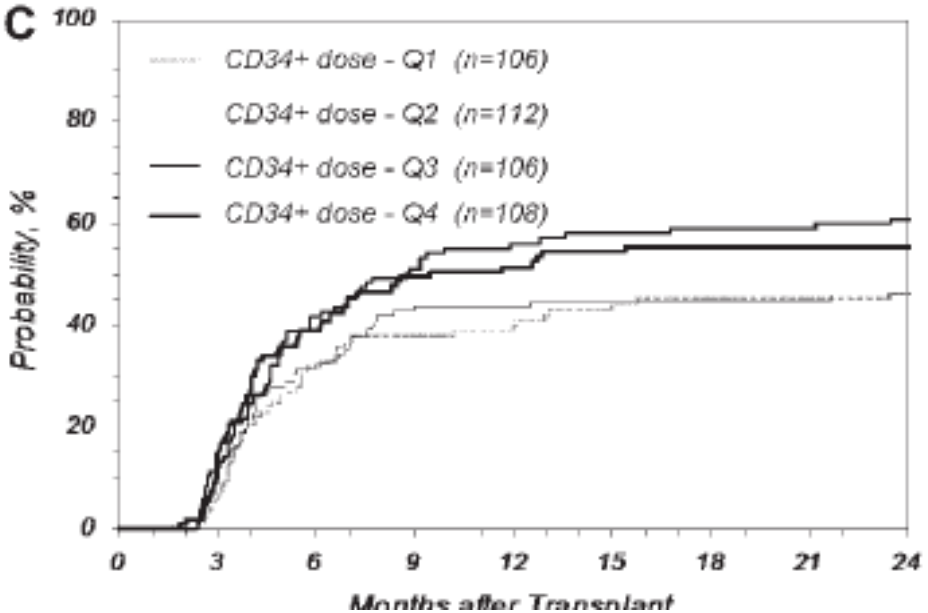
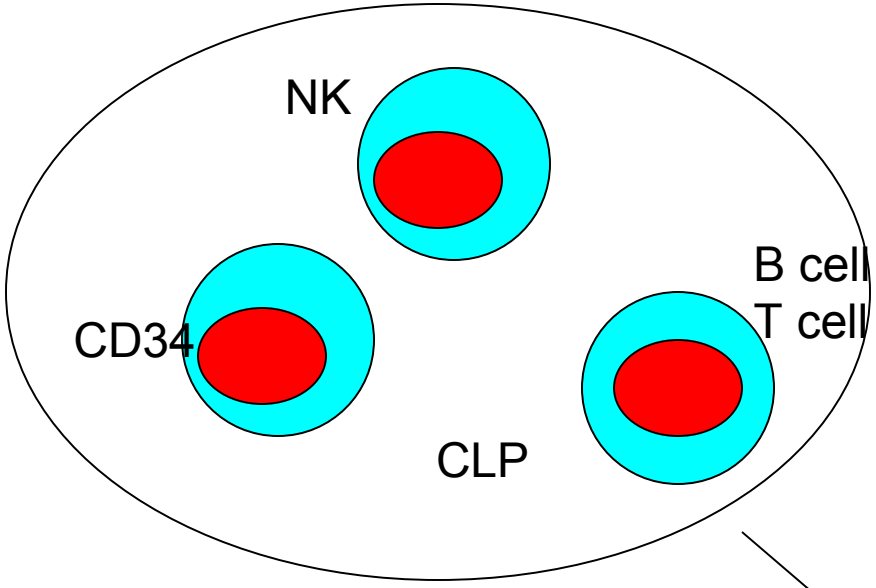


Figure 2 cGVHD is associated with CD34 cell dose. The probability of extensive cGVHD after conventional transplantation of G-PBMC from HLA-identical sibling donors is increased in those patients receiving $>10 \times 10^6$ CD34+ cells/kg.

CD34+ >9,4x10e6/Kg (Q4)





INOCULO
EMOPOIETICO

RICOSTITUZIONE
EMOPOIETICA
(Neutrofili>500)

RICOSTITUZIONE
IMMUNOLOGICA
(Linfociti>500
Monociti >300)

INFEZIONI

TRM

CONTROLLO
DELLA
MALATTIA MINIMA

Br J Haematol. 2005 Mar;128(5):659-67.

Allogeneic peripheral blood stem cell graft composition affects early T-cell chimaerism and later clinical outcomes after non-myeloablative conditioning.

Panse JP, Heimfeld S, Guthrie KA, Maris MB, Maloney DG, Baril BB, Little MT, Chauncey TR, Storer BE, Storb R, Sandmaier BM.
Fred Hutchinson Cancer Research Center, Seattle, WA 98109-1024, USA.

Abstract

We have studied the influence of cell subsets [CD34, CD3, CD4, CD8, CD14, CD20, natural killer (NK; CD3(-)/CD56(+)), NKT (CD3(+)/CD56(+)), DC1, and DC2 cells] of granulocyte colony-stimulating factor mobilized peripheral blood stem cells (PBSC) on early T-cell chimaerism and later clinical outcomes in 125 patients with haematological malignancies who received human leucocyte antigen (HLA)-matched related grafts after non-myeloablative conditioning. Conditioning consisted of 2 Gy total body irradiation (TBI) alone (n = 28), or 2 Gy TBI preceded by either 90 mg/m(2) fludarabine (n = 62) or planned autologous haematopoietic cell transplantation (HCT) (n = 35). Post-transplant immunosuppression included mycophenolate mofetil and ciclosporin. Multivariate analysis showed that - **higher numbers of grafted NK cells predicted higher early T-cell chimaerism (P = 0.03), while higher numbers of B cells were associated with better clinical outcomes and a higher risk for chronic graft-versus-host disease (P = 0.05).** Higher numbers of CD14(+) cells were associated with worse overall survival (P = 0.03), while higher numbers of CD34(+) cells showed better survival (P = 0.03). The addition of fludarabine or autologous HCT predicted higher early T-cell chimaerism (P = 0.001), while advanced donor age predicted lower chimaerism (P < or = 0.02). Patients with aggressive diseases were at higher risk for relapse/disease progression, and shorter progression-free and overall survival (P < 0.01). These results suggest that the dosing of certain cellular subsets of PBSC products can influence important outcomes post-HCT after non-myeloablative conditioning.

J Haematol. 2005 Oct;75(4):299-308.

Transplantation with higher dose of natural killer cells associated with better outcomes in terms of non-relapse mortality and infectious events after allogeneic peripheral blood stem cell transplantation from HLA-matched sibling donors.

Kim DH, Sohn SK, Lee NY, Baek JH, Kim JG, Won DI, Suh JS, Lee KB, Shin IH.
Department of Hematology/Oncology, Kyungpook National University Hospital, 50

BACKGROUND: Little is known about the role of the CD56+ natural killer (NK) cell dose on the outcome of allogeneic peripheral blood stem cell transplantation (PBSCT). Recently, higher dose of NK cells has been associated with a lower incidence of severe graft-versus-host disease (GVHD). The current study attempted to evaluate the effect of the NK cell dose on transplant outcomes in allogeneic PBSCT setting.
METHODS AND MATERIALS: Sixty-one cytokine mobilized PBSC recipients were analyzed according to the infused dose of CD34+ cells and NK cells in relation to overall survival (OS), non-relapse mortality (NRM), GVHD, and infectious events.
RESULTS: **The group received a higher dose of NK cells (> or =5 x 10(7)/kg) showed a lower incidence of NRM (P = 0.0186) and infectious events (P = 0.0107).** In a multiva analysis, a higher dose of NK cells was correlated to **better transplant outcomes for NR** (P = 0.042) with CD34+ cell dose (P = 0.018), and for infectious events (P = 0.013) with CD34+ cell dose (P = 0.016). **Higher NK cell infusion group also showed a faster immune recovery in serial measurements at days +90, +180, and +365.**
CONCLUSIONS: High dose of NK cells may play an important role in improving transplant outcomes, in terms of reducing NRM and infectious events together with CD34+ cells.

Blood. 2005 Mar 15;105(6):2300-6. Epub 2004 Nov 30.

Engraftment and survival following reduced-intensity allogeneic peripheral blood hematopoietic cell transplantation is affected by CD8+ T-cell dose.

Cao TM, Shizuru JA, Wong RM, Sheehan K, Laport GG, Stockerl-Goldstein KE, Johnston LJ, Stuart MJ, Grumet FC, Negrin RS, Lowsky R.
Division of Blood and Marrow Transplantation, Department of Medicine, Stanford University Schol of Medicine, 300 Pasteur Dr, H3249, MC 5623, Stanford, CA 94305-5623, USA.

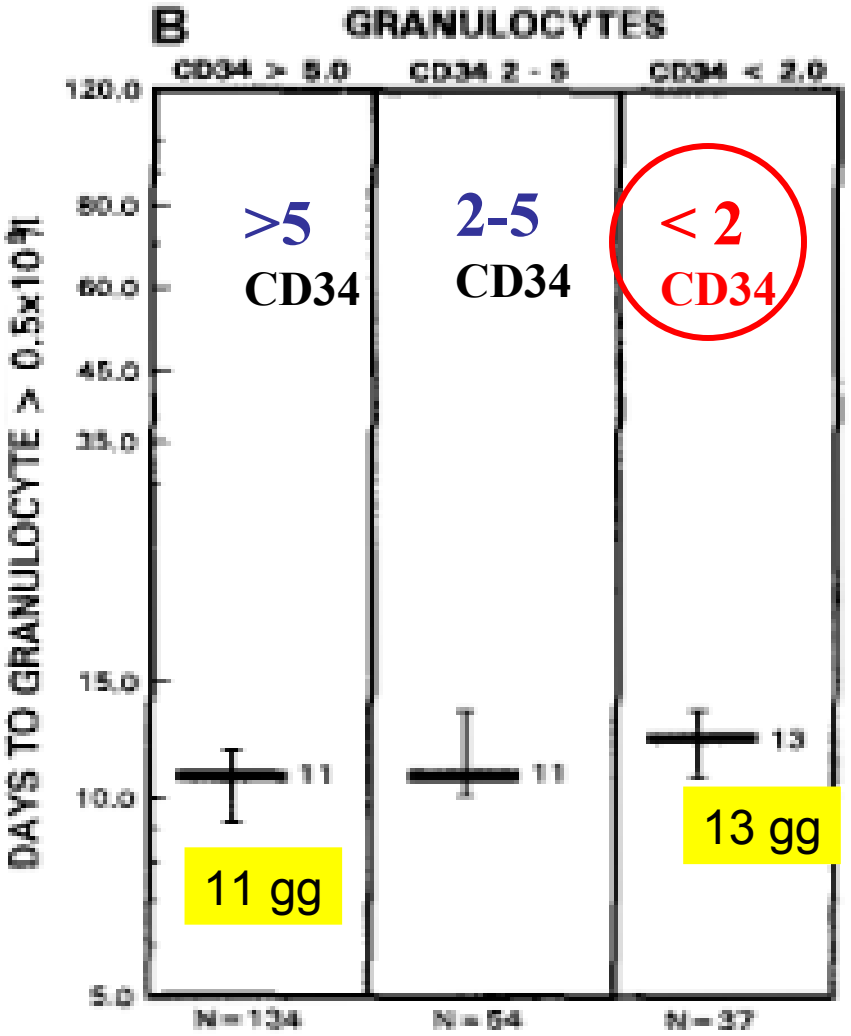
Abstract

The influence of graft composition on clinical outcomes after reduced-intensity conditioning is not well-characterized. In this report we prospectively enumerated CD34+, CD3+, CD4+, and CD8+ cell doses in granulocyte colony-stimulating factor-mobilized peripheral blood mononuclear cell (G-PBMC) allografts in 63 patients who received transplants following non-myeloablative conditioning with total body irradiation 200 cGy plus fludarabine as treatment for malignant diseases. Donors were HLA-identical siblings (n = 38) or HLA-matched unrelated individuals (n = 25). **By univariate analyses G-PBMC CD8+ T-cell dose in at least the 50th percentile favorably correlated with full donor blood T-cell chimerism (P = .03),** freedom from progression (P = .001), and overall survival (P = .01). No G-PBMC cell dose influenced grade II to IV acute or extensive chronic graft-versus-host disease. In multivariate analysis only G-PBMC CD8+ T-cell dose (P = .003; RR = 0.2, 95% CI = 0.1-0.6) was associated with improved freedom from progression. Infusion of low G-PBMC CD8+ T-cell dose for reduced-intensity allografting may adversely affect T-cell engraftment and survival outcome.

IN ambito AUTOLOGO, UTILIZZARE una dose di CD34+ sotto 2 x 10e6 CD34+/Kg **(dose minima)** diminuisce la velocità media di attecchimento per i N>0.5

Peripheral Blood Stem Cell Transplants for Multiple Myeloma: Identification of Favorable Variables for Rapid Engraftment in 225 Patients

Guido Tricot et al.



COMPARAZIONE DEI COSTI PER LE ALTE DOSI E TEMPI DI ATTECCHIMENTO NEI GRUPPI DI GOOD E POOR MOBILIZER (**<2x10e6/Kg)**
(Stocler-Goldstein)

	POOR MOBILIZER (<2x10e6/Kg)		GOOD MOBILIZER **> 2x10e6**
BMT COST **dollari**	**140.000 dollari**	vs	**80.000**
N. RECOVERY	13 d.	vs	10 d.
PLT RECOVERY 25.000	36 d.	vs	14 d.
TRM	**11%**	**vs**	**3,6%**

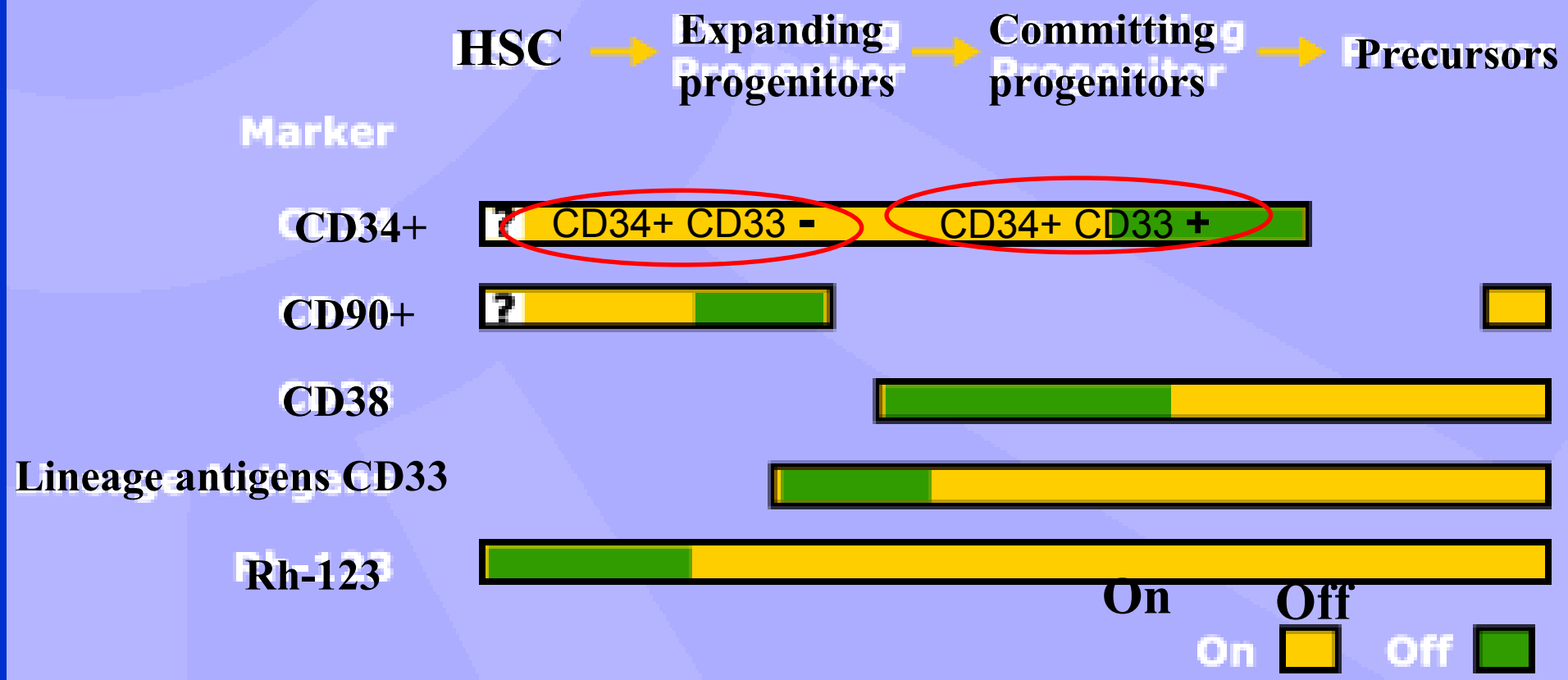
General Overview: Mobilization/Risks

# Stem Cells for Transplant	Patient Mobilization (growth factor only)	Risk Factors Associated with Number of cells transplanted
Optimal $\geq 5x10^6$ /kg	50%	90% transplant success rate Reduced risk of infection
Average/ Minimal $>2x10^6$ /kg	30%	Delayed re-engraftment Increased risk of infection
Poor/ Insufficient $<2x10^6$/kg	20%	Ineligible for transplant Additional mobilizations Requires use of chemotherapy Failure to re-mobilize

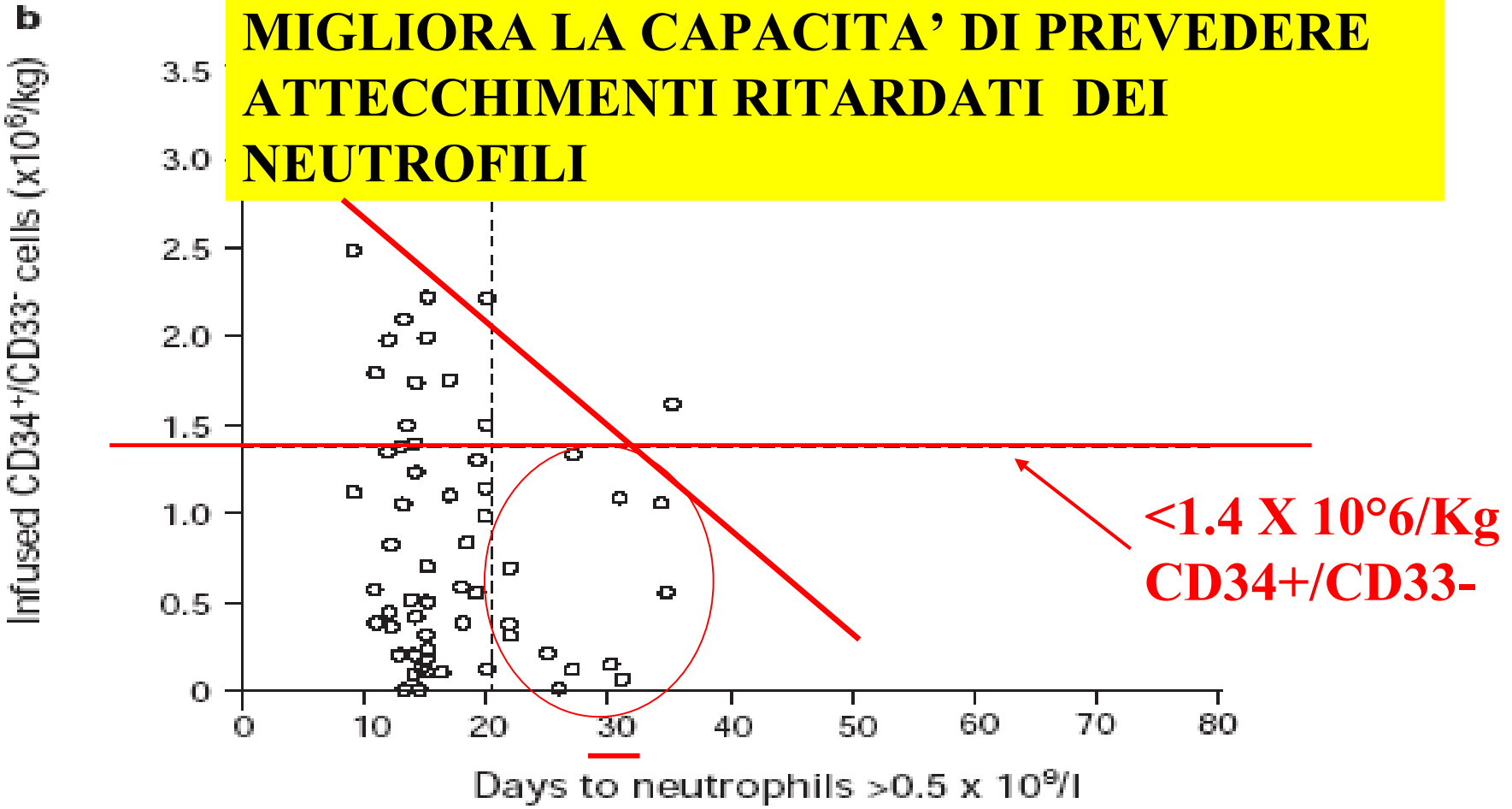
There is no method to predict a patient's ability to mobilize stem cells

Human Stem Cell Phenotype

STUDIARE LE SOTTOPOPOLAZIONI DELLE CELLULE STAMINALI CD34+
AIUTA LA IDENTIFICAZIONE DELLA DOSE MINIMA DI CD34+



CONSIDERARE IL NUMERO DI CD34+/CD33- INVECE CHE IL NUMERO DI CD34 TOTALI MIGLIORA LA CAPACITA' DI PREVEDERE ATTECCHIMENTI RITARDATI DEI NEUTROFILI



Relationship between the number of CD34+/CD33– cells/kg infused and the time to recover ((**b**) neutrophils >0.5 x 109/l

BC Millar
Bone Marrow Transplantation, (1998) 22, 469–475

Nella identificazione della dose minima sufficiente considerare se il paziente è obeso.

Infatti raccolte aferetiche considerate insufficienti se espresse per CD34+ /peso reale possano invece essere considerate sufficienti quando rapportate al peso ideale.

(I DATI esistono nel TRAPIANTO AUTOLOGO, nessun dato invece nell'Allogenico)

ORIGINAL ARTICLE

Actual or ideal body weight to calculate CD34+ cell dose in patients undergoing autologous hematopoietic SCT for myeloma?

V Singh[1], J Krishnamurthy[1], S Duffey, R Meagher, M Villa, J Monreal, A Evens, O Frankfurt, J Altman, L Gordon, M Tallman, S Williams, J Winter, S Singhal and J Mehta

IBW
(kg) was calculated by a standard formula
using gender and
height:

50+(2.3 x (height in inches - 60))
for men and

45.5+ (2.3 x (height in inches - 60))
for women

CD34+ CELL DOSE BASED ON IBW IS A BETTER PREDICTOR OF NEUTROPHIL RECOVERY AFTER AUTOTRANSPLANTATION.

Bone Marrow Transplantation (2003) 31, 861–864

Is this observation of any practical significance? Obviously, it is of no consequence in patients in whom an excellent quantity of stem cells is collected rapidly. However, in patients who require a number of aphereses to reach a predefined target and in whom ABW exceeds IBW by a significant margin, measuring CD34+ cells based upon IBW would help decrease the number of apheresis procedures while ensuring that enough cells were available for prompt engraftment.

INCIDENZA DI "CD34+ POOR MOBILIZER" IN CASISTICHE DI LINFOMA DOPO VARIE TERAPIE DI MOBILIZZAZIONE

Sugrue	<1x10e6/Kg	G-CSF:	48%
Stiff	<1x10e6/Kg	G-CSF	26%
EMATOLOGIA CT		G-CSF	50%

35%

Stockler-Goldstein	<2x10e6/Kg	CTX+G:	20%
Watts	<1 x 106/Kg	CTX+G	16%
EMATOLOGIA CT		CTX+G	3
MACQUAKER	<2x10e6/Kg	CTX+G	38%

20%

Mollee	<2x10e6/Kg	CTX+VP16	18%
PAVONE	<2x10e6/Kg	DHAP	14%
EMATOLOGIA CT		VP16+G	17%
MACQUAKER	<2x10e6/Kg	G-IVE	12%
LEE	<2x10e6/Kg	ESHAP	8%

15%

Biology of Blood and Marrow Transplantation 14:1045-1056 (2008)

1083-8791/08/1409-0001$32.00/0
doi:10.1016/j.bbmt.2008.07.004

ASBMT American Society for Blood and Marrow Transplantation

Impact of Mobilization and Remobilization Strategies on Achieving Sufficient Stem Cell Yields for Autologous Transplantation

Iskra Pusic, Shi Yuan Jiang, Scott Landua, Geoffrey L. Uy, Michael P. Rettig, Amanda F. Cashen, Peter Westervelt, Ravi Vij, Camille N. Abboud, Keith E. Stockerl-Goldstein, Diane S. Sempek, Angela L. Smith, John F. DiPersio

Se i Poor Mobilizer sono Rimobilizzati Con G-CSF+ Chemio le possibilità Di successo sono limitate (20%).

Il PLERIXAFOR INDUCE INVECE IL SUCCESSO DI UNA SECONDA MOBILIZZAZIONE NELL'80% DI QUESTI PAZIENTI (INDICAZIONE UFFICIALE)

G-CSF +GM-CSF

CHEMIO + G-CSF

PLERIXAFOR + G-CSF

ble 3. *Outcomes of Remobilization*

Remobilization regimen used	G-CSF / GM-CSF N = 217	G/C N = 34	G/P N = 18
First mobilization with G-CSF			
Median $CD34^+$ cell/kg yield	1.1×10^6	0.8×10^6	1.0×10^6
Median apheresis days	4 days	3 days	2.5 days
emobilization			
Median $CD34^+$ cell/kg yield	1.2×10^6	0.9×10^6	4.6×10^6
Median apheresis days	3 days	2 days	2.5 days
Failure rate*	81.6%	73.5%	27.8%
ooled cells (first and second mobilization)			
Median $CD34^+$ cell/kg yield	2.5×10^6	2.1×10^6	5.5×10^6
Median apheresis days	6	7	6
Overall failure rate†	28.1%	47.1%	16.7%

Successso 19%

Successo 17%

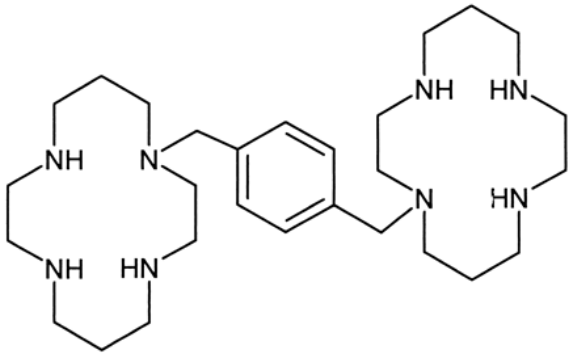
Successo 73%

-CSF indicates granulocyte colony-stimulating factor; G/C, G-CSF + chemotherapy.

$P \leq .001$ comparison among all 3 groups.

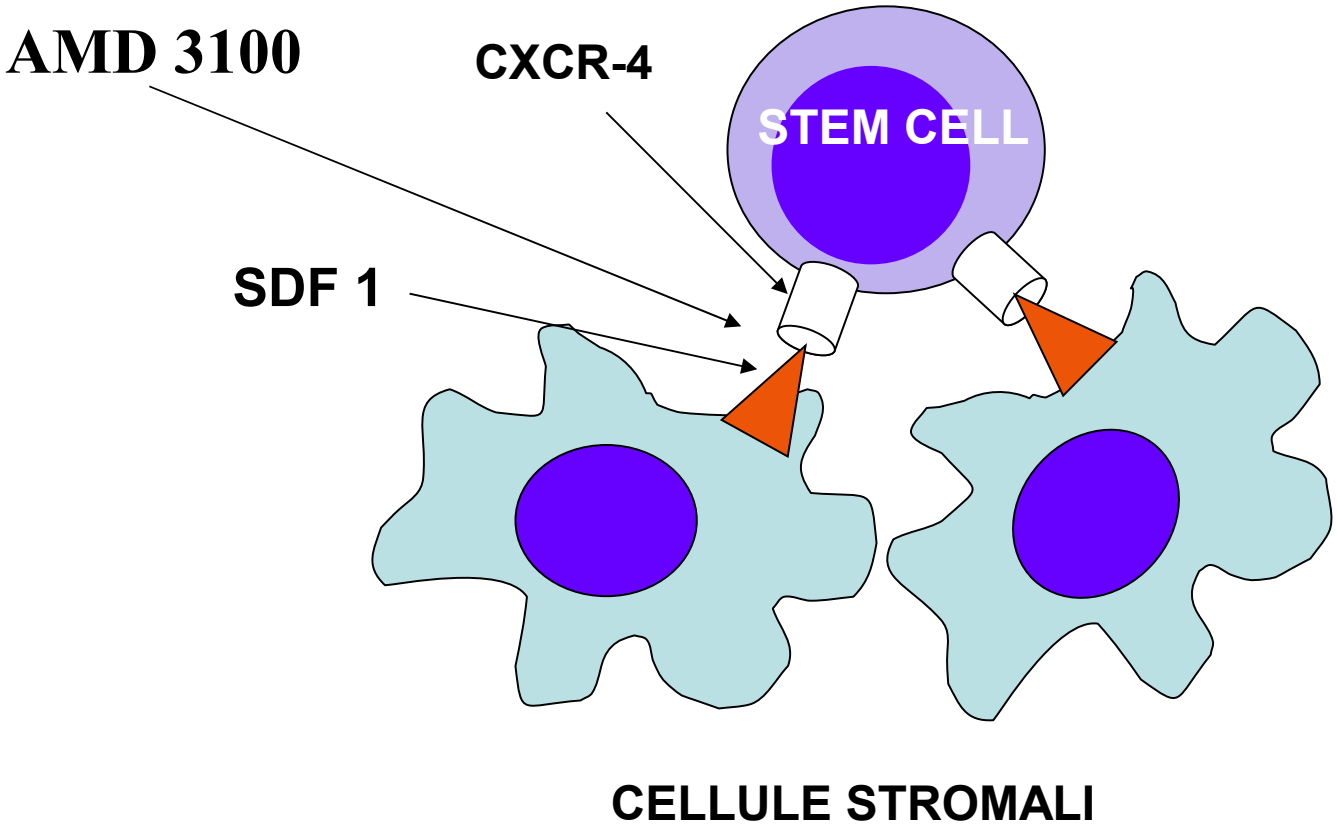
Plerixafor (AMD3100)

- A bicyclam molecule
- Reversible inhibitor of SDF-1α/CXCR4 binding
- Initially developed as an inhibitor of HIV entry into CD4+ cells
- Caused rapid, transient leukocytosis in patients with HIV infection and healthy volunteers, stimulating interest in capacity to mobilize CD34+ cells
- Very water soluble
- Highly charged (plus 4 at physiological pH
- Low molecular weight (MW = 502)

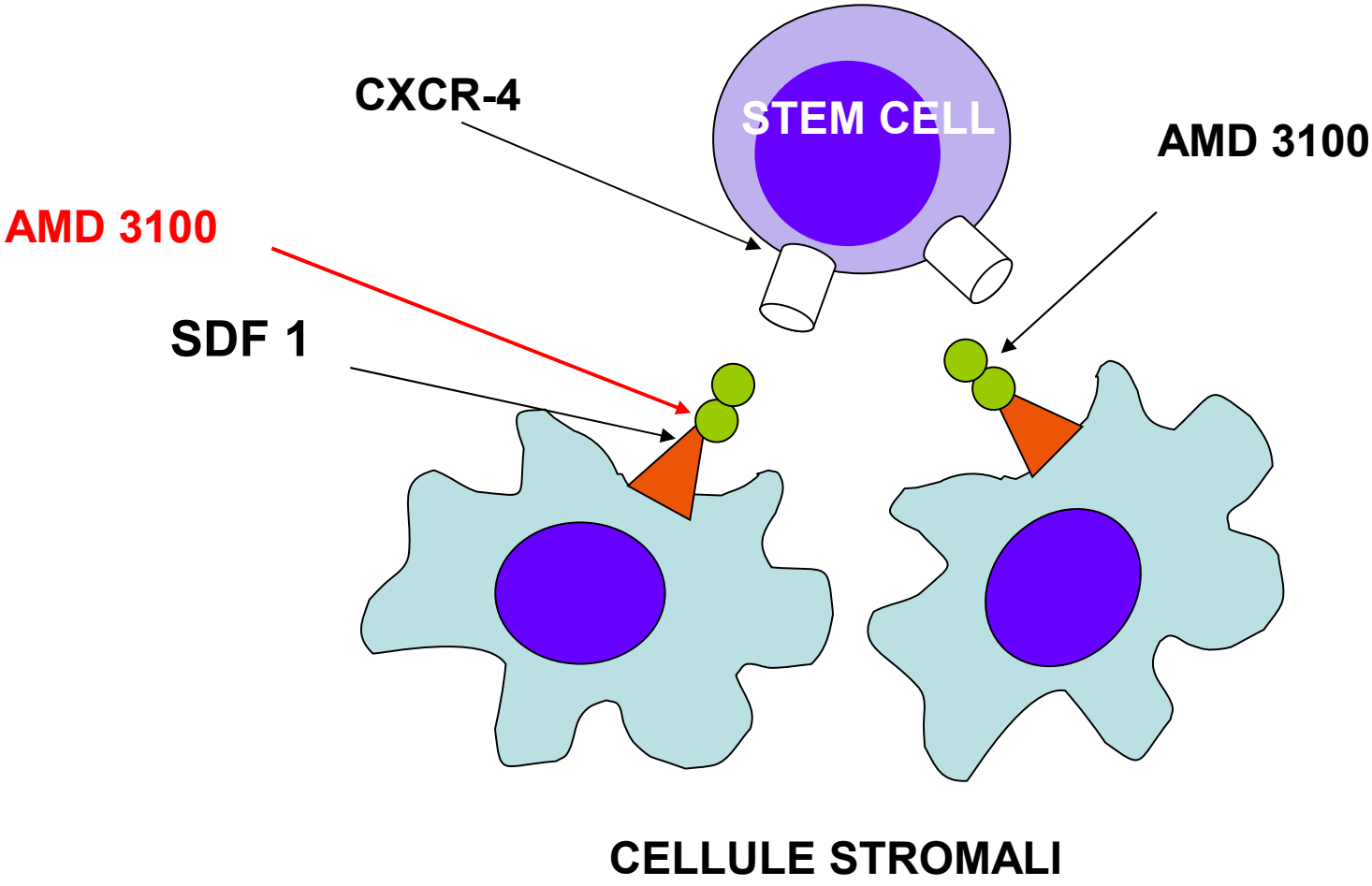


De Clercq E. *Nat Rev Drug Discov*. 2003; 2:581-7.

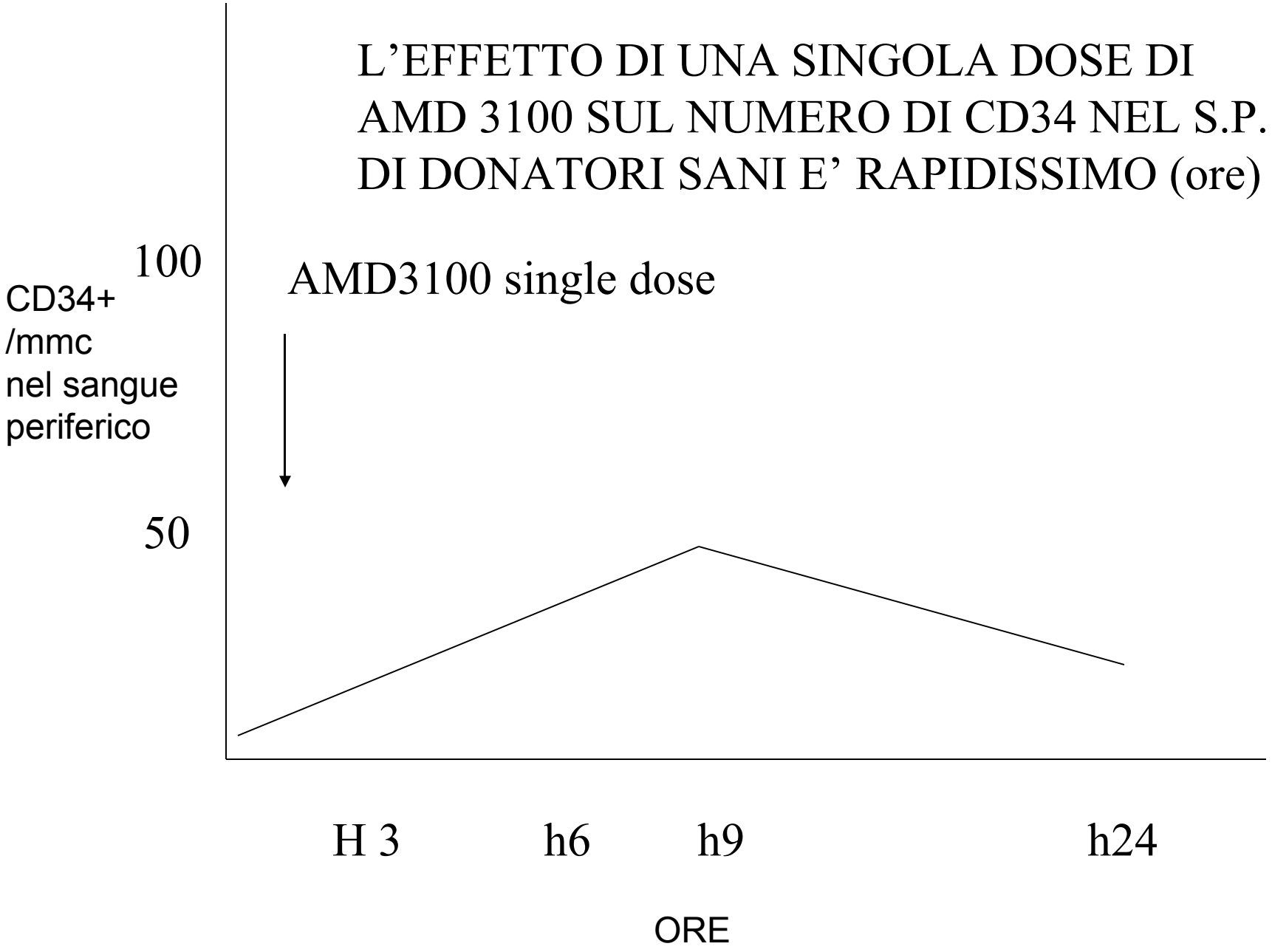
- AMD 3100 è un agente che interfererisce nel legame fra SDF1α presente sulle cellule stromali ed il recettore CXCR-4 presente sulla CSE,
- inibibisce così il legame fra Cellule Stromali e CSE .



Attraverso questo meccanismo AMD 3100 determina un effetto mobilizzante le CSE



L'EFFETTO DI UNA SINGOLA DOSE DI AMD 3100 SUL NUMERO DI CD34 NEL S.P. DI DONATORI SANI E' RAPIDISSIMO (ore)



Modalità di utilizzo di PLERIXAFOR nella mobilizzazione:

c) IN SECONDA LINEA SOLO A CHI FALLISCE ?

G-CSF + PLERIXAFOR Nel 10% dei pazienti che non mobilizza
(indicazione approvata)

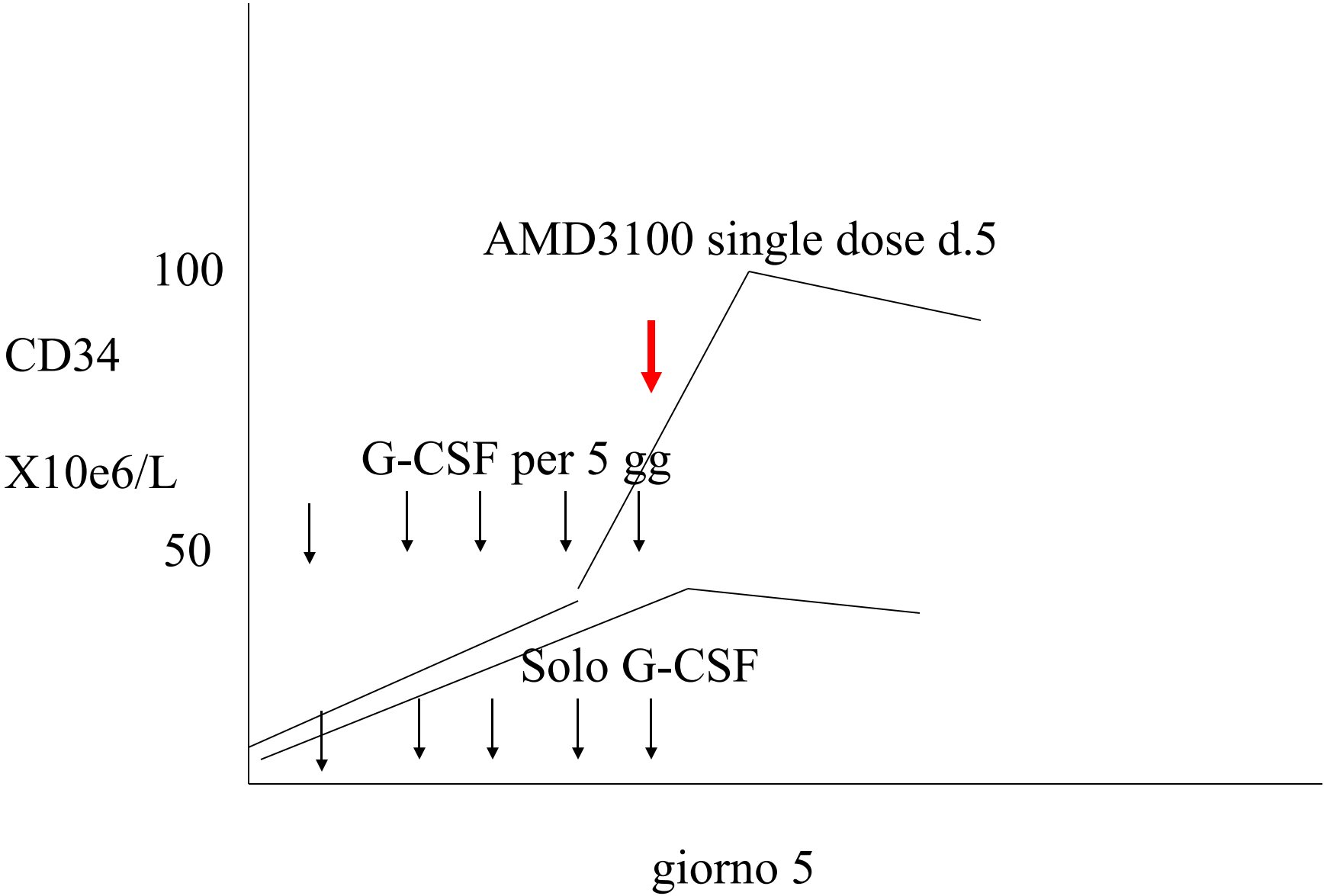
(necessita ri-mobilizzare il paziente)

b) IN PRIMA LINEA A TUTTI ?

G-CSF + PLERIXAFOR (quale rapporto costo-beneficio?)
Indicazione non approvata

c) ON DEMAND (in corsa durante una mobilizzazione che si mostra scarsa)

PER TRAMUTARE IN SUCCESSO UNA MOBILIZZAZIONE CHE SI STA' RIVELANDO UN FALLIMENTO, (si risparmiano i costi per ri-mobilizzare il paziente restringendo comunque il suo impiego solo a casi di dimostrata necessità)
(decidere estemporaneamente sulla base di una conta di CD34
che lascia pensare a una scarsa mobilizzazione, la aggiunta del Plerixafor)


AMD3100 single dose d.5
100
CD34
X10e6/L
G-CSF per 5 gg
50
Solo G-CSF
giorno 5

MOBILIZZAZIONE E RACCOLTA NEL DONATORE SANO

DOSE G-CSF

FRAZIONAMENTO DELLA DOSE

MONITORAGGIO DEL PAZIENTE E RILEVAZIONE EVENTI AVVERSI ALLA MOBILIZZAZIONE E RACCOLTA

TRATTAMENTO E PROFILASSI EFFETTI COLLATERALI

PIANO PER EVENTUALE POSSIBILE MANCATA MOBILIZZAZIONE

Nella mobilizzazione con solo G-CSF DEL DONATORE SANO evidente l'effetto dose-risposta sulla quantità di CD34 raccolte.

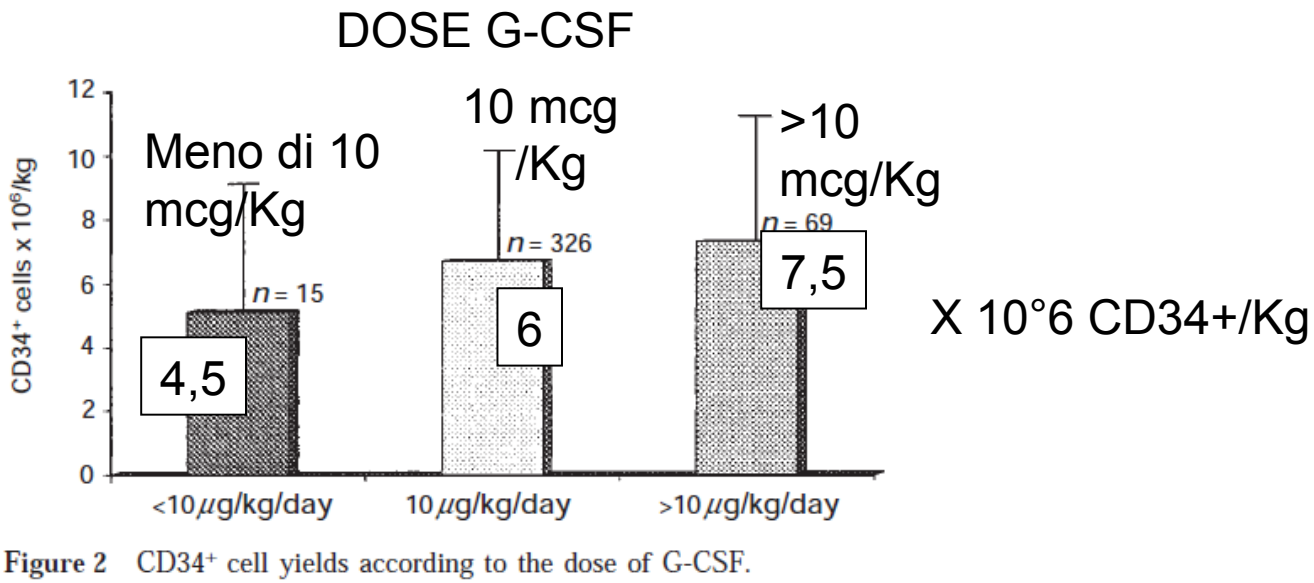


Figure 2 CD34+ cell yields according to the dose of G-CSF.

Dose G-CSF

10 versus 20

The number x 106/kg of CD34+ cells collected after the first apheresis session was higher in group in 20 mcg /Kg (P = 0.0003).
20 mcg/Kg: 5.9 (3.4-10.4), x 10(6)/kg
10 mcg/Kg: 3.1 (1.1-6.8), x 10(6)/kg
Martínez C, .Bone Marrow Transplant. 1999 Dec;24(12):1273-8.

10 versus 24

24 mcg/Kg: 3. 7 x 10(6)/kg recipient BW/apheresis
10 mcg/Kg: 2.0 x 10(6)/kg recipient BW/apheresis
Engelhardt M,

SCHEDULA DI SOMMINISTRAZIONE DEL G-CSF
LA SOMMINISTRAZIONE IN DUE FRAZIONI INDUCE UNA MAGGIORE MOBILIZZAZIONE

1 microg/Kg versus 5 microg/Kg x2

ONE subcutaneous daily injection of 10 microg/kg G-CSF (n = 25) compared with

TWO injections daily of 5 microg/kg

The CD34(+) cell count in the first apheresis was 5.4 x 10(6)/kg donor weight (range 2.8-13.3) in the 2 x 5 microg/kg group compared with 4.0 x 10(6)/kg (range 0.4-8.8) in the 1 x 10 microg/kg group (P = 0.007).

A randomized comparison of once versus twice daily recombinant human granulocyte colony-stimulating factor (filgrastim) for stem cell mobilization in healthy donors for allogeneic transplantation.
Kröger N, Renges H, Krüger W, Gutensohn K, Löliger C, Carrero I, Cortes L, Zander AR.

G-CSF DEL DONATORE SANO

Kröger N, Zander AR.

Department of Bone Marrow Transplantation,
University Hospital Hamburg-Eppendorf, Hamburg, Germany.

Dose between 10 and 16 microg/kg split into two doses is recommended.

Leukapheresis should be performed on day 4 or 5.

A higher dose of G-CSF might be appropriate in donors with low CD34+ baseline cell count (< 2000/ml) or if a high CD34+ cell number is required.

Analgesics, mainly acetaminophen, are sufficient to control the pain

Severe events in donors after allogeneic hematopoietic stem cell donation

Joerg Halter,[1] Yoshihisa Kodera,[2] Alvaro Urbano Ispizua,[3] Hildegard T. Greinix,[4] Norbert Schmitz,[5] Geneviève Favre,[1] Helen Baldomero,[6] Dietger Niederwieser,[7] Jane F. Apperley,[8] and Alois Gratwohl[1] for the European Group for Blood and Marrow Transplantation (EBMT) activity survey office

They had performed a total of 51,024 first allogeneic hematopoietic stem cell transplantations, of which 27,770 were bone marrow and 23,254 peripheral blood. They observed five donor fatalities, one after a bone marrow donation and four after peripheral blood donation

severe adverse events
12 in bone marrow donors (4.32/10,000;)
25 in peripheral blood donors (10.76/10,000;;
$p<0.05$)

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

EVENTI AVVERSI SEVERI DELLA DONAZIONE DI PBSC

Sono molto rari

Possono avvenire **PRIMA** **DURANTE** e **DOPO** la donazione

PRIMA (NELLA FASE DI MOBILIZZAZIONE)

DURANTE LA AFERESI

DOPO LA DONAZIONE

- ACUTE LUNG INJURY
- SPLENIC RUPTURE
- CNS HAEMORRHAGE
- STROKE
- CARDIAC ARREST or other CARDIAC EVENTS
- SICKLE CELL CRISIS
- CAPILLARY LEAK SYNDROME
- UNEXPECTED THROMBOCYTOPENIA

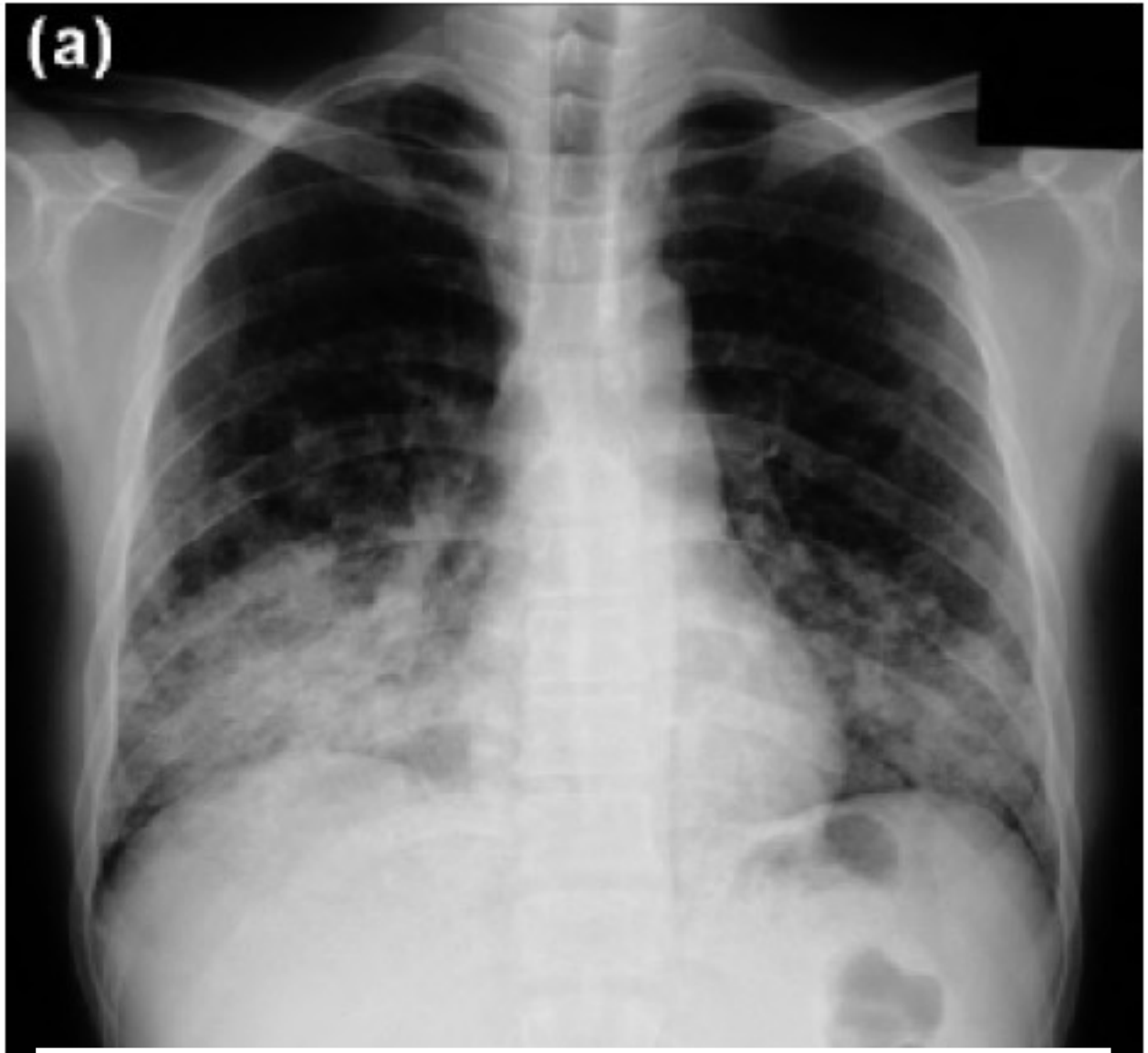
With the increasing use of GCSF,
it is important to be aware of this potentially fatal complication and to educate both clinicians and patients to watch out for signs and symptoms that might be a clue to possible splenic rupture.

In six cases, splenic rupture occurred between day 5 to day 10
after initiation of G-CSF therapy,
but ***in three cases, it occurred as early as day 2 and 3.***

Rotture di milza:

prima dell'aferesi
o
dopo l'aferesi

In four of the cases (including our case), the ***rupture occurred 1–3 days following leukapheresis.***



Acute Lung Injury in a Healthy Donor during Mobilization of Peripheral Blood Stem Cells Using Granulocyte-Colony Stimulating Factor Alone
Haematologica 2005; 90:(3)e27-e29 *Kosei Arimura,1*

PaO2 of 53.8 mmHg

WBC, 28,900 /μL

on Day 4 of G-CSF
administration revealed
marked
infiltrative shadows
in bilateral lung fields,
particularly in
the lower lobes

A ruptured blood vessel
and active bleeding was discovered during the operation
subdural to the left temporal lobe.
The histopathologic diagnosis after the operation was consistent with vascular malformation and subdural hemorrhage
at the left temporal
lobe (Figure 2).

On the **evening of the fifth day,**
the donor developed a
headache,

which was intermittent and of mild intensity,

accompanied by nausea and vomiting

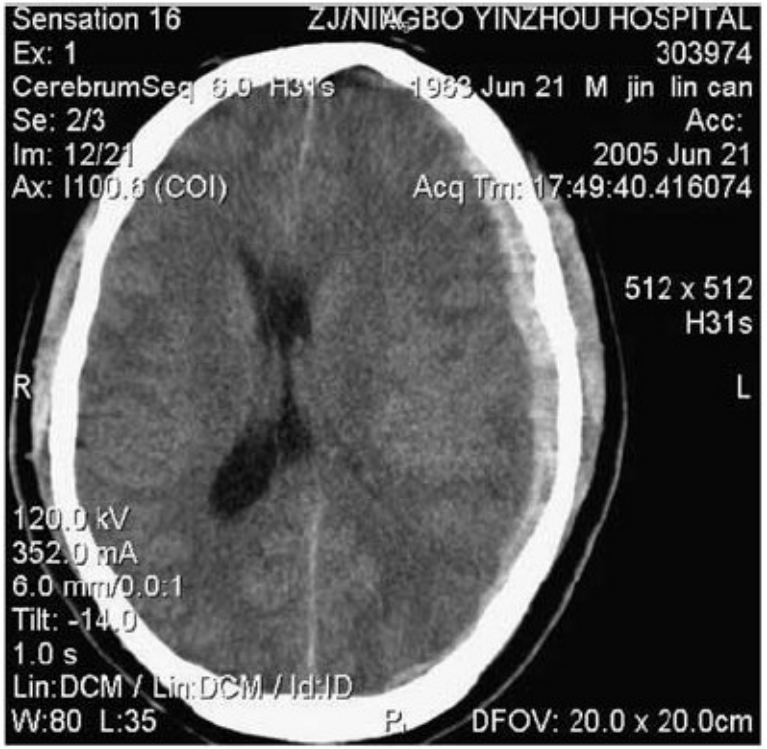


Figure 1 The second head computerized tomography scanning showing the enlarged subdural hematoma.

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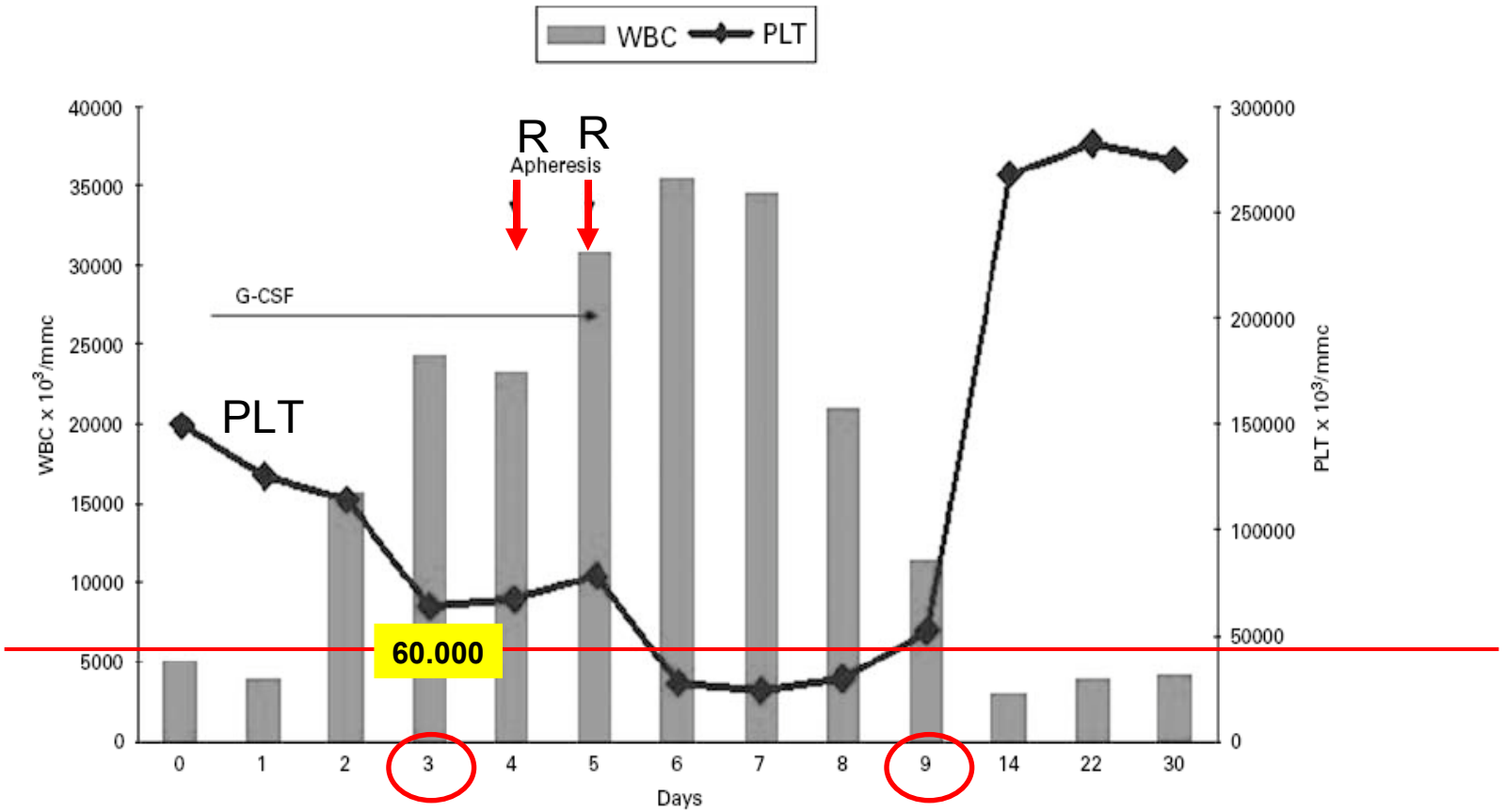
Another donor, a 40-year-old Caucasian female, developed typical immune thrombocytopenic purpura
a

Bone Marrow Transplantation (2008), 1–2

www.nature.com/bmt

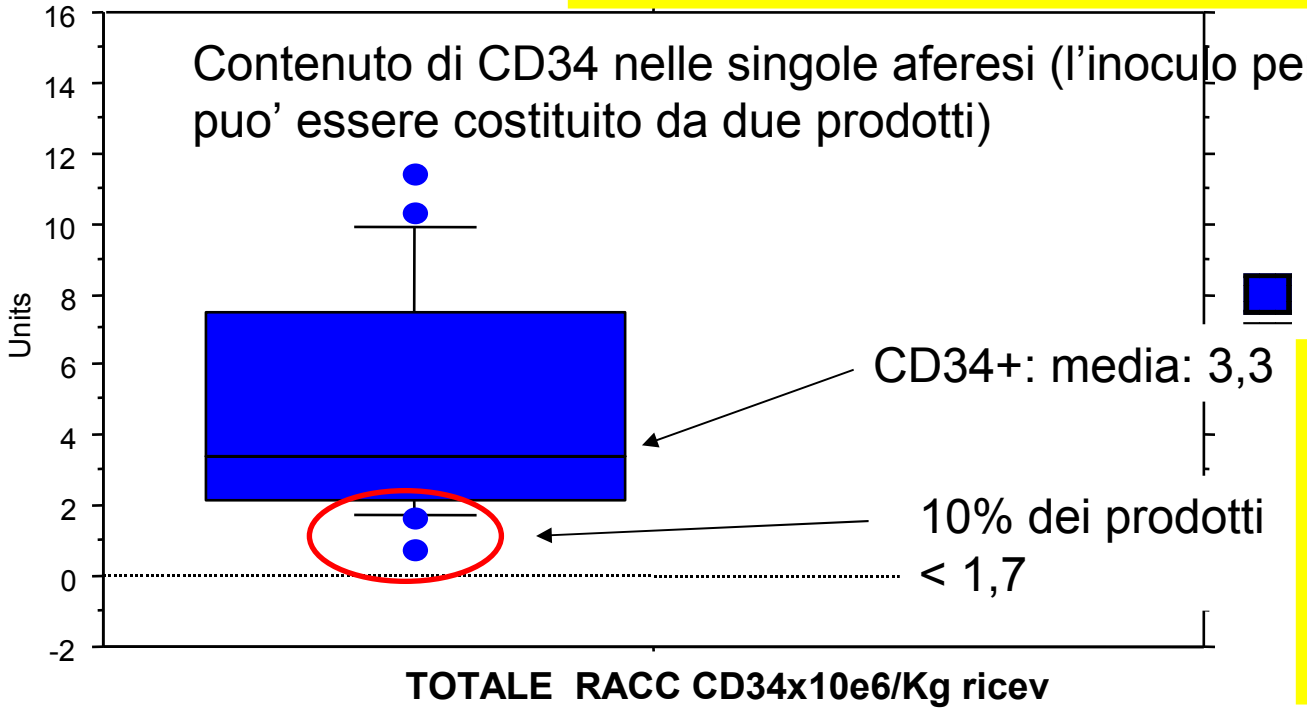
LETTER TO THE EDITOR

G-CSF-induced thrombocytopenia in a healthy donor



WBC and plt counts during G-CSF administration and apheresis procedure. plt recovery is also indicated.

IL 10% DELLE HPC-A ottenute da vari centri di raccolta (tramite IBMDR) HA UN CONTENUTODI CD34+ NON OTTIMALE



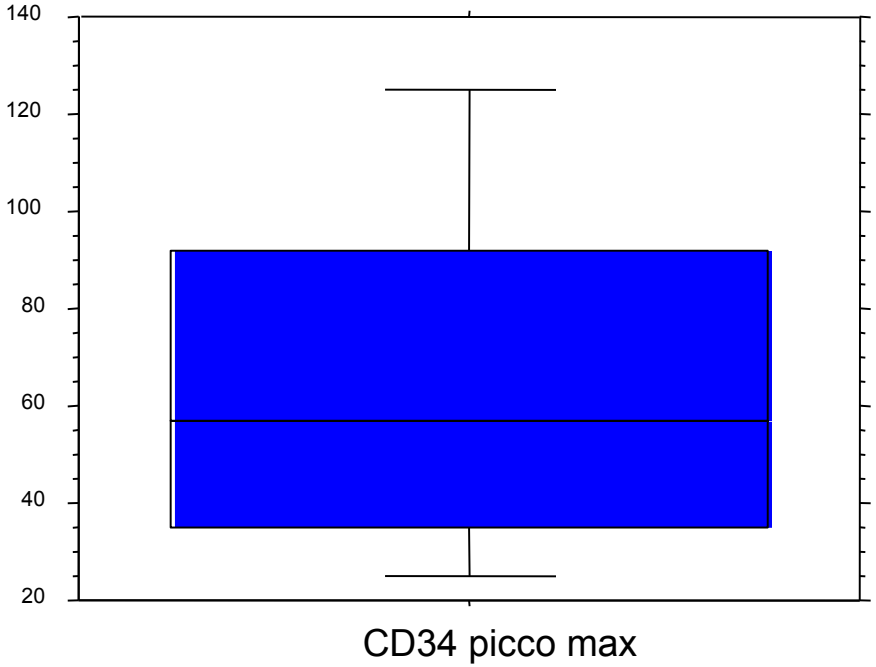
Se in media il contenuto di CD34+ dei prodotti arrivati a noi è di
3,3 x 10°6/Kg
Tuttavia nel 10% è Inferiore a 1,7 x 10°6

PERCENTILI

		TOTALE RACC CD34x10e6/Kg ricev: CD34 X10e6/Kg	
10	#	1,760	#
25	#	2,125	#
50	#	3,385	#
75	#	7,470	#
90	#	9,900	#

ENTITA' DELLA MOBILIZZAZIONE NEL DONATORE SANO (il 10% sono poveri mobilizzatori hanno un picco < 25 mmc)

PROGRAMMA DI TRAPIANTO CIC 792 CATANIA



%	CD34 picco max
10	25,200
25	35,050
50	57,100
75	92,150
90	125,000

CD34/ mmc

Descriptive Statistics
Split By: provenienza aferesi

	età, Total	età, esterna	età, interna
Mean	36,009	33,300	36,400
Std. Dev.	16,189	8,486	16,848
Std. Error	1,572	2,683	1,729
Count	106	10	95
Minimum	7,000	22,000	7,000
Maximum	75,000	46,000	75,000
# Missing	12	12	0

Results for totals may not agree with results for individual cells because of missing values for split variables.

A giudicare dal picco di CD34+ nel S.P. lo scarso contenuto di CD34 per alcune aferesi è attribuibile a scarsa mobilizzazione (basso picco CD34+) Piuttosto che a scarsa cellection efficiency

ANCHE NEL DONATORE SANO È POSSIBILE UNA RACCOLTA "POVERA" DI PBSC PER RIDOTTA MOBILIZZAZIONE

INCIDENZA 0.5 - 4%

Fattori di rischio:

- sesso femminile (rapporto M/F a favore del M nei registri MUD)
- eta' (eta' piu' elevata nei donatori familiari rispetto MUD)
- basso indice massa corporea
- Dose G-CSF
- PLT basali
- Razza bianca (versus ispanici, asiatici e nella razza nera)

PIANO DI EMERGENZA PER DONATORE ALLOGENICO POOR MOBILIZER

SE PROCEDURA DI MOBILIZZAZIONE (DUE AFERESI)
HANNO UN TOTALE DI CD34 < 2 X10E6/KG
ED IL RICEVENTE E' STATO GIA' SOTTOPOSTO A TERAPIA DI CONDIZIONAMENTO

NESSUN altro provvedimento (se CD34 > 1.5 x10e6/Kg) ??

ESPIANTO di midollo aggiuntivo (provvedimento consueto se CD34 < 1 x 10e6/Kg)

BACK UP autologo criopreservato ????

Da considerare:

PLERIXAFOR al 4°g. di nuova mobilizzazione con G: (G-CSF+PLERIXAFOR)
PLERIXAFOR on demand in corso della prima fallita mobilizzazione
(dopo 1 o 2 aferesi insufficienti condotte a +4 o +5)
somministrato prima della seconda o terza aferesi (giorno +6)
(INDICAZIONE NON APPROVATA necessita approvazione Comitato Etico sec. 648).

Conclusioni:

La esperienza nella raccolta di HPC-A è vasta, tuttavia il processo di mobilizzazione necessita ancora di essere ottimizzato allo scopo di migliorare i risultati del trapianto allogenico.

Gli effetti della dose non solo di CD34 ma anche di altre cellule sulla prognosi dopo trapianto autologo e allogenico attendono ancora di essere chiariti o confermati.

L'utilizzo di nuovi farmaci costituisce un motivo di interesse per nuovi studi e potrebbe essere risolutore sul problema delle scarse raccolte nel trapianto autologo e allogenico.