SIdEM
Società Italiana di Emaferesi e Manipolazione Cellulare

Definizione e gestione del "predicted e proven poor mobilizer"

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Background

- Autologous stem cell transplantation (ASCT) is a mainstream therapy for patients with lymphoma or multiple myeloma (MM) and allogeneic HSCT still remains the most powerful anti-leukemic tool
- **All autologous and three quarters of allogeneic transplants are performed using mobilized HSC (CIBMTR reports).**
- Mobilization of PBSC fails in a relevant portion of patients (5 to 30% of Poor Mobilizers)
- Definition of "poor" or "failed" mobilization is very heterogeneous

Is there an optimal dose of CD34+ cells to be collected for a safe ASCT?

- The **minimal threshold** CD34+ cell dose to be infused is agreed to be ≥ 2-2.5 million CD34 cells/kg for a single ASCT.
- The **optimal dose** for ideal platelet recovery is 4–6 million CD34 cells/kg.
- Reinfusion of high doses of $CD34^+$ cells is associated with:
- long term stable engraftment
- fast platelet and neutrophil engraftment
- reduction in the need for supportive measures, leading to a significant cost sparing
- reduced toxicity and increased survival rates

Factors That Influence Collection and Engraftment of Autologous Peripheral-Blood Stem Cells

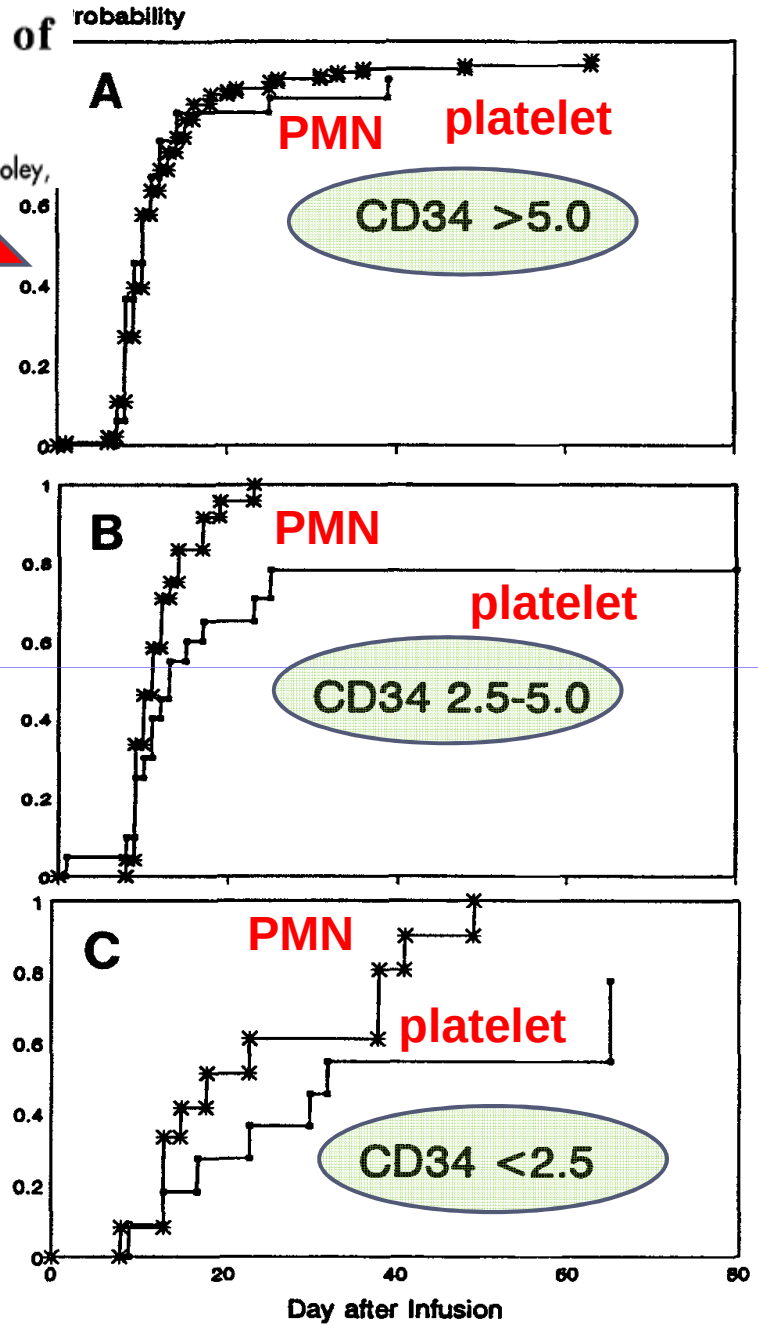
By William Bensinger, Fred Appelbaum, Scott Rowley, Rainer Storb, Jean Sanders, Kathy Lilleby, Ted Gooley,

J Clin Oncol 13:2547-2555. © 1995

tempo of PMN engraftment was indistinguishable between patients who received 2.5 to 5.0 and >5.0 x 10e6 CD34+ cells/kg.

In contrast, the probabilities for achieving platelet independence were distinct for each cell dose level

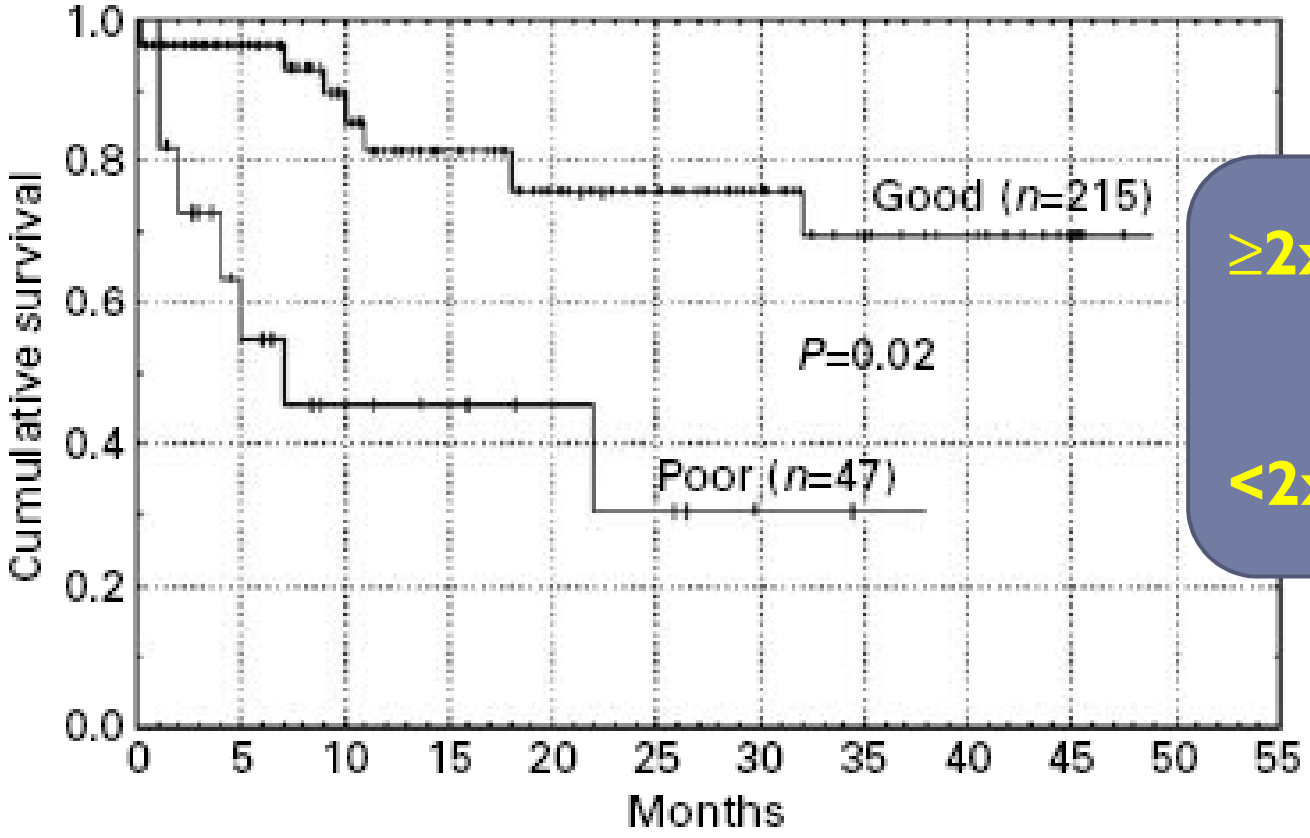
CD 34+ dose



Poor mobilization is an independent prognostic factor in patients with malignant lymphomas treated by peripheral blood stem cell transplantation

V Pavone[1,2], F Gaudio[1], G Console[3], U Vitolo[4], P Iacopino[3], A Guarini[1], V Liso[1], T Perrone[1]

Bone Marrow Transplantation (2006) 37, 719–724



≥2x10e6/kg CD34+

<2x10e6/kg CD34+

Overall survival in 262 patients with malignant lymphoma: good and poor mobilizers

How to identify the“poor mobilizer” ?

✓different parameters proposed to evaluate the extent of mobilization:

✓absolute increase (peak) of CD34+ cells in PB

✓fold increase of CD34+ cells in PB

✓cumulative aphaeresis yield*

✓ percent candidate patients undergoing ASCT

✓transplant outcome

✓ *in a single attempt or with a pre-fixed number of aphaeresis days)

Possible defects causing poor mobilization

- 1)insufficient number of HSC due to HSC intrinsic factors,
- 2) insufficient HSC number due to low number or defective niches,
- 3) inadequate number or response of effector/supporter cells such as BM macrophages or β-adrenergic nerves
- 4) technical reasons (inadequate dose of G-F or timing…)
- ***…..these possible defects are not mutually exclusive***

Effect of underlying disease

BM involvement is associated with poor yields

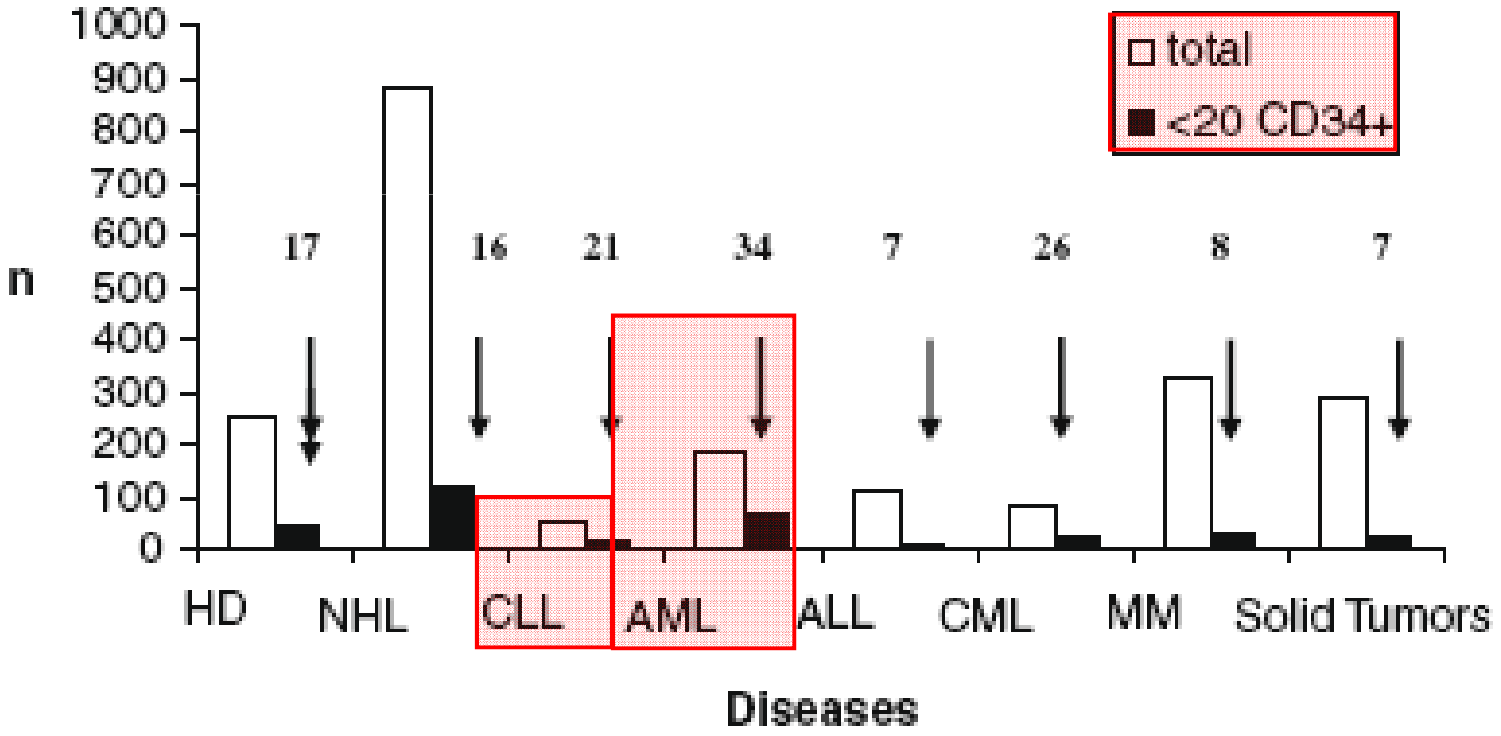
Impairment of healthy niches by malignant cells in the BM or direct competition between HSC and malignant cells for a limited number of niches.

Indolent lymphoproliferative disease , and acute leukemia have been identified as independent risk factors.

Management of poor peripheral blood stem cell mobilization: Incidence, predictive factors, alternative strategies and outcome. A retrospective analysis on 2177 patients from three major Italian institutions ☆

Paolo Perseghin [a,*], Elisabetta Terruzzi [b], Maria Dassi [a], Valentina Baldini [a], Matteo Parma [b], Paola Coluccia [c], Patrizia Accorsi [d], Giorgio Confalonieri [a], Luisa Tavecchia [a], Luisa Verga [b], Fernando Ravagnani [c], Antonio Iacone [d], E.M. Pogliani [b], Pietro Pioltelli [b]

Overall incidence of PM: 15%



Transfusion and Apheresis Science 41 (2009) 33–37

3.1. Incidence of poor mobilizers

A total of 2177 adult patients who were mobilized in the three participating institutions (Table 2) with different mobilization regimens were retrospectively investigated to determine the percentage of individuals who failed to reach a threshold of at least 20 CD34+ cells/μL and, among them, those who subsequently failed to achieve a minimum CD34+ cell dose of 2×10^6/Kg/BW in a single mobilization attempt. A wide range of PM was observed in different diseases (Fig. 1). Overall, 335 out of 2177 patients (15%) failed to reach 20 CD34+ cells/μL, Monza, Milan and Pescara had 21%, 13% and 14% of PM amongst their patient

Effect of prior treatment

Mobilization failure correlates with the number of prior lines of treatment

- Most cytotoxic treatments and molecules utilized in targeted therapies can have deleterious effects on HSC and the niches.
- DNA cross-link agents such as melphalan or carmustine and purine analogs such as fludarabine associated with high risk of mobilization failure (Stem Cell Poisons).
- Repetitive cycles of chemotherapy may also damage niches for HSC and BM macrophage effector cells

Lenalidomide and Poor mobilization

- Lenalidomide may suppress HSC motility similar to the way it reduces the motility of marrow endothelial cells in multiple myeloma.

- The antiangiogenic effect of lenalidomide could also impair mobilization

Prior radiotherapy

- Prior radiotherapy to significant amounts of red marrow associated with mobilization failure , due to several combined effects:
- direct HSC toxicity
- niche toxicity and toxicity to the niche supporting cells.

Radiotherapy may also increase the expression of protease inhibitors such as α1-antitrypsin that would diminish the protease storm during mobilization.

Age-related poor mobilization

- Poor mobilization is often noted in patients over 60yrs
- Possible mechanisms:
- age related 'senescence' of HSC due to progressive telomere shortening.
- reduction in the HSC reserve due to decreased niche function with depletion of mesenchymal stem cells and osteoprogenitors.
- aging is associated with a decrease in bone formation and osteoblast numbers, so endosteal osteoblastic niches for HSC are likely to be reduced

Failed mobilization in patients with no obvious risk factors: constitutive poor mobilizers

- Up to **5% of healthy donors fail to mobilize** with conventional regimens, and some patients with no obvious risk factors will also. …..
- The mechanisms understanding of these 'constitutive poor mobilizers' are uncertain ……..

- ***several loci linked to poor mobilization have been identified in mice*** (polymorphisms of genes encoding GCSFR, adhesion molecules (VCAM-1, CD44) and chemokines (SDF-1)

How to select in the current clinical practice "poor mobilizers" or patients at risk of poor mobilization candidate for a rescue procedure?

The International Myeloma Working Group "consensus guidelines regarding the current status of SC collection and ASCT for MM and the role of Plerixafor

Table 4

Risk factor		
Age	Patients over 60 years of age have inferior stem cell mobilization	Consider plerixafor mobilization
Melphalan exposure	Melphalan exposure has traditionally been associated with poor stem cell collection	Observation needs to be confirmed in the context of novel therapies. Current practice of avoiding melphalan should continue until studies performed In patients with history of melphalan exposure consider upfront chemomobilization or plerixafor
Extensive prior therapy or prolonged disease duration	Collection failures are associated with disease duration and extent of prior therapy	Consider harvesting early in the course of the disease even in patients opting out of early high-dose therapy consolidation Consider upfront plerixafor or chemomobilization Assess marrow for secondary dysplastic changes before to collection (that is, morphology and cytogenetics)
Extensive radiotherapy to marrow bearing tissue	Collection failures increase	Consider collection before radiotherapy Consider upfront plerixafor or chemomobilization Assess marrow for secondary dysplastic changes before collection (that is, morphology and cytogenetics)

Giralt S.
Leukemia 2009

Rescue Procedure with Plerixafor: when and for who?

- ✓ Patients who failed to collect ≥ 0.8 x 10^6 $CD34^+$ cells/kg after 2 days of apheresis (??)
- ✓ or <2 x 10^6 $CD34^+$ cells/kg in 4 apheresis days
- ✓ or patients planned for tandem ASCT and did not collect ≥ 4 x 10^6 $CD34^+$ cells/kg in ≤ 4 apheresis days
  - *….were given the option to participate in an open-label rescue procedure*

Dipersio JF, et al. JCO. *2009 Aug 31.*

ORIGINAL ARTICLE

Safety and efficacy assessment of plerixafor in patients with multiple myeloma proven or predicted to be poor mobilizers, including assessment of tumor cell mobilization

G Tricot[1], MH Cottler-Fox[2] and G Calandra[3]

Bone Marrow Transplantation (2010) 45, 63–68

The study consisted of two phases:

1- the first phase included patients proven to be poor mobilizers (group A): previous mobilization failure (harvest<2x10e6 CD34+/kg)

2-the second phase included patients who were predicted to be poor mobilizers (group B):

a-extensive earlier chemotherapy

b-pre-mobilization plt count<100,000/mcl

c-CD34+ peak<12/mcl during mobilization

Poor Mobilization of Hematopoietic Stem Cells—Definitions, Incidence, Risk Factors, and Impact on Outcome of Autologous Transplantation

Patrick Wuchter,[1,*] Dan Ran,[1,2,*] Thomas Bruckner,[3] Thomas Schmitt,[1] Mathias Witzens-Harig,[1] Kai Neben,[1] Hartmut Goldschmidt,[1] Anthony D. Ho[1]

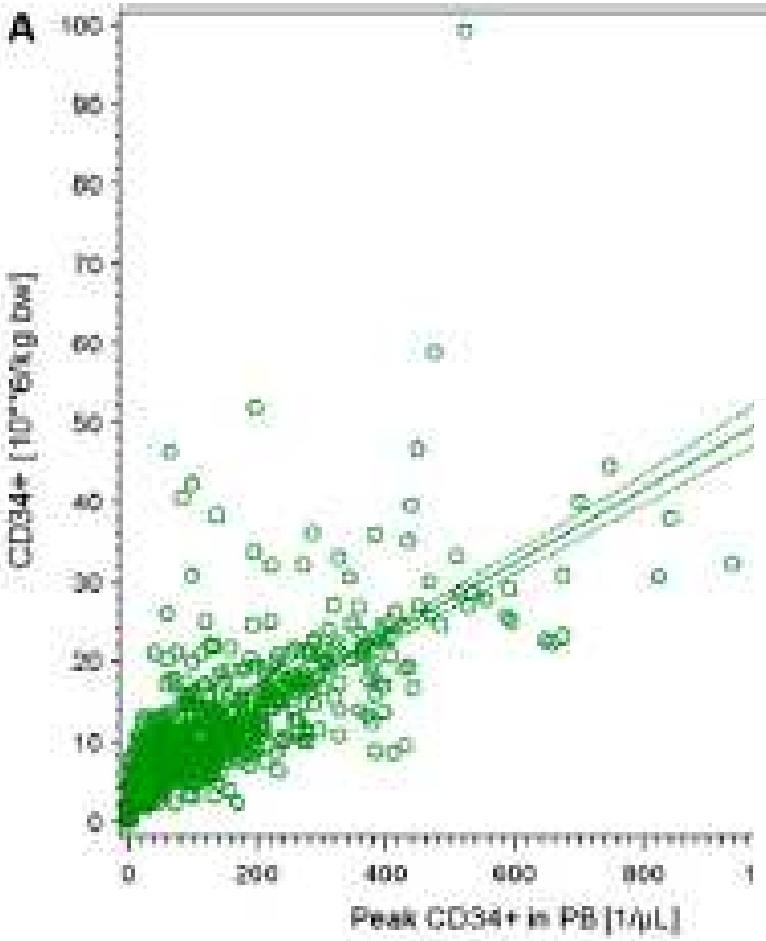
- Of the 840 patients with Lymphoma or Myeloma, **29 (15%)** were considered PMs
- **defined as** patients who had a peak concentration of <20/mcl of CD34+ cells upon stimulation with G-CSF (**dose ?**) + CHT *appropriate* (….)
- *38 (4.5%) patients had CD34+ levels between 11-19/mL defined as "borderline" PM*
- *49 (5.8%) patients had CD34+ levels between 6-10/mL, defined as "relative" PM*
- 42 patients (5%) with levels of 0-5/mL, defined as "absolute" PM

Biol Blood Marrow Transplant 16:490-499, 2010

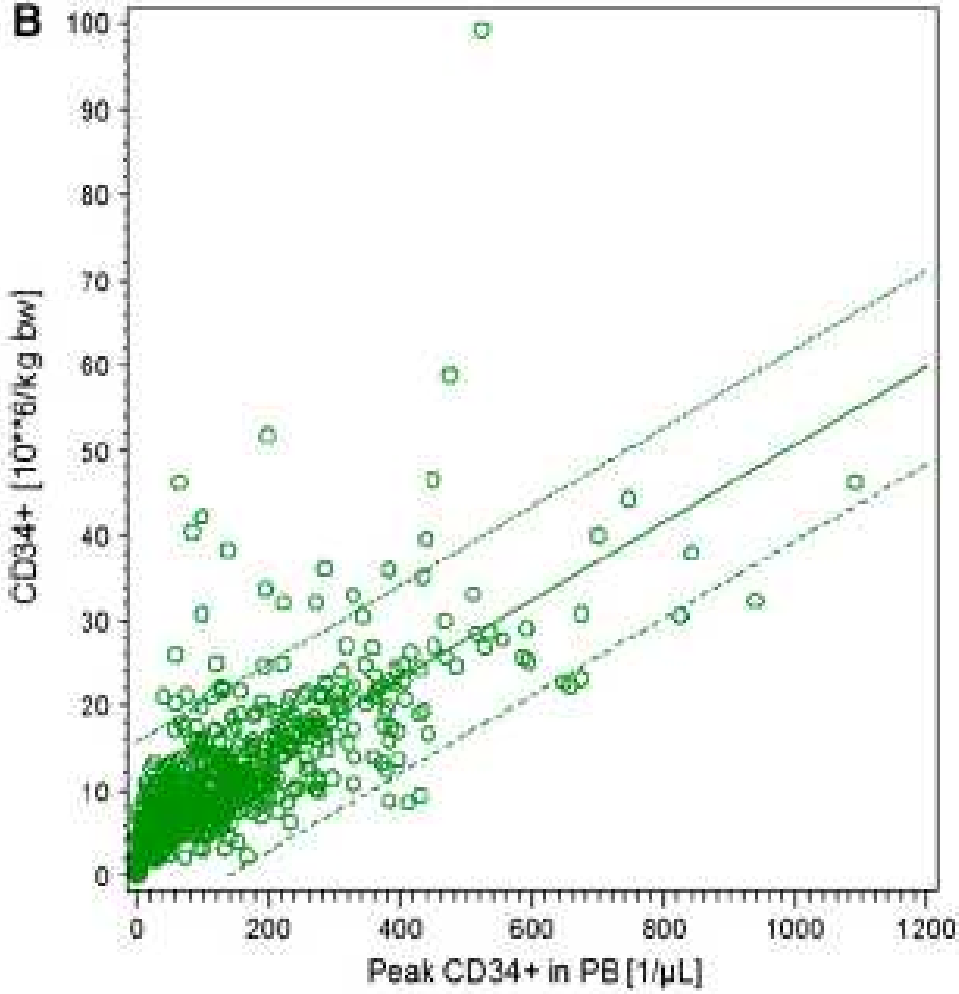
Correlation between peak CD34+ in PB and harvested CD34+ cells

Biol Blood Marrow Transplant 16:490–499, 2010

mean predicted values



individual predicted values.



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

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

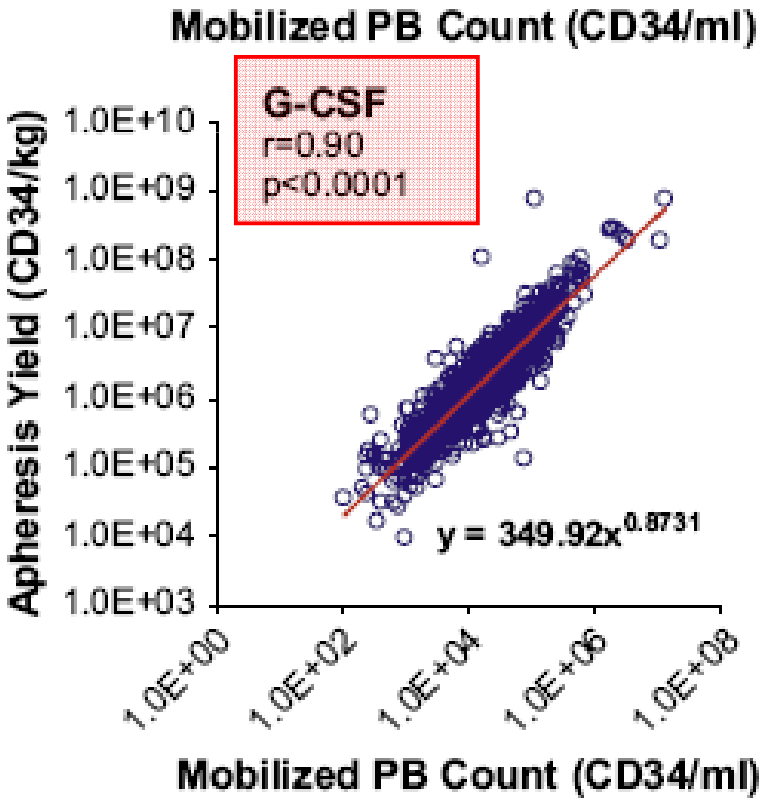
Iskra Pusic, Shi Yuan Jiang, Scott Landua, Geoffrey L. Uy, Michael P. Rettig, Amanda F. Cashen, Peter Westervelt, Ravi Vij, Camille N. Abboud, Keith E. Stockerl-Goldstein, Diane S. Sempek, Angela L. Smith, John F. DiPersio

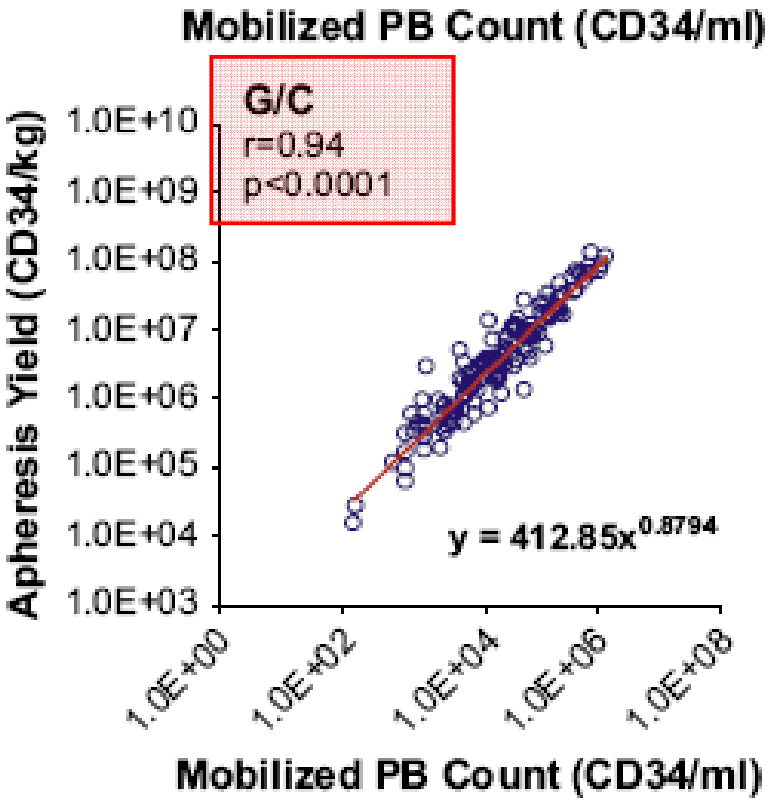
- **Retrospective study of 1040 lymphoma/MM patients who mobilized for ASCT**
- **976 pts received G-CSF alone and 64 G-CSF plus CHT**
- **19% failed to collect ≥ 2 10e6 CD34+ cells/kg after ≥ 5 aphaereses**
- **Only 23% of remobilized patients achieved ≥2 10e6 CD34+ cells/kg and 30% failed to pool sufficient number of stem cells from both collections.**

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

correlation between CD 34+ peak in PB and CD 34+ in the harvest





The GITMO-WG project

GOALS

Make the best decision about definition of poor mobilizer: (proven or predicted PM)

MOTIVATIONS

Increase ASCT feasibility

Avoid delay to transplantation)

Avoid side effects of remobilization

Reduce time to engraftment

Optimizing resource use

CRITERIA

Criteria for "Poor Mobilizer"

Open

Bone Marrow Transplantation (2011), 1–10

www.nature.com/bmt

ORIGINAL ARTICLE

Proposed definition of 'poor mobilizer' in lymphoma and multiple myeloma: an analytic hierarchy process by *ad hoc* working group Gruppo italianoTrapianto di Midollo Osseo

A Olivieri[1], M Marchetti[2], R Lemoli[3], C Tarella[4], A Iacone[5], F Lanza[6], A Rambaldi[7] and A Bosi[8] on behalf of the Italian Group for Stem Cell Transplantation (GITMO)

The GITMO-WG Consensus Process

- Formulating a definition of "PM" valid in different clinical scenarios; a potential endpoint for prospective clinical trials comparing different mobilization strategies.
- To achieve this goal, the GITMO-WG choose to support the decision making process with AHP.

- **The Analytic Hierarchy Process (AHP)** allows complex decisions to be made by using a multistep process that creates a hierarchy of criteria.
- It has been applied in hemato-oncology to develop criteria of response or resistance (Barosi 2007 Leukemia).

Leukemia (2007) 21, 277–280

www.nature.com/leu

ORIGINAL ARTICLE

A unified definition of clinical resistance/intolerance to hydroxyurea in essential thrombocythemia: results of a consensus process by an international working group

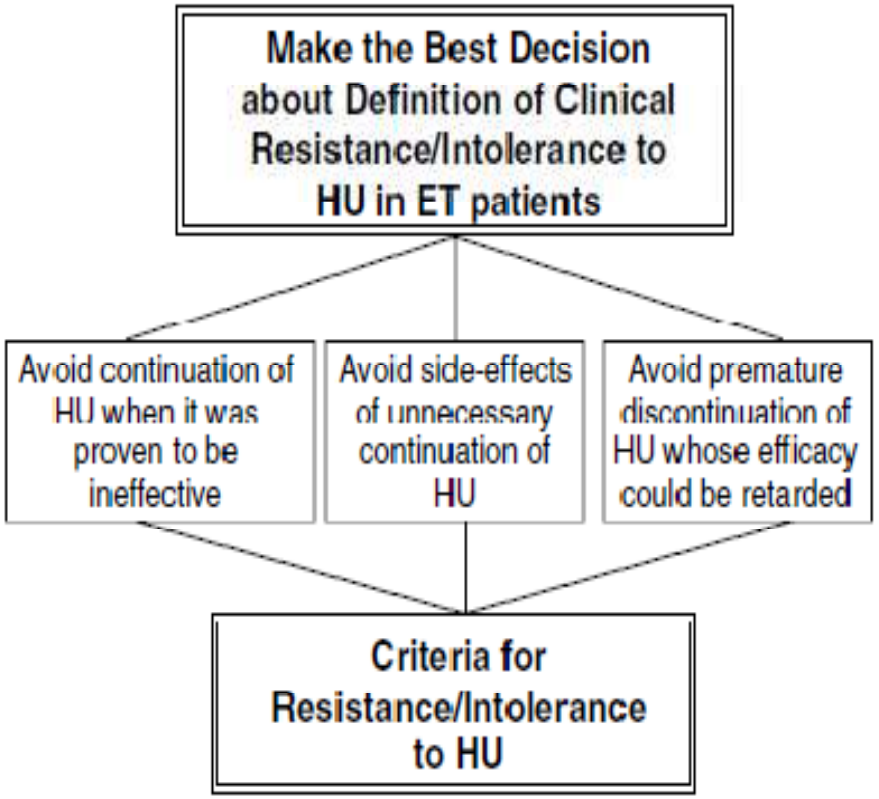
G Barosi[1], C Besses[2], G Birgegard[3], J Briere[4], F Cervantes[5], G Finazzi[6], H Gisslinger[7], M Griesshammer[8], L Guglietta[9], C Harrison[10], H Hasselbalch[11], E Lengfelder[1]

1) Definition of the goal

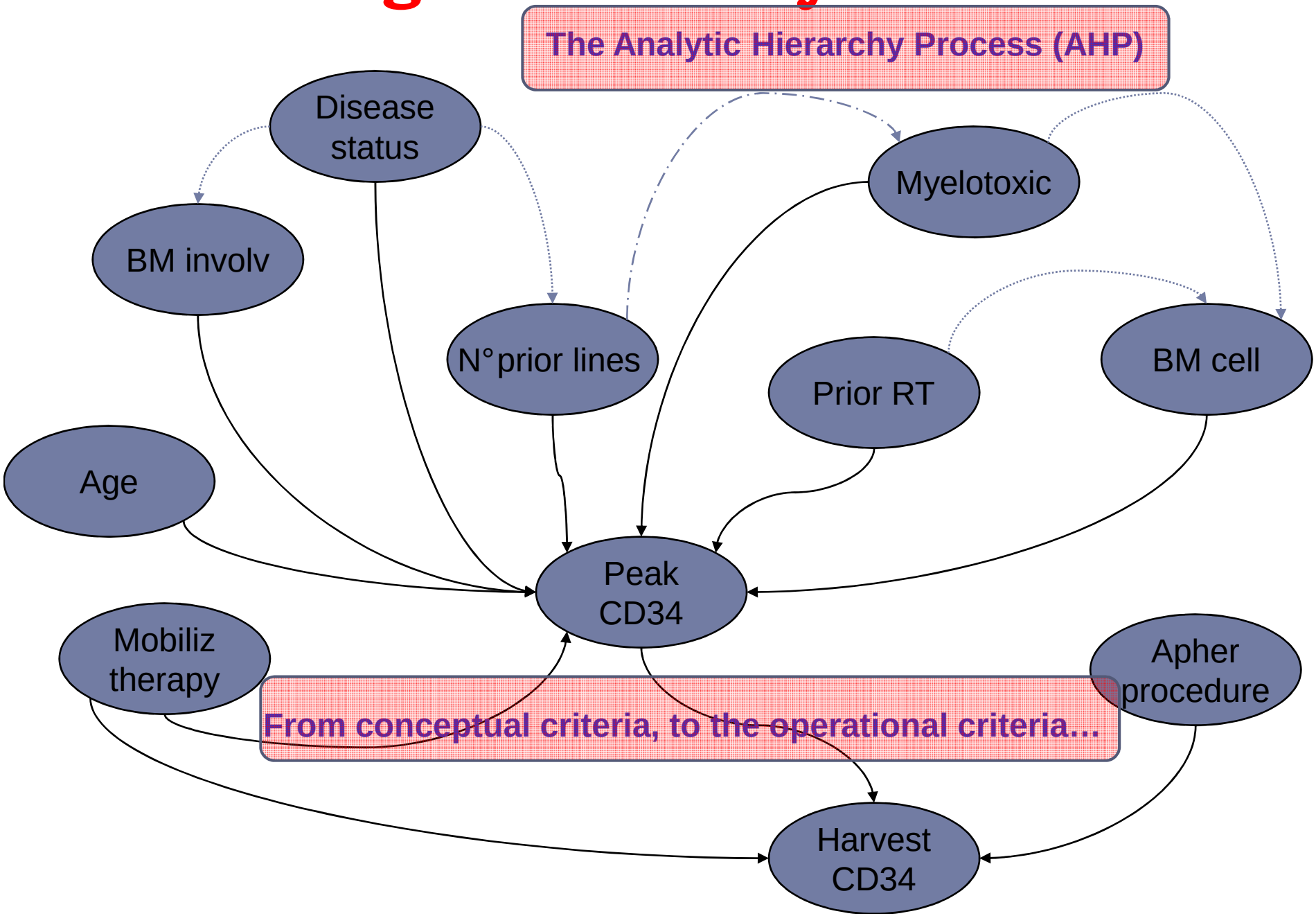
2) decomposing the problem identifying critical issues;

3) categorizing/framing the main criteria

4) defining a hierarchy of the criteria



Creating a hierarchy of criteria



Outline of the AHP-1

- The participants first framed the conceptual criteria, then the operational criteria.
- They are qualitative and quantitative criteria, respectively. *For instance, "old age" is a conceptual criterion, while "older than 65 years" is an operational criterion*
- The participants are forced to quantify their judgments by pairwise comparisons among the decided criteria.
- Conceptual criteria are selected if there is >80% agreement among the participants. (1rst questionnaire)

Outline of the AHP-2

- Each participant analyzed 55 couples of operational criteria and assigned a relative weight of one criterion with respect to the other one (2nd questionnaire):
- if the former criterion was judged to have a higher importance than the latter, a weight from 1 to 9 was indicated;
- if the former criterion was less important than the latter, a weight from 1/9 to 1 was indicated.
- Inter-participant standardized geometric means of the weights for each criterion were calculated, and, subsequently, inter-participant means were also calculated.

Outline of the Analytic Hierarchy Process

- each criterion is weighted in pairwise fashion in order to assign the priority

When you decide to purchase a car you make an AHP……

Criteria	Cost	Efficiency	Power	Delivery	**Priority**
Cost	1	3	2	2	0.398
Efficiency	-	1	1/4	1/4	0.085
Power (KW)	-	-	1	1/2	0.218
Time to delivery	-	-	-	1	0.299

Pairwise comparison allows to built a quantitative hierarchy of conceptual criteria

	Harvest	Peak34	Prior CT	Prior RT	Dis status	BM	Age
Harvest	1-9/; 1/9-1						
Peak34		…5…..					
Prior CT			……3….				
Prior RT				……etc …			
Dis status							
BM						……..	
Age							…….

E.G. the CD34+ cell peak is 5 folds more important than the previous CHT

METHODS

- The GITMO-WG listed **3 categories** for the assessment of "poor mobilization" :

  - **Risk factors:** criteria for predicted poor mobilization assessed before the start of mobilization (e.g.: age, previous administration of CHT/RX)
  - **Markers:** criteria for predicted poor mobilization alongside mobilization (CD 34+ peak monitoring in PB, MNC, Plts etc).
  - **Indexes:** criteria for proven poor mobilization after the mobilization process has finished (CD 34+, MNC, CFU-GM in the harvest) including: **mobilization capacity and the performance of apheresis procedure.**

METHODS (2)

- A literature review allowed to list the factors associated with poor mobilization [Table I]

- A list of conceptual criteria was built based on literature and further integrated by criteria proposed by the experts.

	Conceptual Criteria	Percentage of agreement
1	Harvested CD34⁺ cells	86%
2	Harvested CD34⁺ cells per planned SCT	100%
3	Number of planned ASCT	57%
4	Overall harvested CD34⁺ cells after 2 aphereses	71%
5	Harvested CD34⁺ cells at 1st apheresis	57%
6	Pre and post-apheresis CD34+ cell count	57%
7	Absolute number of circulating CD34⁺ cells/µL	100%
8	Overall number of nucleated cells harvested	14%
9	Overall number of nucleated cells harvested per planned SCT	14%
10	Planned volumes of apheresis	57%
11	Chemo-mobilization	71%
12	Mobilizing G-CSF dose	71%
13	Diagnosis of underlying disease	71%
14	**Age**	**100%**
15	**Disease status**	**100%**
16	**Bone marrow involvement**	**86%**
17	**Pre-mobilization BM cellularity**	**86%**

Strategy*

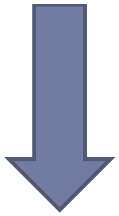
Indexes

Markers

Indexes

Strategy*

Risk factors



	Conceptual Criteria	Percentage of agreement
18	**Number of previous cytotoxic therapy lines**	**100%**
19	**Duration of prior chemotherapy**	**71%**
20	**Risk factors** — terval elapsed since previous chemotherapy	29%
21	**Prior extensive radiotherapy**	**100%**
22	**Prior alkylating therapy**	**86%**
23	**Prior therapy with lenalidomide**	**86%**
24	**Prior therapy with fludarabine**	**86%**
25	Platelet count at 1st apheresis	29%
26	Time to platelet recovery after chemo-mobilization	57%
27	Pre-mobilization WBC/PLT count	14%
28	Circulating $CD34^+$ cells in steady state prior PBSC mobilization	14%
	Markers	
29	Fold-increase of circulating $CD34^+$cells/µL respect to baseline	43%
30	Absolute number of circulating $CD34^+$ cells/µL at a predetermined timing	86%
31	after start of mobilization	43%
32	Kinetics of mobilization of $CD34^+$ cells	57%
33	Time to reach the CD34+ cell peak	43%
	Kinetics of mobilization of MNC cells	

Harvested CD34+ cells , aphaeresis days and mobilization strategy

- peak of PB $CD34^+$ count was timed according to the mobilization strategy, (larger variability in PB $CD34^+$ kinetics is expected after CHT+ G-CSF)
- An adequate dose of GF is required according to the different mobilization strategy (GF alone or GF+CHT)
- the cut-off of harvested $CD34^+$ cells needs to be integrated with the number of aphaeresis procedures performed.
- GITMO-WG established that a condition for excluding a patient from the definition of PM is that he/she should collect the dose of $\geq 2.0 \times 10^6$ $CD34^+$ cells/kg within a single mobilization attempt by ≤3 aphaeresis

(Operative definition)

RESULTS

- **Through a Delphi panel method, the GITMO-WG chose:**
- 1 out of 5 candidate conceptual index criteria:
  CD34+content in the harvest;
- 1 out of 9 candidate marker criteria: **CD34+ peak in PB**;
- 9 out of 14 candidate predictor criteria (Risk factors)

- The WG ranked the selected conceptual criteria

- The WG chose among 2 to 4 operational definitions per each conceptual criterion

- Finally the WG integrated the criteria into 3 definitions.

Criteria a

an insufficient harvest may be caused by technical problems that negatively impact the final yield of CD 34+ cells!!

Provided that the patient has received an adequate dose of G-CSF, i.e. 10 mcg/Kg/d if given alone or 5mcg/Kg/d after chemotherapy

1. Harvested CD34 cells per planned SCT < 2.0*10(6)/Kg by no more than 3 aphereses
2. Peak CD34 circulating cell count < 20/mcl up to 20 days after chemotherapy according to CD34 and leukocyte kinetics and type of chemotherapy OR CD34 circulating cell count < 20/mcl on day 4-6 after start of mobilization with growth factor alone
3. Refractory disease
4. Advanced phase disease
5. Prior extensive radiotherapy to marrow bearing tissue
6. Previous therapy with fludarabine, lenalidomide, melphalan
7. Previous therapies potentially affecting stem cell mobilization (e.g. Zevalin)
8. Extensive BM involvement at mobilization
9. BM cellularity at mobilization
10. Advanced age

Conceptual Criteria (10)	Operational Criteria	Rank (1-9)	Pairwise comparison	Variability
Harvested CD34⁺ cells INDEX	less than 2.0x10⁶ harvested CD34⁺ cells/Kg per planned SCT by no more than 3 apheresis	8.7	0,26	47%
Peak CD34⁺ cells MARKER	peak CD34⁺ cell count <20/µl on day 4-6 after start of mobilization with G-CSF alone or up to 20 days after chemotherapy and G-CSF	8.0	0,26	36%
Refractory disease	RISK FACTORS	6.0	0,08	74%
Advanced disease	advanced disease, i.e. at least two prior cytotoxic lines	5.8	0,12	38%
Extensive radiotherapy	extensive radiotherapy to marrow bearing tissue	7.2	0,08	54%
Prior exposure to fludarabine, melphalan, lenalidomide		6.6	0,06	47%
Prior exposure to other therapies potentially affecting SC mobilization		4.8	0,03	67%
Extensive BM involvement at mobilization		5.2	0,04	47%
Poor BM cellularity at mobilization	BM cellularity <30% at mobilization	4.8	0,04	42%
Old age	Age older than 65 years	5.1	0,02	50%

Proven PM

Predicted PM

36 scenarios have been hypothesized combining the 8 criteria for the predicted PM

- Prior extensive radiotherapy was identified as the most powerful independent criterion.
- The scenarios identified prior exposure to therapies potentially affecting SC mobilization as synergic independent factors.
- The panel decided to include into a unique exhaustive conceptual criterion, therapies definitely proven to affect mobilization and all the other therapies that have been or will be proven to negatively affect SC mobilization.
- **Finally, the GITMO-WG decided to extend the definition of "PM" also to those patients who undergo mobilization after a prior failure (usually defined historically proven PM).**

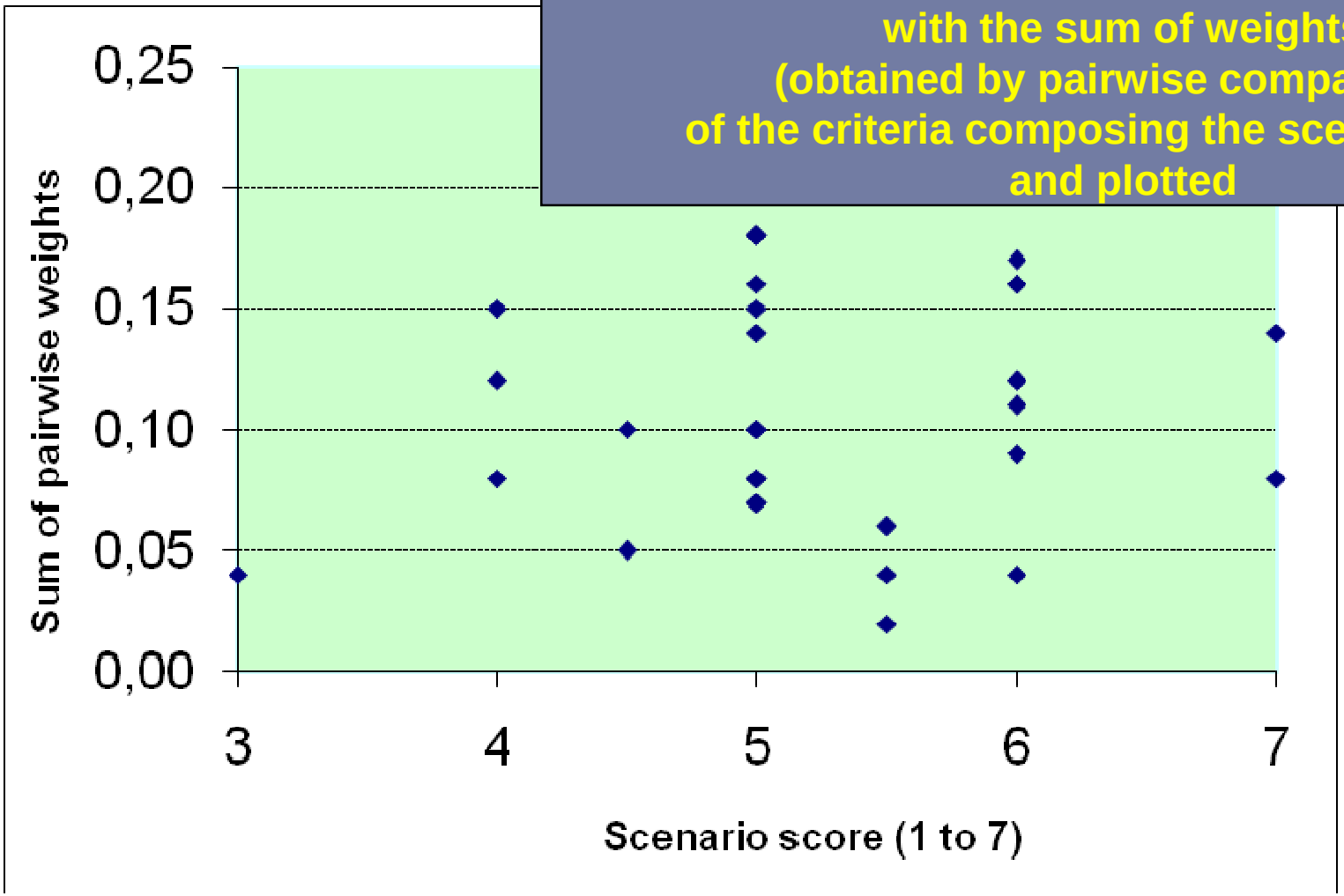
an insufficient harvest may be caused by technical problems that negatively impact the final yield of CD 34+ cells!!

Questionario vs AHP

- Extended RT ha il rank maggiore
  1. L'"extended radiotherapy to marrow bearing tissue" è un criterio di predizione di cattiva mobilizzazione SUFFICIENTE
- Età non ha un rank così basso come previsto da AHP
- L'esposizione a presunti "tossici" non ha ruolo in sé e raramente aggiunge alla predittività degli altri fattori
- La cellularità midollare ha un ruolo da sola ma poco aggiunge in combinazione
- Quattro criteri hanno discreta rilevanza anche in sé:
  - Advanced disease > refractory disease ~ prior exposure to fluda/lena/mel > età
  - La combinazione di advanced disease o refratcory disease con alcuni fattori risulta pleonastica (BM involvement, prior exposure to fluda/lena/mel)

For each scenario the participants were requested to check the definition of "predicted PM". A representative scenario is: "The patient is a predicted poor mobilizer if he or/she is older than 65 years and shows extensive BM involvement at mobilization"

Each scenario received approval by each participant. The agreement of each scenario was compared with the sum of weights (obtained by pairwise comparison) of the criteria composing the scenario itself and plotted



Final definition: a patient with MM or lymphoma candidate to ASCT is a:

Proven poor mobilizer	if he/she received adequate mobilization (G-CSF≥10 µg/Kg alone or ≥5µg/Kg after chemo) and he/she shows: **peak CD34⁺ circulating cell count** <20/µl on day 4-6 after start of mobilization with G-CSF alone or up to 20 days after chemotherapy and G-CSF **OR** in case of **less than 2.0 X10⁶ harvested CD34⁺ cells/Kg** (i.e. minimum safe dose for each planned ASCT) by ≤3 aphaereses
Predicted poor mobilizer **if he/she holds at least** **-one major criterion or** **-at least 2 minor criteria**	**Major criteria:** •**Failed previous mobilization attempt** •**Prior extensive radiotherapy** to marrow bearing tissue •**Full courses of previous therapy including** melphalan, fludarabine or other therapies potentially affecting stem cell mobilization **Minor criteria:** •Advanced phase disease, i.e. at least 2 prior cytotoxic lines •Refractory disease •Extensive BM involvement at mobilization •BM cellularity <30% at mobilization •Age >65 years

ORIGINAL ARTICLE

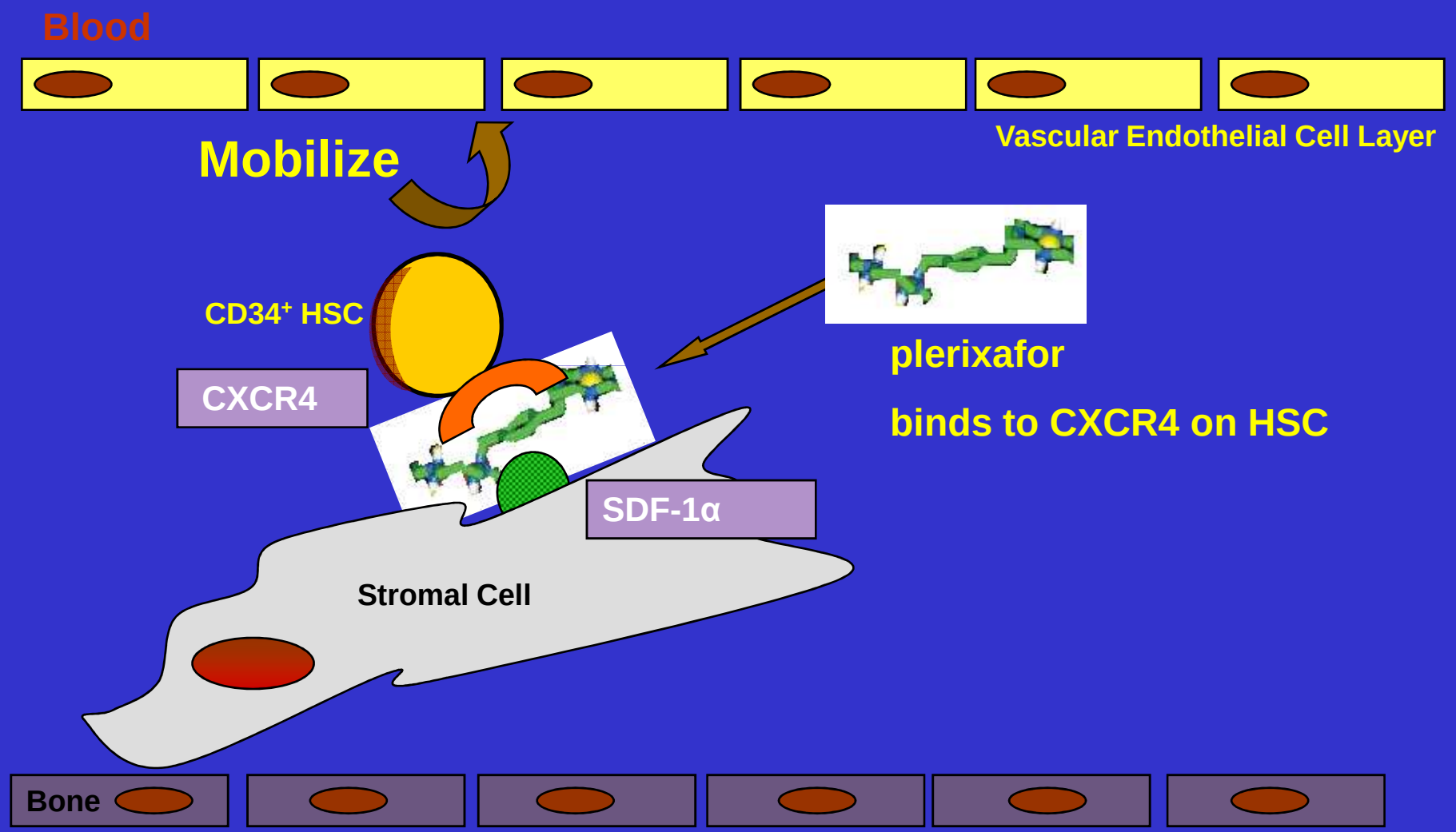
Proposed definition of 'poor mobilizer' in lymphoma and multiple myeloma: an analytic hierarchy process by *ad hoc* working group Gruppo italianoTrapianto di Midollo Osseo

A Olivieri[1], M Marchetti[2], R Lemoli[3], C Tarella[4], A Iacone[5], F Lanza[6], A Rambaldi[7] and A Bosi[8]
on behalf of the Italian Group for Stem Cell Transplantation (GITMO)

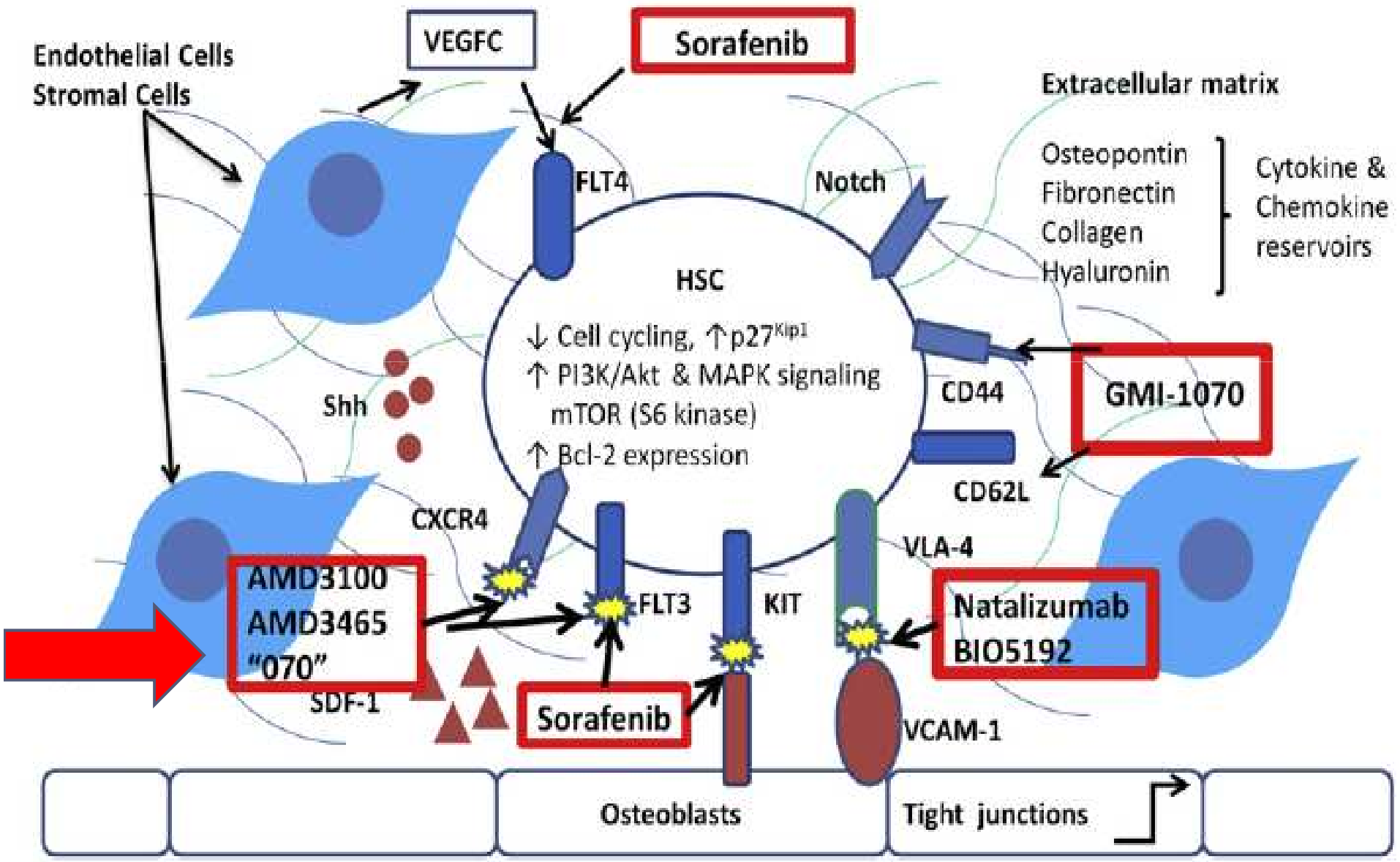
- **This proposal allows to clearly identify 2 categories of PM:**
- **PROVEN PM**
  - **"unsuccessful mobilizer" (biological inability)**
  - **"inefficient collection" (clinical, technical problems)**
- **PREDICTED PM before mobilization**
  - **"risk factors including a previous failure.**
  - ***"dynamic criteria" outside the CD 34+ peak are not reliable and difficult to standardize***

New Agents for Stem Cell Mobilization and their Role in Poor Mobilizers

AMD3100 (PLERIXAFOR): Mechanism of HPC Mobilization



Molecules involved in stem cell-stromal interactions



Potential risk of tumor cell mobilization and increased risk of metastases

Data indicate that tumor cell contamination is

not evident, or not significantly increased, following plerixafor, compared with G-CSF alone, in MM and NHL

However, increased circulating tumor cells have been reported in acute myelogenous leukemia and plasma cell leukemia patients.

Therefore, plerixafor is not recommended for HSC mobilization in leukemia patients

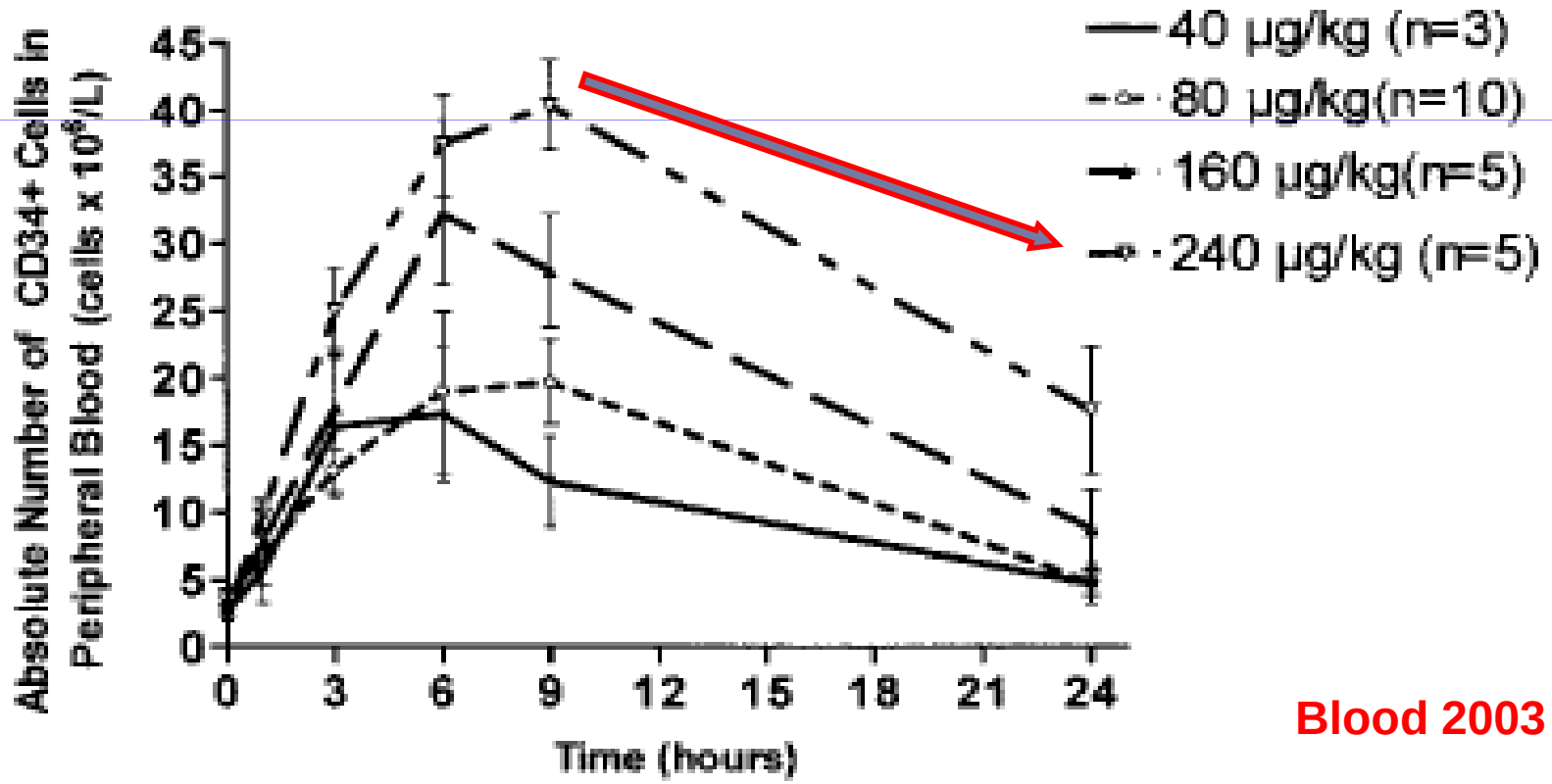
Brief report

Mobilization of hematopoietic progenitor cells in healthy volunteers by AMD3100, a CXCR4 antagonist

W. Conrad Liles, Hal E. Broxmeyer, Elin Rodger, Brent Wood, Kai Hübel, Scott Cooper, Giao Hangoc, Gary J. Bridger, Geoffrey W. Henson, Gary Calandra, and David C. Dale

Dose-response analysis of AMD3100-induced mobilization of CD34 cells into peripheral blood

BLOOD, 15 OCTOBER 2003 • VOLUME 102, NUMBER 8



Blood 2003

Rapid Mobilization of CD34+ Cells Following Administration of the CXCR4 Antagonist AMD3100 to Patients With Multiple Myeloma and Non-Hodgkin's Lymphoma

Steven M. Devine, Neal Flomenberg, David H. Vesole, Jane Liesveld, Daniel Weisdorf,

Devine S.M. et al

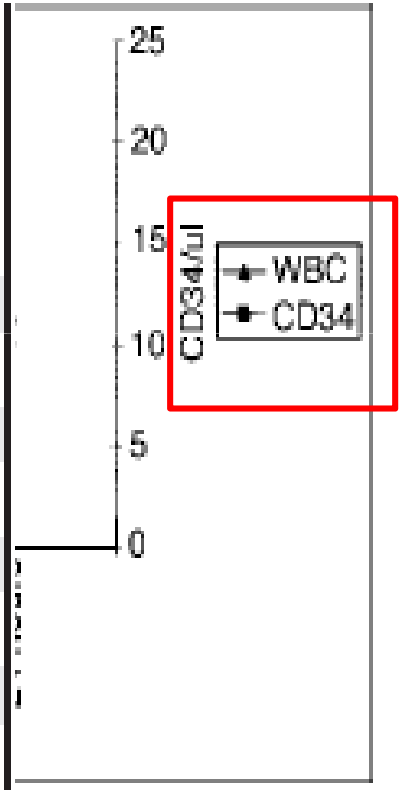
VOLUME 22 · NUMBER 6 · MARCH 15 2004

JOURNAL OF CLINICAL ONCOLOGY

Table 2. Toxicities of AMD3100

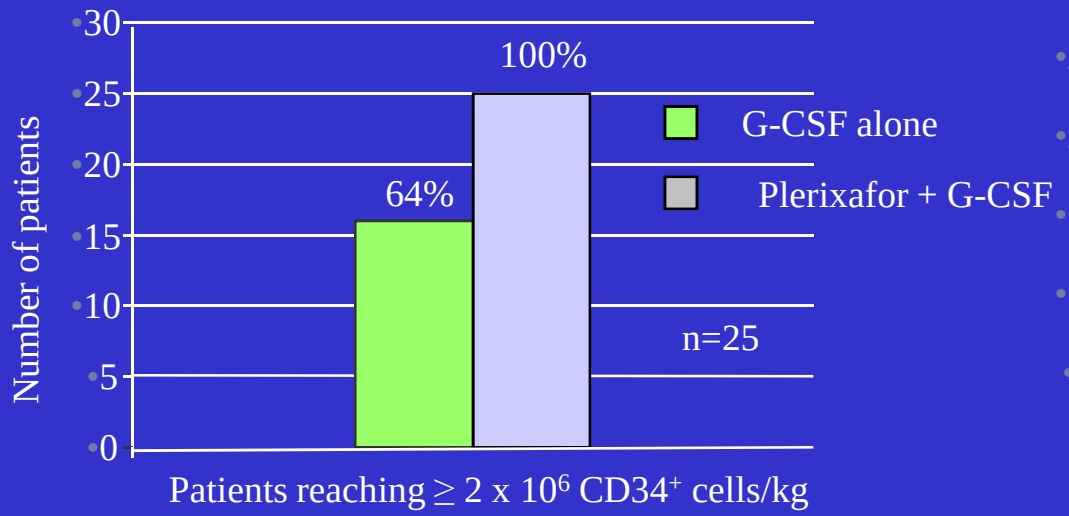
Toxicity*	No. of Affected Patients (N = 13)
Injection site erythema or edema	10
Abdominal bloating or cramping	5
Flatulence	3
Diarrhea or soft stools	3
Nausea	2
Facial paresthesias	3
Lightheadedness	2
Warm sensation, "fuzzy" vision, eyelid heaviness, neck rash, petechiae, hypotension	1

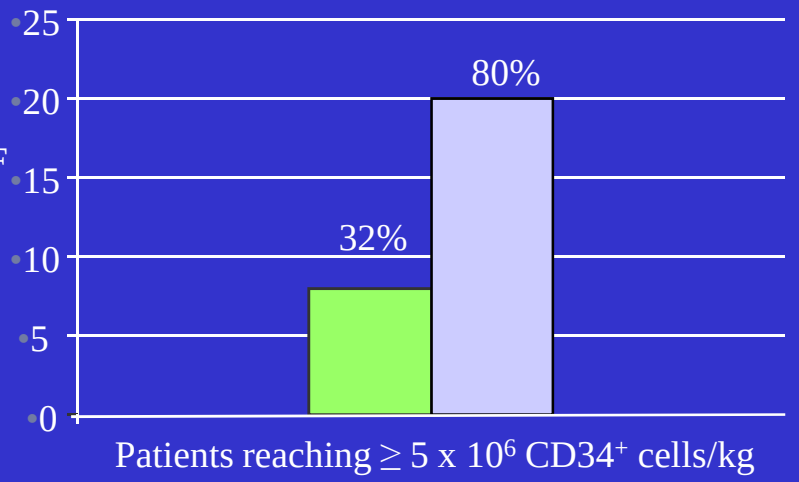
*All toxicities encountered were grade 1 only.



cell count observed in
g at baseline and 4, 6,
he dose. Each value

Plerixafor + G-CSF is a Superior Mobilizing Regimen Compared to G-CSF Alone

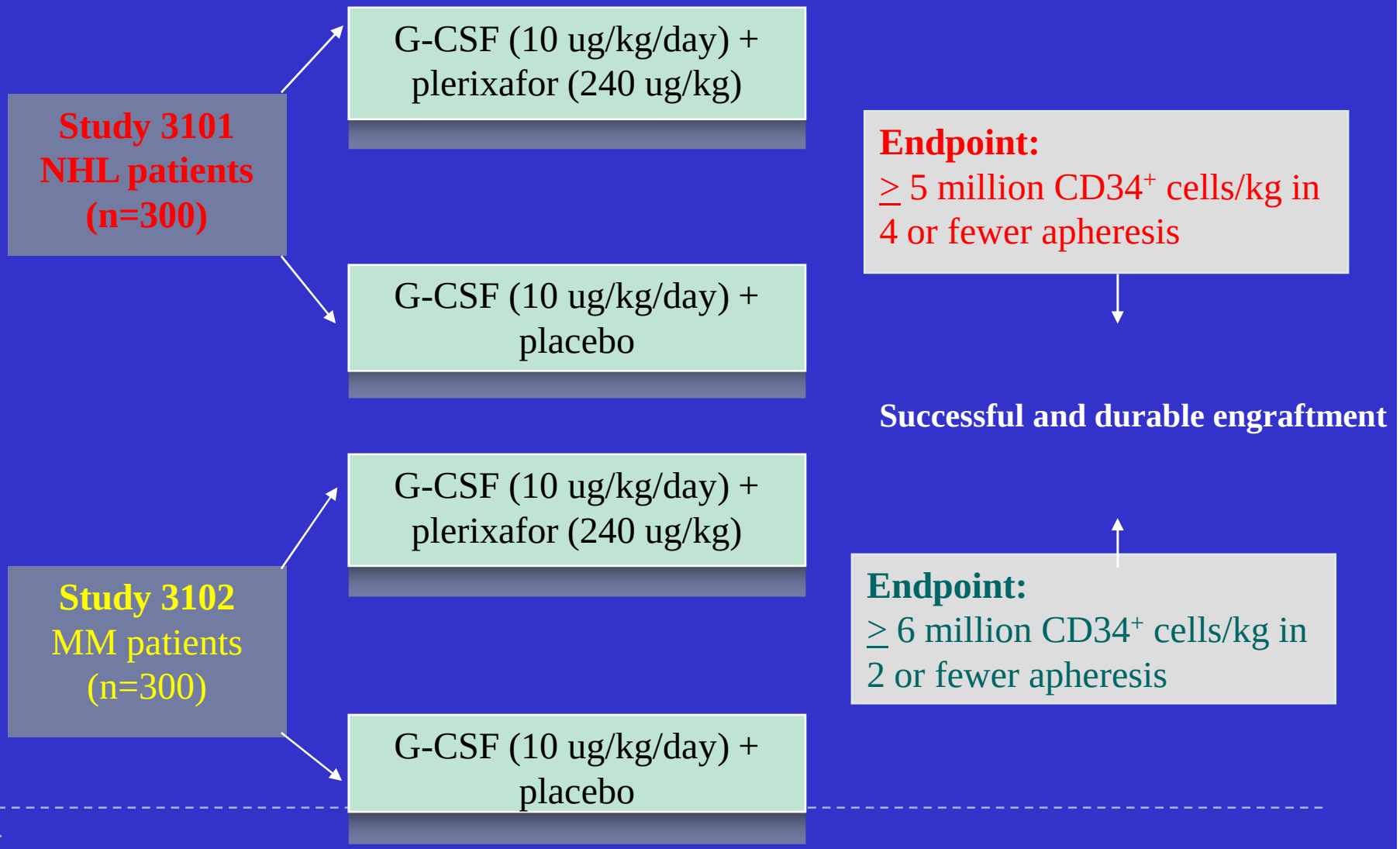




- 9 patients failing on G-CSF successfully mobilized on plerixafor + G-CSF
- 12 patients who received plerixafor + G-CSF required 1- 3 fewer aphereses to reach the optimum target
- All patients collected more cells with plerixafor + G-CSF

Flomenberg N, et al. *Blood*. 2005;106:1867.

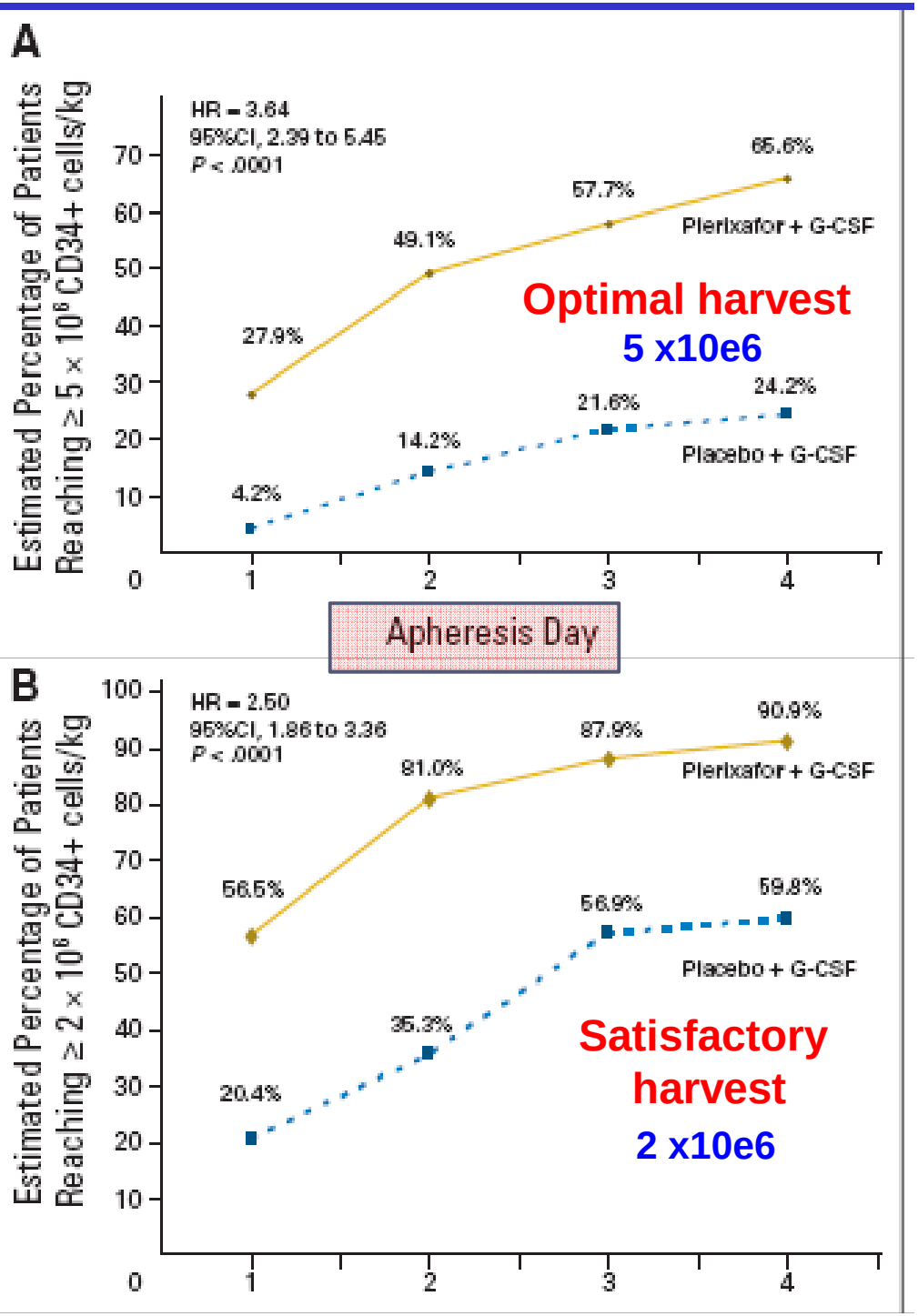
Plerixafor Phase III Trials – Study Design



Study 3101
NHL patients
(n=300)

Proportion of patients reaching 5 or 2 x10e6 CD34 cells/kg

Median number of apheresis days required to achieve 5x10e6 CD34 cells/kg was 3 days in the plerixafor group, and not estimable in the placebo group, as less than 50% of patients reached the target within 4 apheresis days.



blood
2009 113: 5720-5726
Prepublished online Apr 10, 2009;
doi:10.1182/blood-2008-08-174946

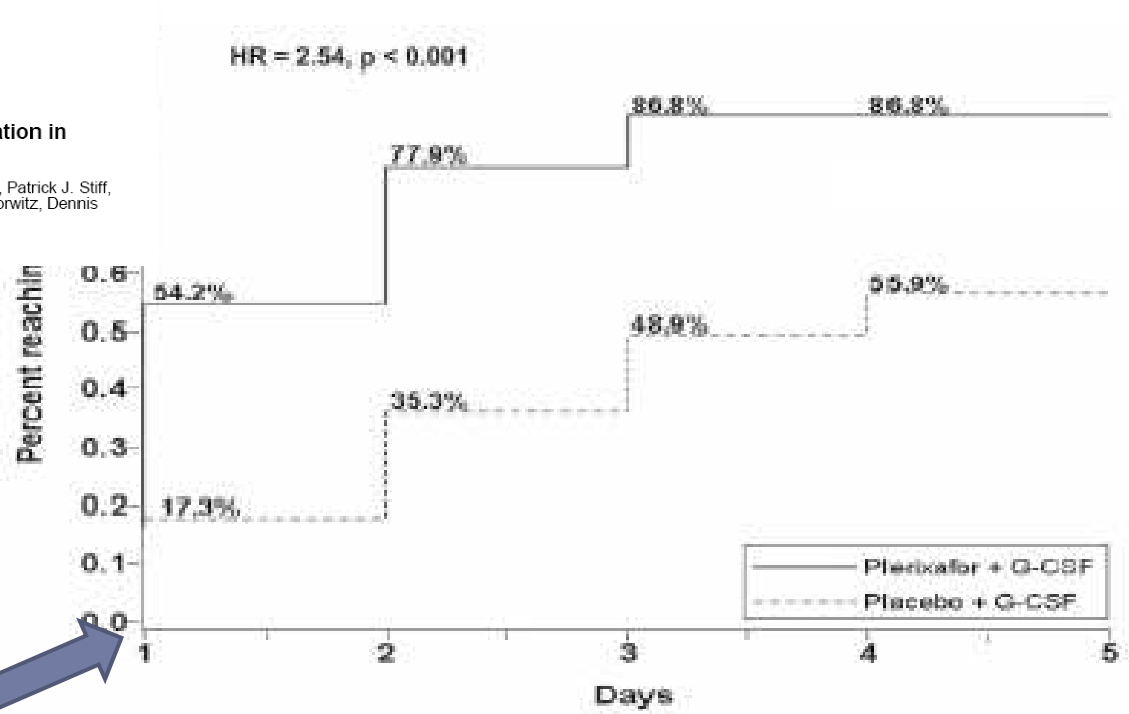
Plerixafor and G-CSF versus placebo and G-CSF to mobilize hematopoietic stem cells for autologous stem cell transplantation in patients with multiple myeloma

John F. DiPersio, Edward A. Stadtmauer, Auayporn Nademanee, Ivana N. M. Micallef, Patrick J. Stiff, Jonathan L. Kaufman, Richard T. Maziarz, Chitra Hosing, Stefan Früehauf, Mitchell Horwitz, Dennis Cooper, Gary Bridger, Gary Calandra and for the 3102 Investigators

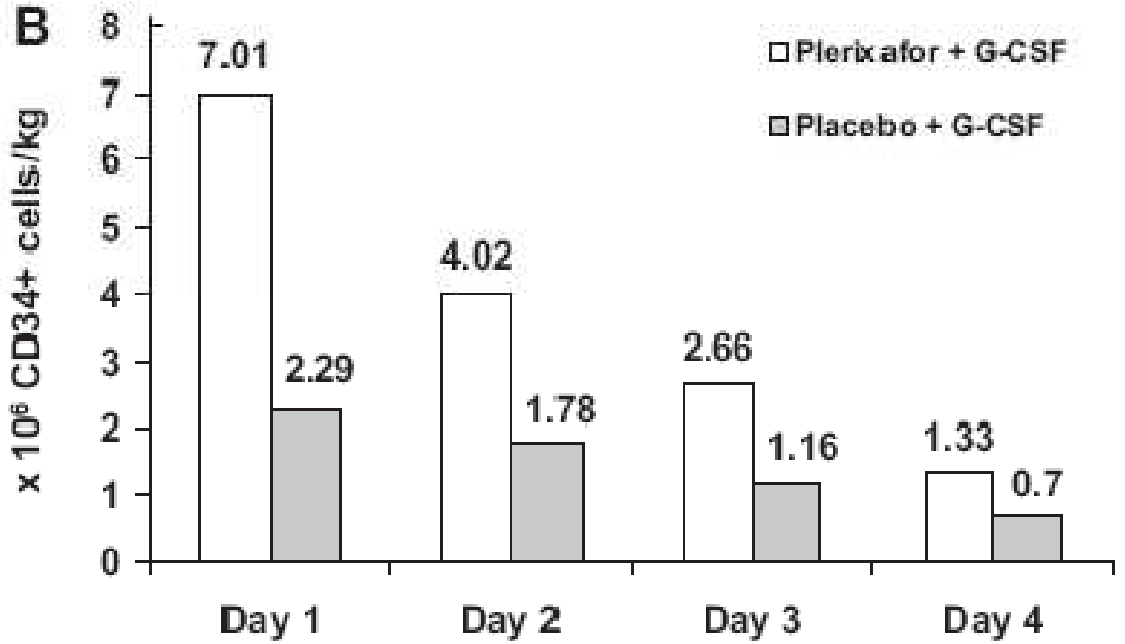
Study 3102
MM patients
(n=300)

Kinetics of collections

% of patients reaching ≥6 x 10e6 CD34+/kg



Median CD34+ cells collected on each apheresis day



Compassionate use programs with Plerixafor

Compassionate Use Protocols (CUP)

Bone Marrow Transplantation (2008) 41, 331–338

www.nature.com/bmt

ORIGINAL ARTICLE

AMD3100 plus G-CSF can successfully mobilize CD34+ cells from non-Hodgkin's lymphoma, Hodgkin's disease and multiple myeloma patients previously failing mobilization with chemotherapy and/or cytokine treatment: compassionate use data

G Calandra[1], J McCarty[2], J McGuirk[3], G Tricot[4], S-A Crocker[1], K Badel[1], B Grove[1], A Dye[1] and G Bridger[1]

66% of these patients collected ≥2e06 CD34+ /kg after Plerixafor

CUP study

A cohort of 115 data-audited

Document failure of mobilization due to
- Low PB CD34+ counts

or
- Inadequate apheresis collection

Success rates (harvest>2x10e6 CD34+/kg) for patients who previously failed mobilization were 65, 75 and 75% for NHL, MM and HD

75% of patients (87) were able to proceed to transplant

G-CSF mobilization (Days 1-4)
- 10 µg/kg/day G-CSF (morning)

Treatment/Apheresis (Starting Day 4)
- 240 µg/kg/day AMD3100 (evening)
- 10 µg/kg/day G-CSF (following morning)
- Apheresis begins 10 hours after AMD3100

Repeated daily, or until $\geq 2 \times 10^6$ CD34+ cells collected

Follow-up
- Engraftment
- 3 and 6 month post transplant follow-up
- Graft durability at 12 months post-transplant

Calandra et al BMT 2008

Collections and Engraftment

Disease	NHL[a,b]			MM		
Previous mobilization regimen[c]	Cytokines	Chemotherapy	All	Cytokines	Chemotherapy	All

The success rates for patients who previously failed chemotherapy mobilization were 65, 75 and 75% for NHL, MM and HD

75% of patients (87) were able to proceed to transplant

cells per kg (%)[b]						
Patients collecting $\geq 2 \times 10^6$ CD34+ cells per kg (%)[b]			38 (60.3)	7 (63.6)	18 (75.0)	25 (71.4)
Proceeded to transplantation (%)[d]			45 (71.4)	6 (54.5)	21 (87.5)	27 (77.1)
Days to PMN engraftment						
N	23	18	42	6	21	27
Median	12	11	11	13	11	11
Min, Max	8, 36	9, 16	8, 36	10, 20	9, 17	9, 20
Days to PLT engraftment						
N	21	16	36	6	18	24
Median	20	18	18	20	21	21
Min, Max	10, 155	12, 37	10, 155	15, 25	12, 57	12, 57

Calandra, BMT 2008

Strategies to Improve the Likelihood of Success in Poor Mobilizers

- **up-front Plerixafor in predicted PM (mobilization plan always including Plerixafor)**
- **pre-emptive Plerixafor only in patients with low CD 34+ count during mobilization (decision "real time")**
- **salvage Plerixafor** in **failed mobilizers (adding Plerixafor in the second mobilization attempt)**
- **……..**
- Plerixafor-containing regimens have a 30% failure rate among prior failed mobilizers probably because it could not restore low or defective HSC reserve or niche
- **Salvage bone marrow harvest**
- **Larger volume apheresis (processing ≥ 3x the blood volume instead of 2x)**

ASBMT
American Society for Blood and Marrow Transplantation

Plerixafor (Mozobil®) Alone to Mobilize Hematopoietic Stem Cells from Multiple Myeloma Patients for Autologous Transplantation

Table 2. Summary of Outcomes: CD34⁺ Cell Yield, Engraftment, and Graft Durability

		CD34⁺ Cells Collected (10^6 Cells/kg) by Central Lab					Days to Engraftment		
Patient Number	Patient Age	Day 1	Day 2	Day 3	Day 4	Total	PMN	PLT	12-Month Graft Durability
01-101	49	0.65	0.63	0.80	0.66	2.74	11	33	Durable
01-102	63	1.81	0.90	1.69	2.24	6.64	10	21	Durable
01-103	57	2.66	1.16	0.43	0.39	4.64	11	26	Dead at 6 months
01-104	55	1.40	1.02	1.32	1.06	4.80	10	19	Not evaluable*
03-105	63	1.37	1.01	0.69	0.75	3.82	11	21	Durable
03-106	74	1.85	1.59	1.55	—	4.99	10	23	Durable
03-107	70	0.50	0.59	0.67	0.51	2.27	11	NA†	Dead at 6 months
03-108	58	0.47	0.60	0.68	0.92	2.67	10	15	Durable
03-109	69	0.88	0.76	0.95	1.07	3.66	11	17	Durable

Possible option in case of G-CSF contra-indication?

Adverse factors for PBSC mobilization:

ASBMT American Society for Blood and Marrow Transplantation

Plerixafor Added to Chemotherapy Plus G-CSF Is Safe and Allows Adequate PBSC Collection in Predicted Poor Mobilizer Patients with Multiple Myeloma or Lymphoma

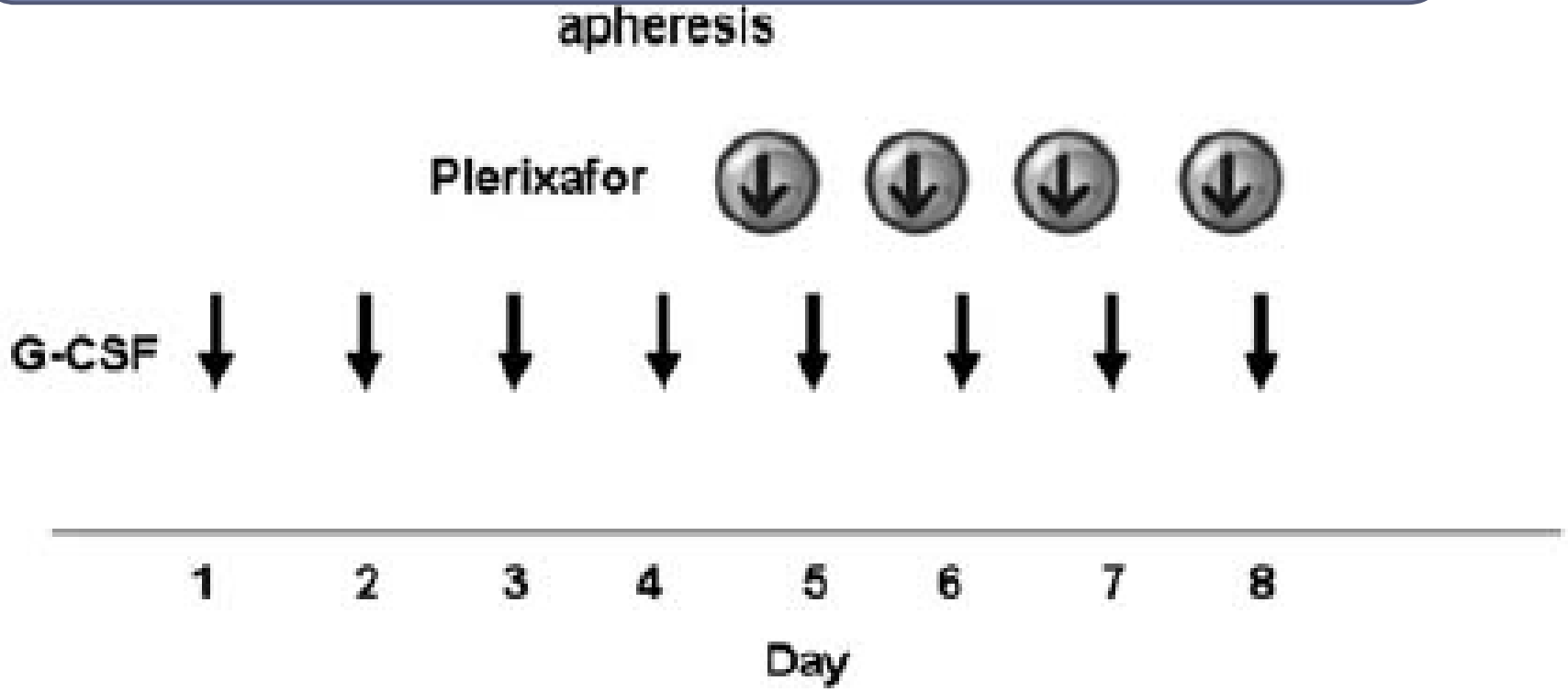
Immacolata Attolico,[1] Vincenzo Pavone,[2] Angelo Ostuni,[2] Bernardo Rossini,[2] Maurizio Musso,[3] Alessandra Crescimanno,[3] Massimo Martino,[4] Pasquale Iacopino,[5] Giuseppe Milone,[6] Patrizia Tedeschi,[6] Sabrina Coluzzi,[1] Roberta Nuccorini,[1] Sara Pascale,[1] Elvira Di Nardo,[7] Attilio Olivieri[1]

27 of the 37 patients (73%)
rescued with CHT*G-CSF+P
collected ≥2 10e6 CD34+ cells/kg
in 1-3 aphaeresis days
and 24 undergo ASCT (65%)
with fast and complete engraftment

Schedule for plerixafor with G-CSF as described in phase III trials and currently approved for clinical use

1 2 3 4

Current indication in Europe for Plerixafor is 'in combination with G-CSF patients with lymphoma and MM, whose cells mobilize poorly……



Effectiveness and cost analysis of "just-in-time" salvage plerixafor administration in autologous transplant patients with poor stem cell mobilization kinetics

Jie Li, Ellie Hamilton, Louette Vaughn, Michael Graiser, Heather Renfroe, Mary Jo Lechowicz, Amelia Langston, Jefferson Mark Prichard, Darlene Anderson, Charise Gleason, Sagar Lonial, Christopher R. Flowers, Jonathan L. Kaufman, and Edmund K. Waller

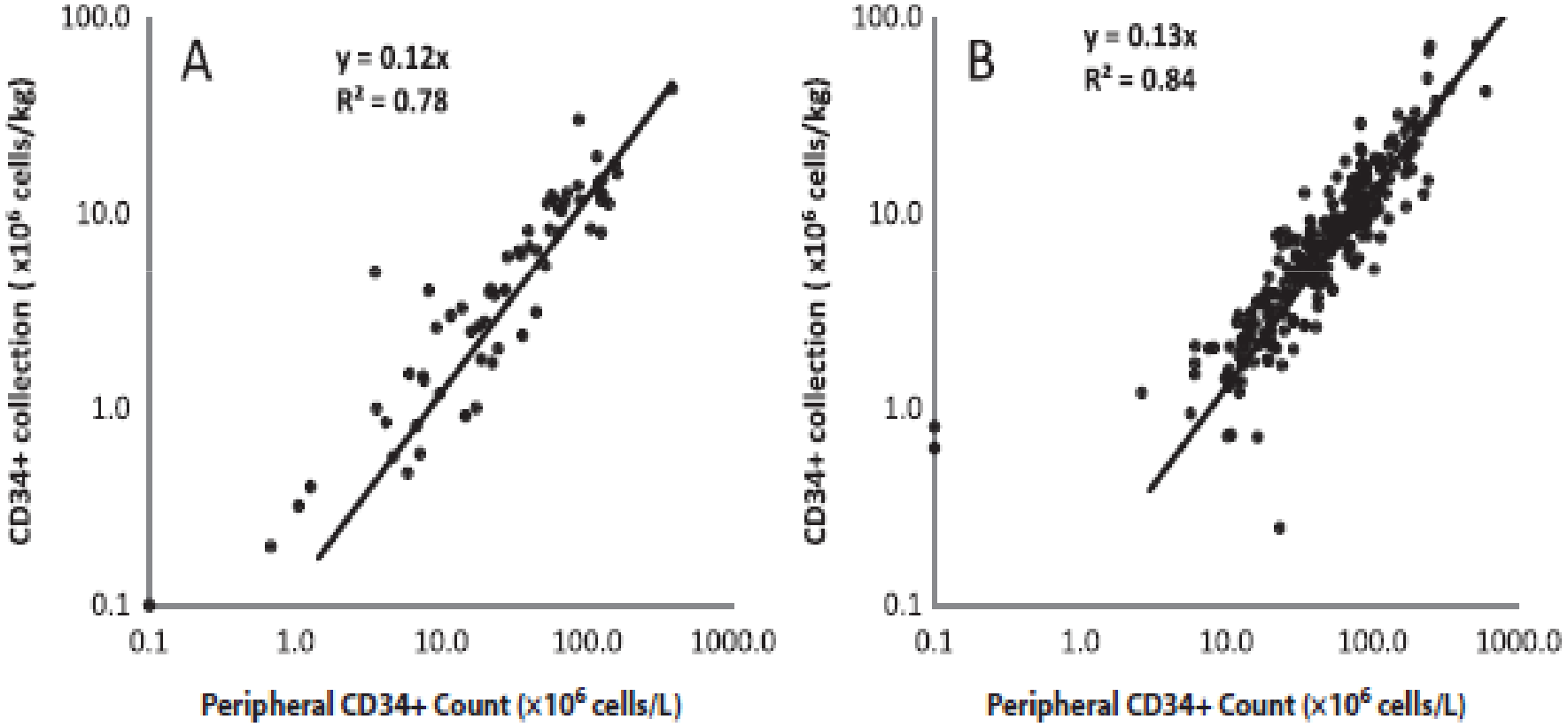
- plerixafor given after 5 days of G-CSF, to 64 of 188 patients (36%) deemed to be at risk for mobilization failure
- 41 had low CD 34+ peak (<15/mcl) after 5 days of G-CSF
- 23 were "high-risk" PM due to:
- prior mobilization failure (7)
- previous therapy with lenalidomide (12)
- refractory disease with multiple lines of chemotherapy (4)

Transfusion 2011

Effectiveness and cost analysis of "just-in-time" salvage plerixafor administration in autologous transplant patients with poor stem cell mobilization kinetics

Transfusion 2011

Jie Li, Ellie Hamilton, Louette Vaughn, Michael Graiser, Heather Renfroe, Mary Jo Lechowicz, Amelia Langston, Jefferson Mark Prichard, Darlene Anderson, Charise Gleason, Sagar Lonial, Christopher R. Flowers, Jonathan L. Kaufman, and Edmund K. Waller



Correlation of CD34+ cell count with CD34+ cell collection on the first apheresis day in patients with plerixafor (A) and patients without plerixafor (B).

RESULTS

- 47% of lymphoma patients and 36% of MM patients who received Plerixafor collected the target dose of CD34+ cells (>5x10e6/kg in Lymphoma and 10x10e6/kg in MM patients) compared to 33% of lymphoma patients and 19% of MM patients receiving G-CSF alone (p = 0.07).

- 93% collected minimum safe dose≥2x10e6 CD34+ cells/kg with plerixafor versus 72% with G-CSF alone (p = 0.02)

Effectiveness and cost analysis of "just-in-time" salvage plerixafor administration in autologous transplant patients with poor stem cell mobilization kinetics

Transfusion 2011

Jie Li, Ellie Hamilton, Louette Vaughn, Michael Graiser, Heather Renfroe, Mary Jo Lechowicz, Amelia Langston, Jefferson Mark Prichard, Darlene Anderson, Charise Gleason, Sagar Lonial, Christopher R. Flowers, Jonathan L. Kaufman, and Edmund K. Waller

Transfusion 2011

Effectiveness and cost analysis of "just-in-time" salvage plerixafor administration in autologous transplant patients with poor stem cell mobilization kinetics

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Patient characteristics	2008 (before plerixafor approval) Total	Good mobilizer nonplerixafor	Poor mobilizer nonplerixafor
Number of patients	148	112	36
Myeloma patients	92	66	27
Lymphoma patients	56	46	9
Percentage of patients with CD34+ count ≥15 × 10^6 cells/L and WBC count >10 × 10^9 cells/L after at least 5 days of G-CSF administration	76	100	0
Percentage of patients with CD34+ cell count ≥15 × 10^6/L and WBC count >10 × 10^9/L by more days of G-CSF or G-CSF plus plerixafor treatment	80	100	17
Percentage of patients who collected target cell dose of CD34+ cells (≥5 × 10^6 cells/kg for lymphoma, ≥10 × 10^6 cells/kg for myeloma)	61	73	22
Percentage of patients collected a minimum transplant dose of CD34+ cells (≥2 × 10^6 cells/kg)	93	100	72
Percentage of patients collected a minimum transplant dose of CD34+ cells (≥2 × 10^6 cells/kg) on Day 1 of apheresis	84	99	39
Median (range) number of CD34+ cells collected (×10^6 cells/kg)	8.8 (0.6-72.3)	10.4 (2.8-72.3)	4.4 (0.6-14.9)

Transfusion 2011

2009 (after plerixafor approval)

Pts number	Good mobilizer nonplerixafor	High-risk patients plerixafor	Poor mobilizer just-in-time plerixafor
Total	188	124	23	41
MM	138	97	20	22
Lymph	50	28	3	19
>15 CD34+/mcl (%) after G-CSF 5 days	70	100 %	30 %	0
>15 CD34+/mcl (%) after >5 days of G-CSF+/-P	89	100	83	61
>5x10e6/kg CD34	64	70	70	42
>2x10e6/kg	98	100	96	93
>2x10e6/kg 1°aph	86	94	83	61
Median CD34+ (range)	8.2 (0.6-135.3)	10.9 (2.7-135.3)	11.7 (1.8-43.3)	6.8 (0.6-13.8)

After P

Transfusion 2011

LI ET AL.

Cost analysis

sum of charges* for growth factor, plerixafor, apheresis, and product cryopreservation from 1 day before apheresis to the last day of apheresis

just-in-time Plerixafor increased average charges $2468 per patient compared with G-CSF alone. However Plerixafor increased the likelihood of successful collection from 72% to 93%

Mean cost/patient	$16,234	$13,550	$27,796	$18,981	$15,299	$20,761	$30,264

* Table 3 has fewer patients th[a]ble 2 because patients who failed to mobili[z]sufficient stem cells for a single transplant (10 patients in 2008 and five patients in 200[9] [w]ere not included in the cost analysis.

***charges associated with chemotherapy before mobilization, with G-CSF administration before apheresis, and the charges associated with stem cell thawing and infusion were not included**

Hematopoietic recovery kinetics predicts for poor CD34+ cell mobilization after cyclophosphamide chemotherapy in multiple myeloma

Guner Hayri Ozsan,[1] Ivana N. Micallef,[2]* Angela Dispenzieri,[2] Shaji Kumar,[2] Martha Q. Lacy,[2] David Dingli,[2] Suzanne R. Hayman,[2] Francis K. Buadi,[2] Robert C. Wolf,[2] Dennis A. Gastineau,[2] William J. Hogan,[2] and Morie A. Gertz[2]

Autologous stem cell transplantation is an important part of therapy in patients with multiple myeloma. Some patients fail to collect the desired number of stem cells while others require multiple apheresis to reach the desired apheresis target. The aim of this study was to determine the predictive factors and if the hematopoietic kinetics of recovery were predictive for outcome of stem cell mobilization in cyclophosphamide + growth factor (CY-GF) mobilized patients. Three hundred and ninety six consecutive CY-GF mobilization attempts between January 2000 and December 2009 at Mayo Clinic, Rochester, MN were analyzed. Patients were divided into three groups: optimal (>5 × 10^6 CD34/kg), suboptimal (2–5 × 10^6 CD34/kg) and poor (<2 × 10^6/kg CD34+ cells) mobilization groups. About 86% of patients had optimal stem cell collection, whereas 8% had suboptimal collection and 6% had poor (or failed) collections. Age, Hb, WBC, and platelet levels had an impact on mobilization results. Time to peripheral blood (PB) CD34+cells >10/μL predicted for efficiency of collection and the interval between recovery of WBC>1 post-CY to PB CD34+ cells>10 was shorter in the optimal collection groups. These findings suggest that for patients with a PB CD34+ cell count below 10/μL on Day 13 following CY or 1 day after the WBC>1 × 10^9/L, addition of plerixafor may be helpful to salvage the mobilization attempt. Am. J. Hematol. 00:000–000, 2011.

benefits and limitations of plerixafor

Benefits	*Limitations*
Predictable time to peak $CD34^+$ cells (~11 h): reliable apheresis planning; more efficient use of healthcare resources	Currently indicated for failed or poor mobilizers in Europe and not in general first-line treatment
Fewer mobilization failures compared with G-CSF alone, reduced need for remobilization	Limited data on outcomes in association with chemomobilization
More patients able to proceed to high-dose chemotherapy	Likely to be more expensive than current mobilization options
Faster time to high-dose chemotherapy	
Reduced risk of disease progression	
More cells per apheresis: higher cell doses for auto-HSCT; possible option of collecting cells for tandem/salvage transplant	
Fewer apheresis sessions, fewer procedural side effects	
Fewer days of G-CSF	
Adverse events: mild and transient (most commonly diarrhea, nausea and injection site reactions)	

Plerixafor

as a sole mobilizing agent

in the allogeneic stem cell

transplant setting

for the mobilization of

normal HLA matched

sibling donors

……When?

Aknowledgements

- Marchetti Monia, Hematology Unit Asti Hospital
- Lemoli Roberto, Hematology Dpt University Bologna
- Tarella Corrado, Hematology Dpt University Torino
- Iacone Antonio, Blood Bank Pescara Hospital
- Lanza Francesco, Hematology Unit Cremona Hospital
- Rambaldi A, Hematology Dpt Bergamo Hospital
- Bosi Alberto, Hematology Dpt University Firenze

- **on behalf of the Italian Group for Stem Cell Transplantation (GITMO)**

- **Genzyme for supporting the 3 Expert Meetings**