STEM CELL COLLECTION

IN MOBILIZATION FAILURE

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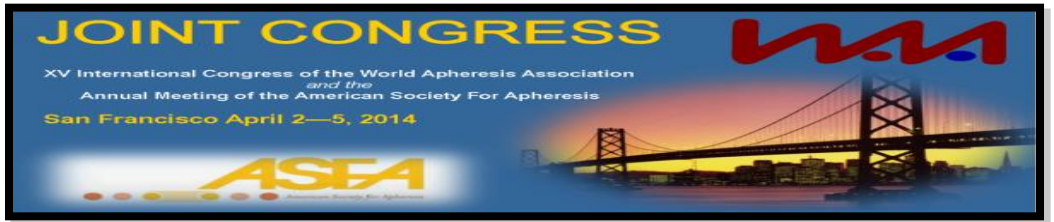


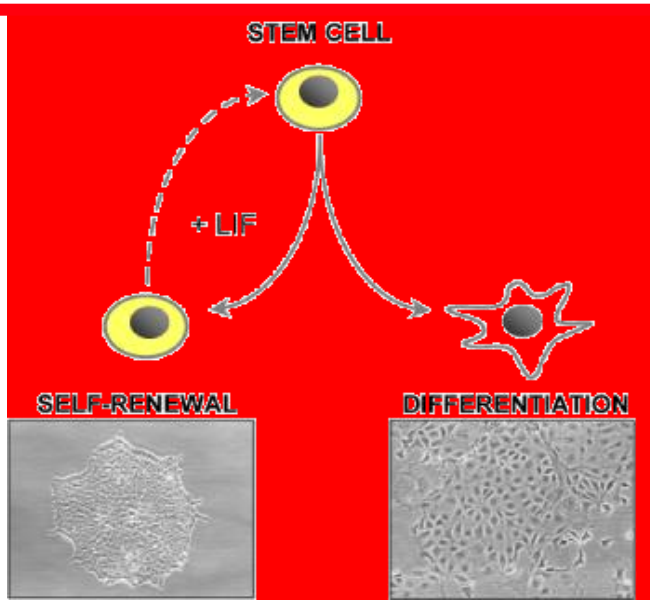
OUTLINE

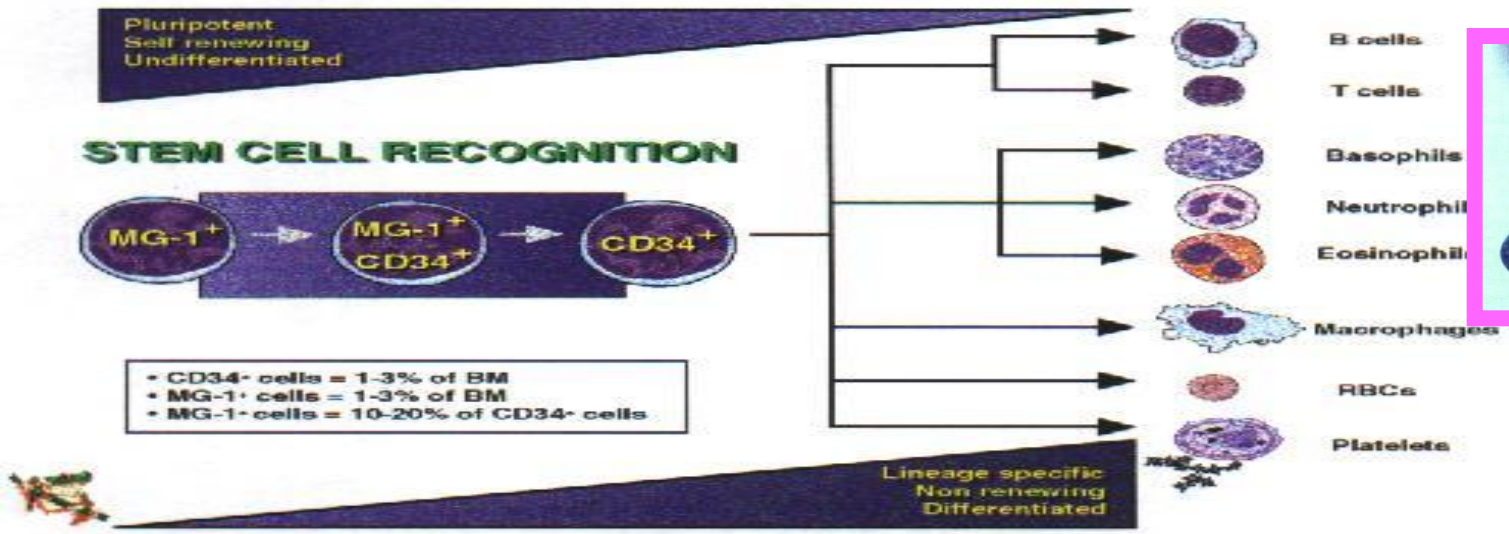
- Introduction
- Current Mobilization Strategies
- Mobilization failure
- Salvage mobilization strategies
  - Plerixafor
  - Other options in mobilization failure
- Mobilization Guides of EBMT and ASBMT

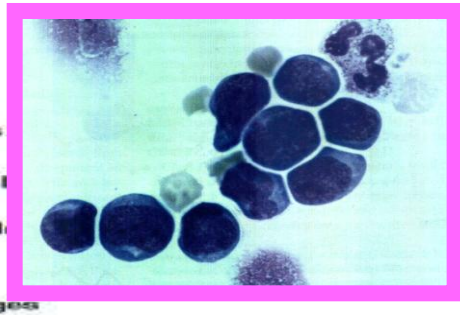
INTRODUCTION

Hematopoietic Stem Cell

- can renew itself (Self-Renewal)
- can differentiate to a variety of specialized cells (Differentiation)
- can mobilize into peripheral blood (Mobilization)
- Clonal cells

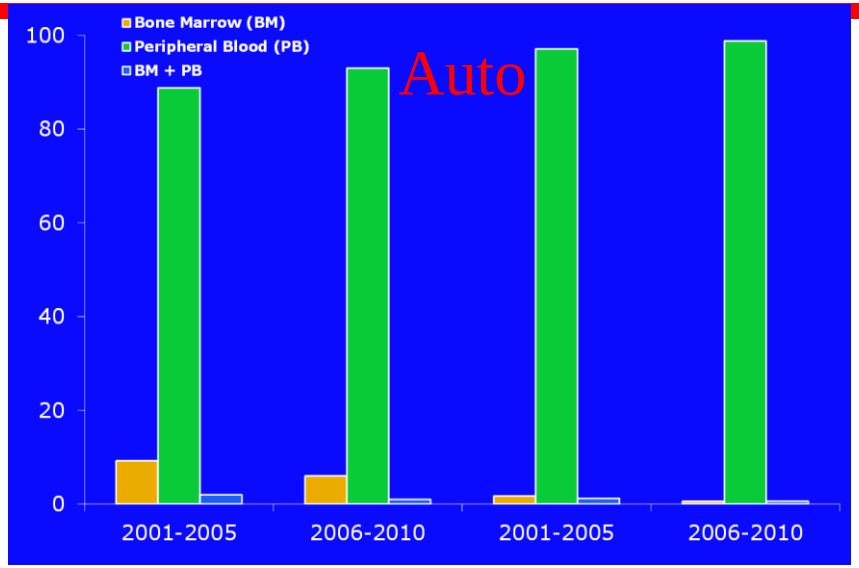


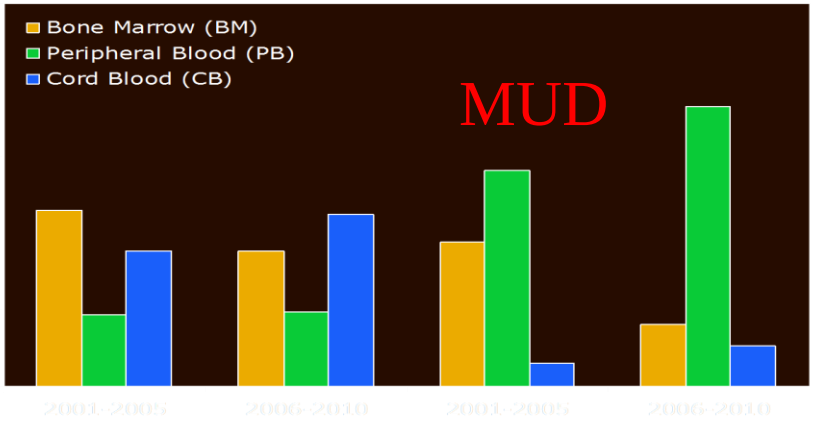


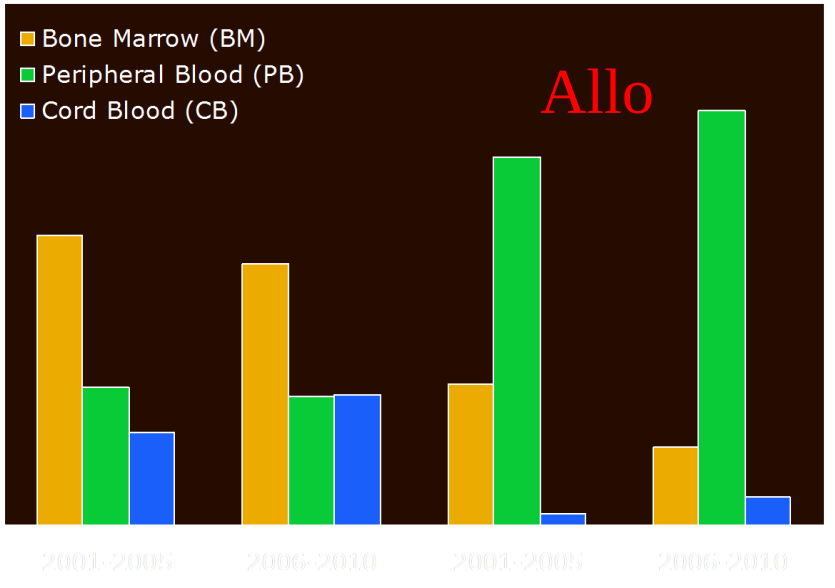


Stem Cell Source

- **Bone marrow**
- **Peripheral Blood**
- **Cord Blood**







Peripheral Blood Stem Cells

- The most frequently used source of HSCs
  - Does not require general anesthesia
  - Decrease risk to donor
  - Faster engraftment compared to BM
- But
  - Need for mobilization regimen
  - Increased risk of chronic GVHD

L. Bik To, et al. How I treat patients who mobilize hematopoietic stem cells poorly. BLOOD 2011; 118(17): 4530-4540

Hematopoietic Stem Cell Mobilization

- The concentrations of HSCs are 10-100 times greater in the BM compared to the PB.
  - 0.1% of PB mononuclear cells
  - 1-4% bone marrow cells
- Therefore, methods to increase the circulating concentrations of HSCs are necessary to ensure adequate and successful collections.
- Agents used to mobilize HSCs include the administration of cytokines with or without chemotherapy prior to scheduled collection periods.

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CURRENT

MOBILIZATION STRATEGIES

“Players” in mobilization & Mobilization Mechanism

- The HSC niche and microcirculation
- The adhesive and chemotactic interactions
  - The role of proteases
  - The role of BM macrophages
  - The role of complement, the thrombolytic pathway, and chemotactic gradients of SDF-1 and sphingosine-1-phosphate
  - The role of -adrenergic sympathetic nerves

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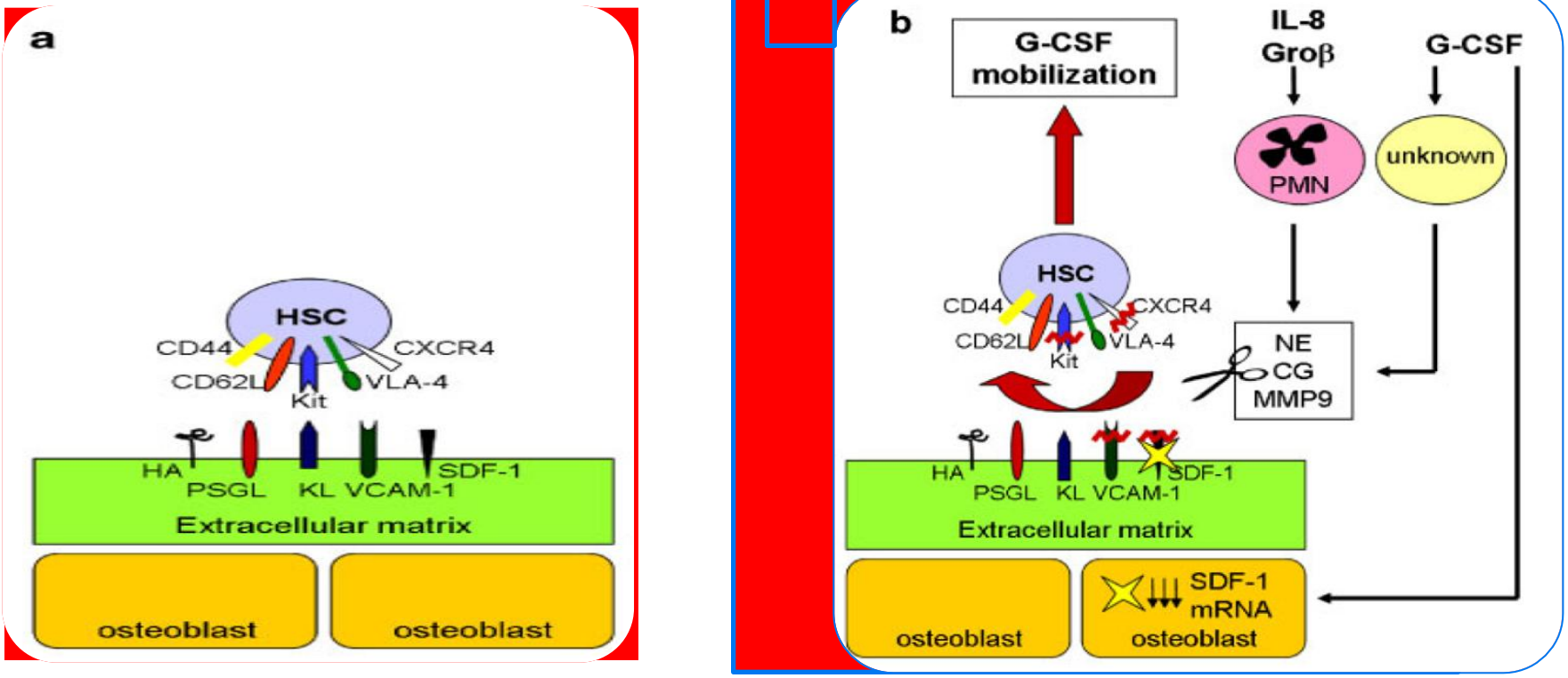
Mechanisms of Stem Cell Mobilization with G-CSF

Adhesive interactions between HSC and matrix components in the BM

G-CSF Mobilization



Cathepsin G (CG), chemokine receptor-4 (CXCR4), hematopoieic stem cell (HSC), hyaluronic acid (HA), interleukin 8 (IL-8), kit ligand (KL), matrix metalloproteinase-9 (MMP-9), neutrophil elastase (NE), stromal cell derived factor-1 (SDF-1), vascular cell adhesion molecule-1 (VCAM-1), very late antigen-4 (VLA-4), P-selectin glycoprotein ligand-1 (PSGL). Source: Nervi B, et al. *J Cell Biochem.* 2006;99:690-705

Is There an Ideal Mobilization Regimen?

- Proposed characteristics of an ideal regimen for autologous-HSCT
  - Capable of mobilizing a sufficient number of stem cells for collection
  - Results in prompt and durable engraftment
  - Able to predict the day of collection
  - Requires a minimal number of apheresis procedures
  - Low failure rate
  - Low toxicity profile
  - Cost Effective
  - Low tumor contamination

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Common Mobilization Regimen

- Hematopoietic growth factors
  - Approved by FDA & EMA
    - G-CSF, GM-CSF, Plerixafor (in combination with G-CSF)
  - Other cytokines
    - Pegfilgrastim, erythropoietin, stem cell factor (SCF)
- Chemotherapy+ Growth factors
  - Cyclophosphamide, cytarabine, etoposide, etc
  - Disease-specific regimens: ICE, IVE, VIGEPP

- D. Sheppard et al. Hematopoietic Stem Cell Mobilization Strategies. Biol Blood Marrow Transplant 2012;18:1191-1203.
- L. Bik To, et al. How I treat patients who mobilize hematopoietic stem cells poorly. BLOOD 2011; 118(17): 4530-4540

Collection time and PB CD34+ cell

Correlation between PB CD34+ cells/μL and CD34+ cells/kg collection

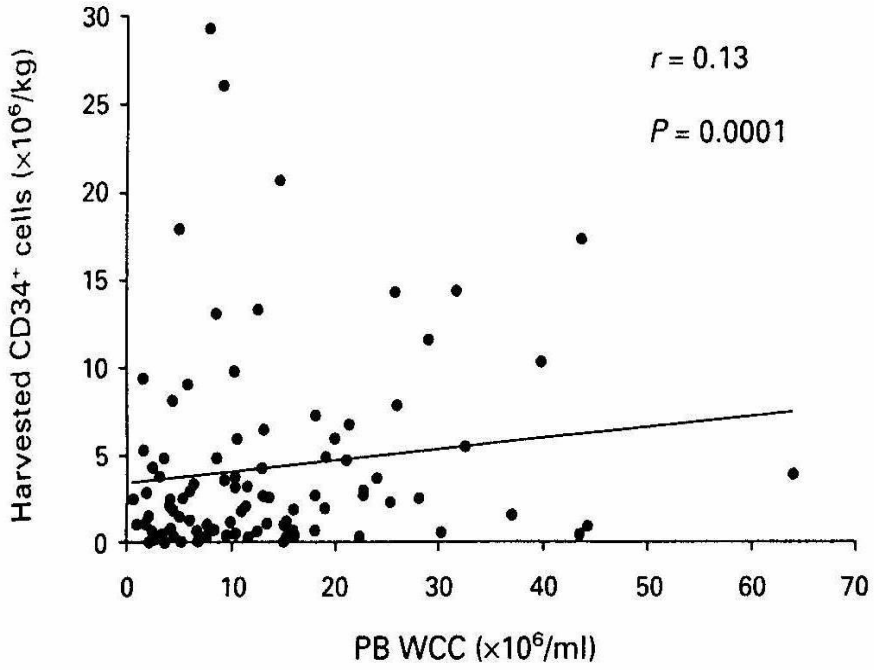

Figure 1 Preceding day peripheral blood WCC *vs* CD34 content of harvest.

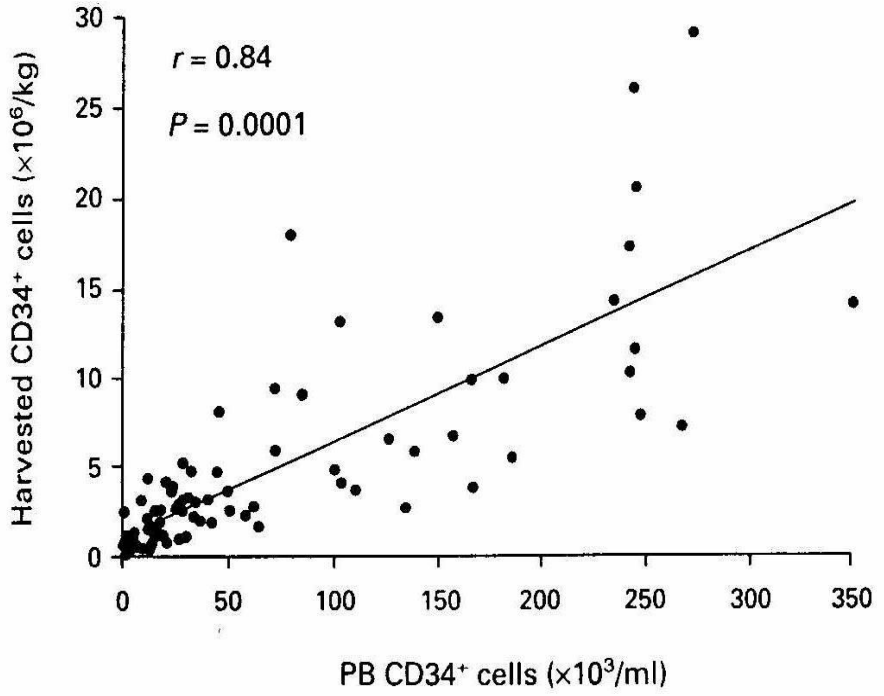

Figure 2 Preceding day peripheral blood CD34 count *vs* CD34 content of harvest.

Armitage S, et al. *Bone Marrow Transplant.* 1997;20:587-591.

MOBILIZATION FAILURE

What's a Poor Mobilizer?

- **Poor or failed mobilization**
  - **Is often defined as a collection of <2 x 10^6 cells/kg**

- Goterris R, et al. Bone Marrow Transplant. 2005;36(10):847-853.
- Micallef IN, et al. Hematol J. 2000;1(6):367-373.
- L. Bik To, et al. How I treat patients who mobilize hematopoietic stem cells poorly. BLOOD 2011; 118(17): 4530-4540

Mobilization Failure Rates with Traditional Approaches

Author	Patient Population	Regimen	$CD34^+$ Yield, $\times 10^6$/kg	FD	Failure Rate, %
Bensinger et al.[39]	MM, lymphoma, BC, other	n = 124 CM + G-CSF/GM-CSF	10.75	O	7
		n = 119 G-CSF	5.21		5
Pusic et al. [20]	MM, lymphoma	n = 976 G-CSF	3.36	M	18.6
		n = 64 CM + G-CSF	5.43		18.75
Gertz et al. [73]	MM, lymphoma	n = 1775 G-CSF ± Cy	NR	O	47
Pavone et al. [72]	Lymphoma	n = 97 Cy + G-CSF	28.8 (median for all cohorts)	O	17.9
		n = 87 DHAP + G-CSF			
		n = 83 MAD + G-CSF			
Roberts et al. [75]	MM, lymphoma	n = 97 CM + G-CSF	NR	O	29.9
		n = 155 G-CSF	NR		38.1
Alegre et al. [21]	MM	n = 18 Cy + GM-CSF	6.8	NA	NR
		n = 22 G-CSF	4.9		NR
Narayanasami et al. [100]	Lymphoma	n = 22 G-CSF	2.5	M	4.5
		n = 24 Cy + G-CSF	7.2		4.2
Desikan et al. [23]	MM	n = 22 G-CSF	5.8	O	23
		n = 22 Cy + G-CSF	33.4		18
Dazzi et al. [101]	NHL	n = 12 G-CSF	2.89	NA	NR
		n = 12 Cy + G-CSF	6.41		NR
Schiller [191]	MM	n = 37 Cy + G-CSF	4.65	M	0

Girald S, et al. Optimizing Autologous Stem Cell Mobilization Strategies to Improve Patient Outcomes: Consensus Guidelines and Recommendations. Biol Blood Marrow Transplant 2013.

Factors Associated with Poor Mobilization

Factors described to be predictive of poor PBSC collection
Age (older patients)[1,2]
Disease (more advanced stage)[1-3]
Prior chemotherapy •Higher no. of prior treatment lines[1-4] •Type of chemotherapy (fludarabine, lenalidomide [controversial] or melphalan)[1-5]
Prior irradiation[1,2]
Low $CD34^+$ cell count in PB before apheresis[3,4,7]
Low platelet count before mobilisation (controversial)[8,9]

$CD34^+$ cell count in PB before apheresis is presumably the most robust predictor for poor PBSC collection[1,3,4,7]

1. Olivieri et al. Bone Marrow Transplant 2012;47:342-51.
2. Perseghin et al. Transfus Apher Sci 2009;41:33-7.
3. Sancho et al. Cytotherapy 2012;14:823-9.
4. Wuchter et al. Biol Blood Marrow Transplant 2010;16:490-9.
5. Kumar et al. Leukemia 2007;21:2035-42.
6. Sinha et al. Leukemia 2012; 26:1119-2.
7. Sinha et al. Bone Marrow Transplant 2011;46:943-9.
8. Duarte et al. Bone Marrow Transplant 2011;46(Suppl 1):abst. O377.
9. Nakasone et al. Am J Hematol 2009;84:809-14.

Factors Associated With Poor Mobilization

Contents lists available at SciVerse ScienceDirect

Transfusion and Apheresis Science

journal homepage: www.elsevier.com/locate/tra

Predicting the successful peripheral blood ... harvesting

Itır Şirinoğlu Demiriz*, Sinem Civriz Bozdağ, Em... z, Bilge Uğur, Gamze Durgun, Şerife Koçubaba, Fevzi Altuntaş

Ankara Oncology Education and Research Hospital, Hematology an... ation Clinic, Ankara, Turkey

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Article history:
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... previously defined factors affecting the mobilization success include age, prior che-...herapy lines, exposure to myelotoxic agents, extended field radiotherapy and bone marrow infiltration with the primary disease. The purpose of this study was to retrospectively analyze the influence of the predictive factors for a successful peripheral stem cell mobilization. We enrolled a total of 145 patients into the study (non-Hodgkin lymphoma (*n*: 40), Hodgkin lymphoma (*n*: 36), myeloma (*n*: 64), solid tumors (*n*:5)) who received autologous stem cell transplantation between 2009 and 2012. In multivariate analysis only platelet count was found to be related with mobilization outcome ($p < 0.05$). Knowing predictive factors for successful mobilization may be useful to define the best timing for mobilization and the most appropriate mobilizing agents for proper patient population.

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Multivariate analyses = Trombocytopenia

Consequences of Suboptimal Mobilization?

- Failure to mobilize a sufficient number of CD34+ cells may result in:
  - Increased number of days of apheresis
  - Need for another mobilization attempt or bone marrow harvest
  - Ineligibility to receive a potentially curative therapy (HSCT)
  - Additional burden on patients

- Use of sub-optimal apheresis product may lead to
  - Delayed, partial, or failed stem cell engraftment[1]
  - Increased need for transfusions[2]

1. Haas R, et al. *Blood* 1994;
2. Schiller G, et al. *Blood* 1995

SALVAGE MOBILIZATION

STRATEGIES

Salvage Mobilization Strategies

- Large volume apheresis
- High dose cytokine
  - High dose G-CSF
  - Pegfilgrastim
  - SCF, GM-CSF, IL-3
  - Combination of cytokines
- Chemomobilization
  - Chemotherapy + G-CSF
- Plerixafor (SDF-1 alfa inhibitor)
  - G-CSF+ Plerixafor
  - Chemotherapy + G-CSF + Plerixafor
- BM harvest
- Experimental: GH, PTH, TPO, SB251353, CTCE-0021

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Limitations of Salvage Mobilization Strategies

Strategy	Complications
Repeat Mobilization	• High product volume when combined with previous collection • Higher cost & morbidity • Associated with high failure rate
Alternative Cytokines • Higher dose of G-CSF • Combine G-CSF with GM-CSF	• Associated with added toxicity or lack of efficacy
Addition of Chemotherapy	• Toxicity, neutropenic fever, admission costs
Traditional Bone Marrow Harvest	• Slower engraftment • Increased cost, risk (due to anesthesia) and pain for patient

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Current PBSC mobilization strategies:
*Chemo-mobilization**

Disease-specific chemo-mobilization
MM:
DPACE, VDT-PACE, CAD
(Relapsed) lymphoma:
ABVD, BEACOPP, (R)-CHOP, (R)-DA-EPOCH, (R)-DHAP, carbo-DHAP, dexa-BEAM, (R)-mini-BEAM, (R)-ICE, IVE, R-AVCBP, R-Bendamustine, VIM

Separate mobilization chemotherapy
Cyclophospamide-based
Etoposide-based

- Cy (range of 1.5–4.0 g/m^2 feasible) plus G-CSF 10 µg/kg on days 3-14
- Leukapheresis: After white count recovery (usually days 12-15)

*Selection based on clinical practise of the expert group

Chemo-mobilization

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journal homepage: www.elsevier.com/lo

Disease specific chemotherapy protocols such as ASHAP /VGEPP are safe and similar mobilization capacity as cyclophosphamide alone

Which regimen is better for stem cell ... oma patients?

Sinem Civriz Bozdağ [a,*], Emre Tekgü... durrahman Sarıca [b], Itır Şirinoğlu Demiriz [a], Şerife Ko...

[a] Ankara Oncology Education and Research Ho... Clinic, Ankara, Turkey
[b] Ankara Oncology Education and Research ... urkey

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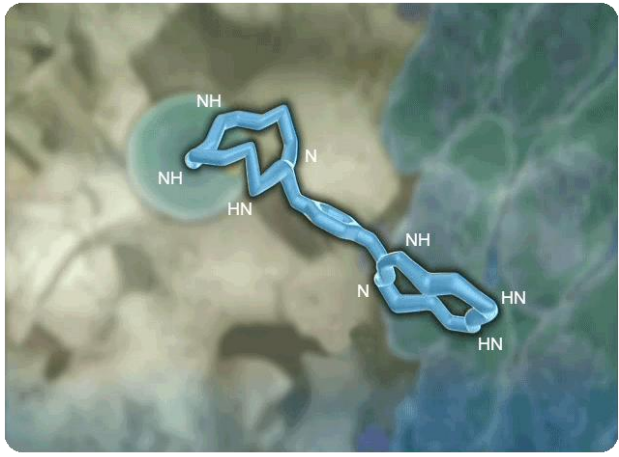
...hemotherapy combined with G-CSF is an effective method for hematopoietic ...ell mobilization, standard chemotherapy protocol leading to best stem cell yield is ...defined. In our study, we aimed to assess the impact of chemotherapy choice on mobilization outcome in lymphoma patients. Patients were mobilized with cyclophosphamide (n:15), ASHAP (n:11) or VGEPP (n:12) protocols. Groups were similar according to collected CD34+ cell count, total nucleated cell count and median apheresis days. Five out of fifteen (33%) patients could not be mobilized in Cy group but there was only one failed mobilization attempt in both salvage groups (9% with ASHAP vs 8% with VGEPP). In conclusion, we showed that VGEPP and ASHAP are safe protocols in terms of stem cell mobilization and have similar mobilization capacity as cyclophosphamide alone.

MOBILIZATION FAILURE:

PLERIXAFOR

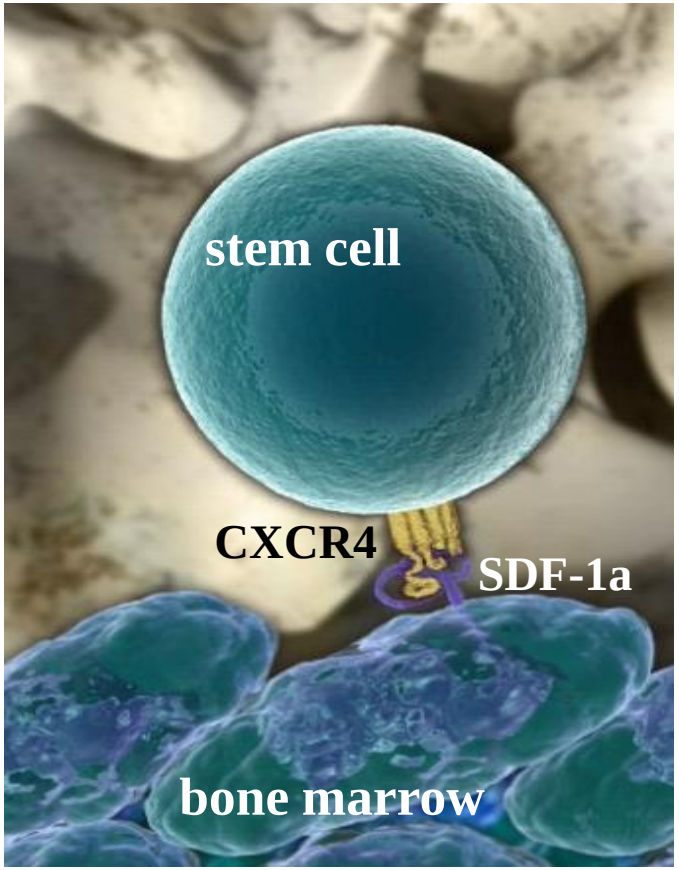
Plerixafor (Mozobil™)

- Reversible inhibitor of CXCR4
- Causes mobilization by disrupting of the SDF-1/CXCR4 interaction.
- Synergizes with G-CSF through its different mechanism of action.
- A single subcutaneous dose of plerixafor at 160–240 μg/kg: 6- to 10-fold increase in $CD34^+$ cell



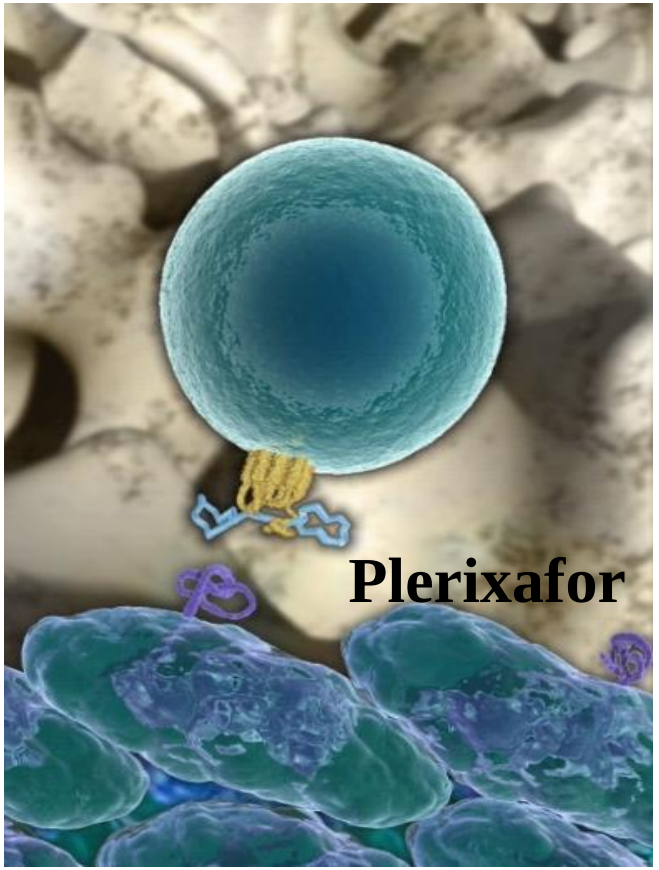
1. Pusic I, DiPersio JF. The use of growth factors in hematopoietic stem cell transplantation. *Curr Pharm Des.* 2008;14:1950-1961.
2. De Clercq E. The bicyclam AMD3100 story. *Nat Rev Drug Discov*. 2003;2:581-7.

Mechanism of Action of Plerixafor



SDF-1α and CXCR4 play key regulatory roles in stem cell trafficking to, and retention by the bone marrow.

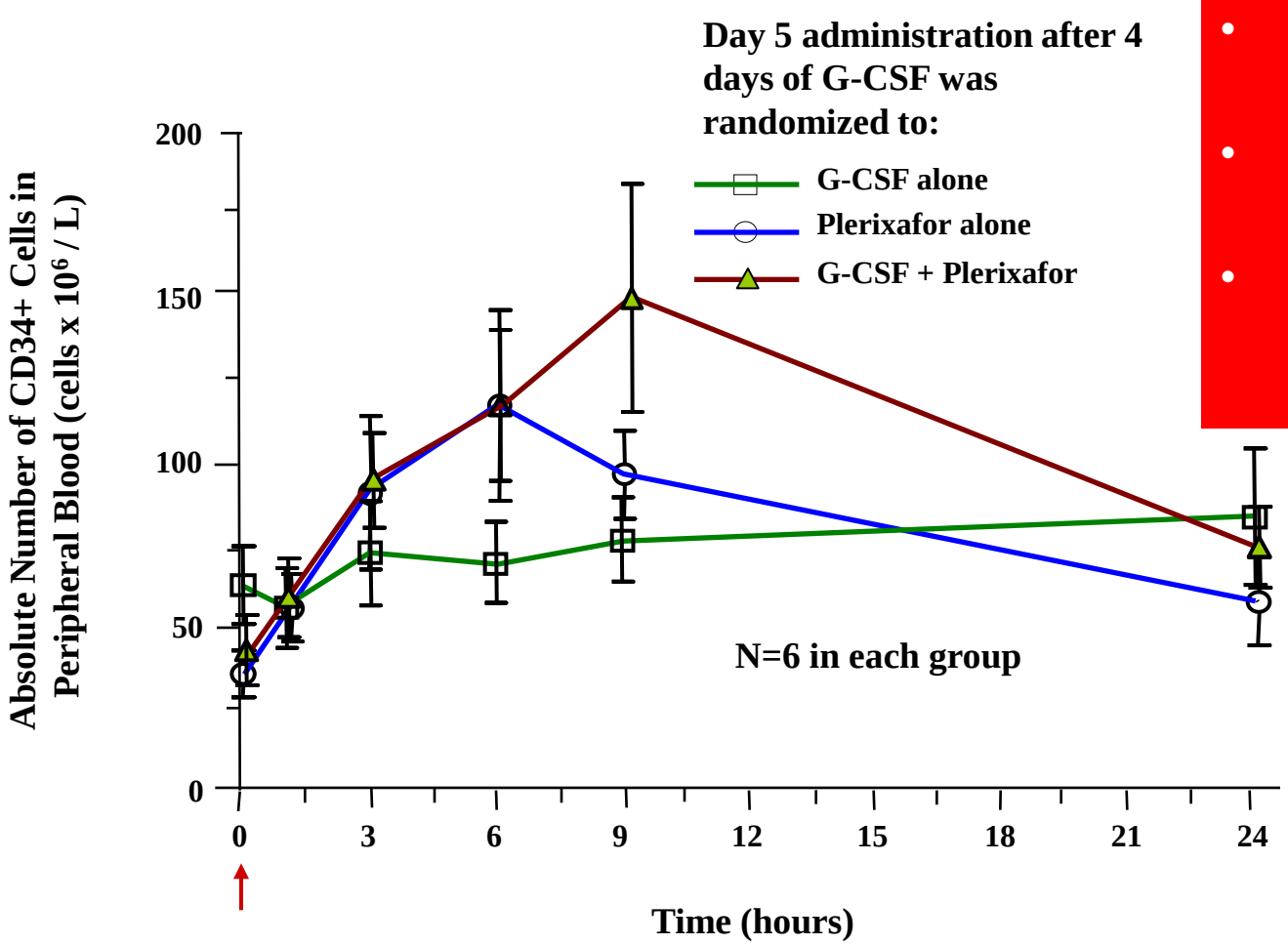
Lapidot T and Petit I. *Exp Hematol*. 2002;30:973



Plerixafor blocks the CXCR4/SDF-1a interaction, releasing stem cells from the bone marrow into the circulating blood.

Martin C, et al. *Br J Haematol*. 2006; 134:326.

Kinetics of Mobilization After Plerixafor + GCSF

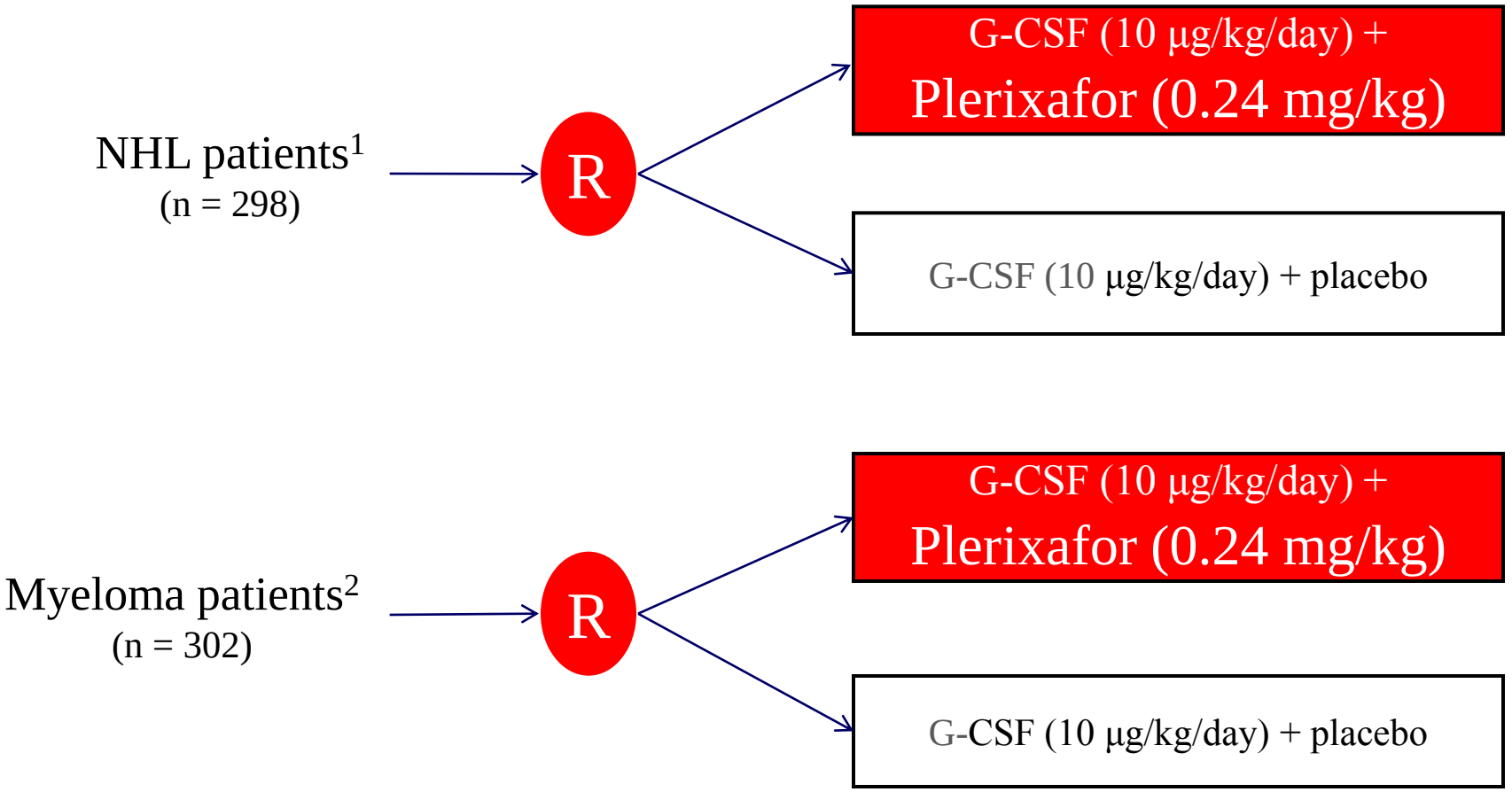


Time calculated after 4 days of G-CSF therapy and randomization to one of three groups on day 5

- Efficacy as single agent
- Synergistic with G-CSF
- Increases likelihood of successful CD34+ cell mobilization

Liles WC, et al. *Transfusion* 2005;45:295.

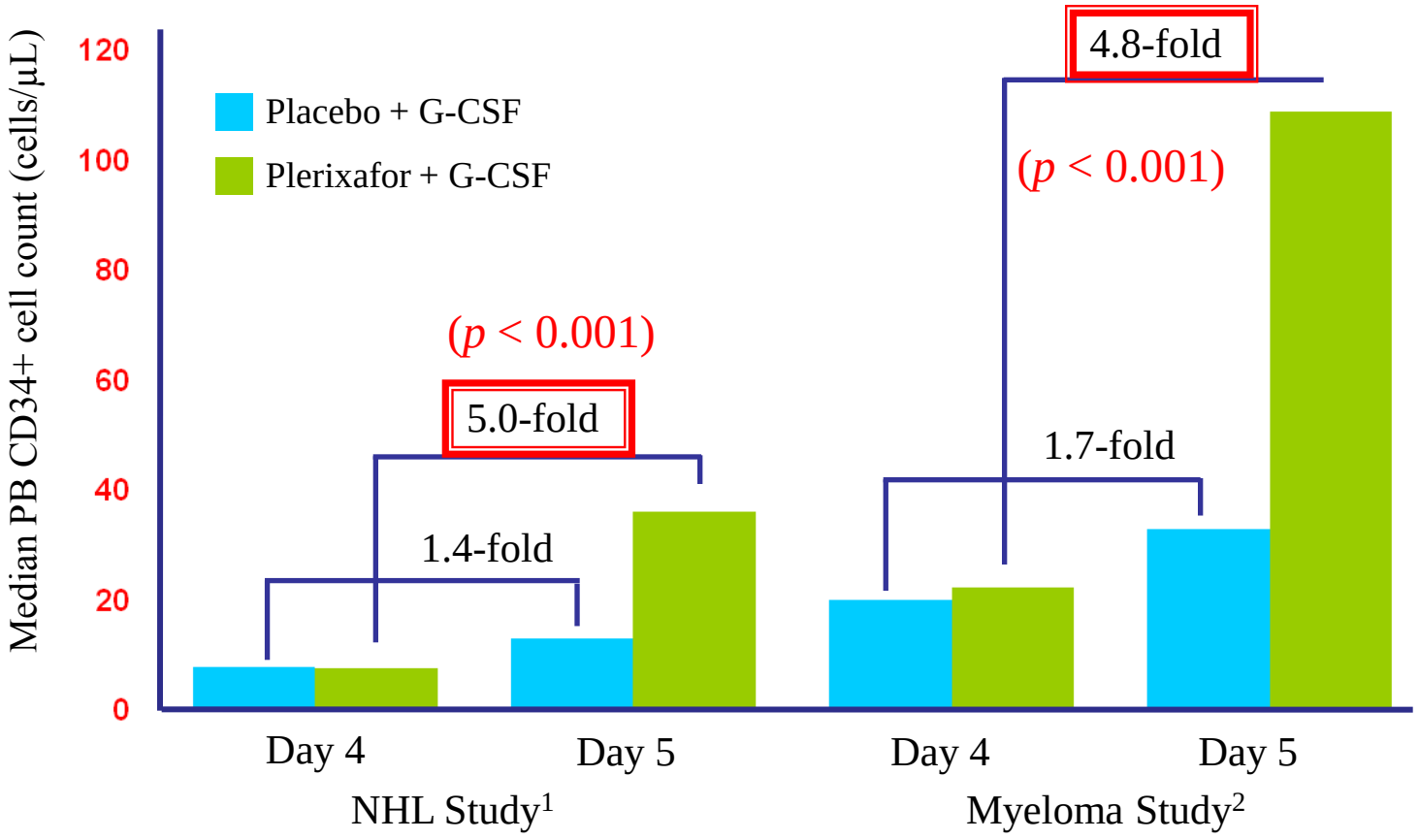
Efficacy – Phase III Trials in MM and NHL



1) DiPersio et al. *J Clin Oncol*. 2009;27(28):4767-4773;
2) DiPersio et al. *Blood* 2009;113:5720-5726.

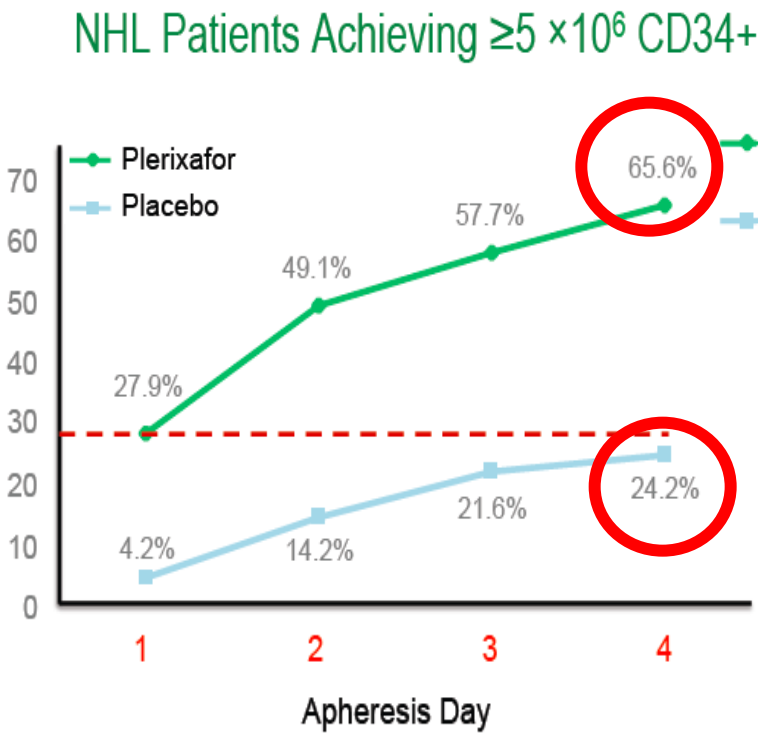
Efficacy – Phase III Trials in MM and NHL

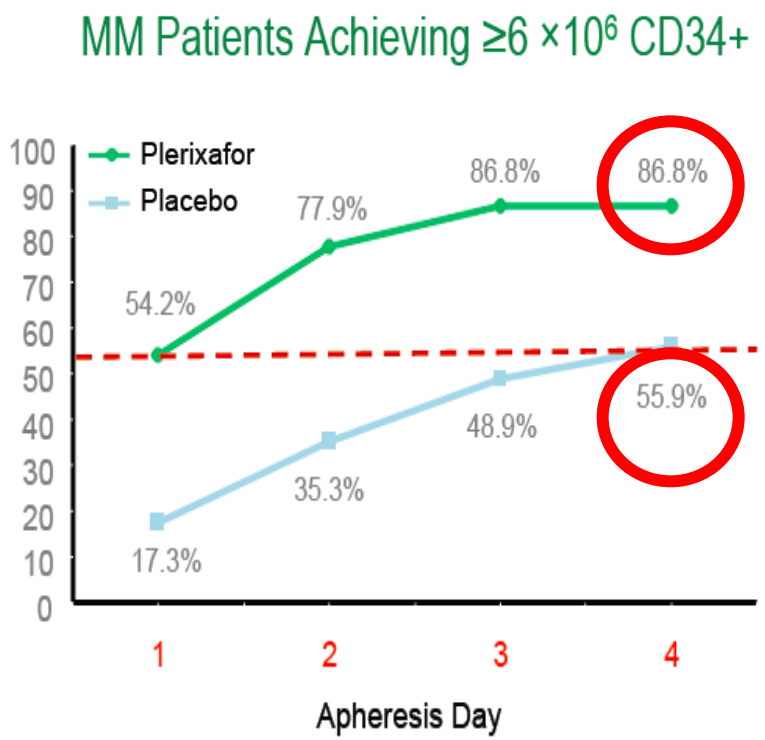
PB CD34+ Cell Levels with G-CSF + Plerixafor



1. DiPersio et al. *J Clin Oncol.* 2009;27(28):4767-4773.
2. DiPersio et al. *Blood*. 2009;113(23):5720-5726.

Efficacy – Phase III Registration Trials in MM and NHL





Efficacy and Safety in Optimal Conditions

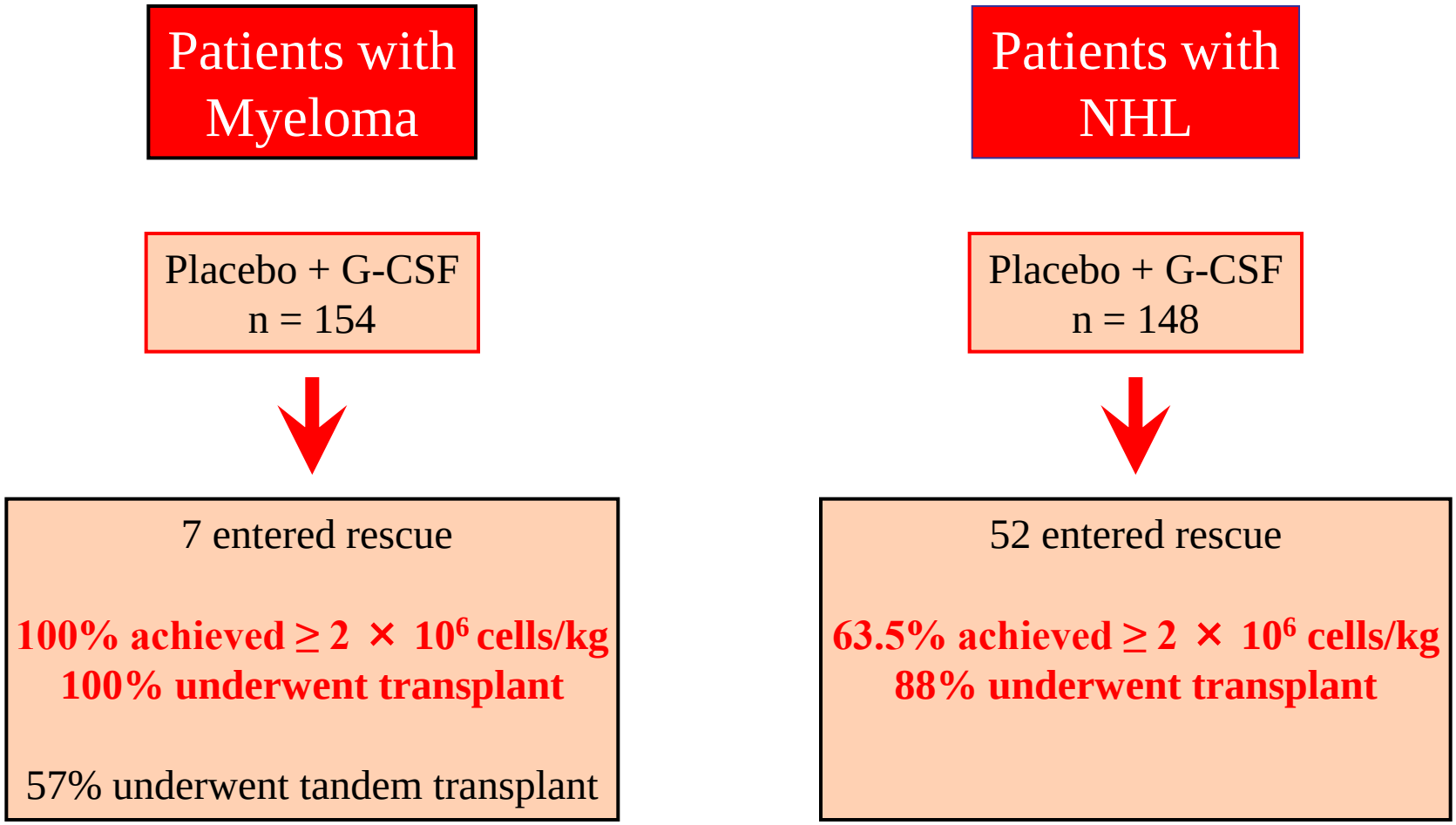
Evidence of Limited Utility in Clinical Context

FDA Approval

EMA Approval

DiPersio et al. *J Clin Oncol.* 2009;27(28):4767-4773.

Efficacy – Phase III Trials in MM and NHL

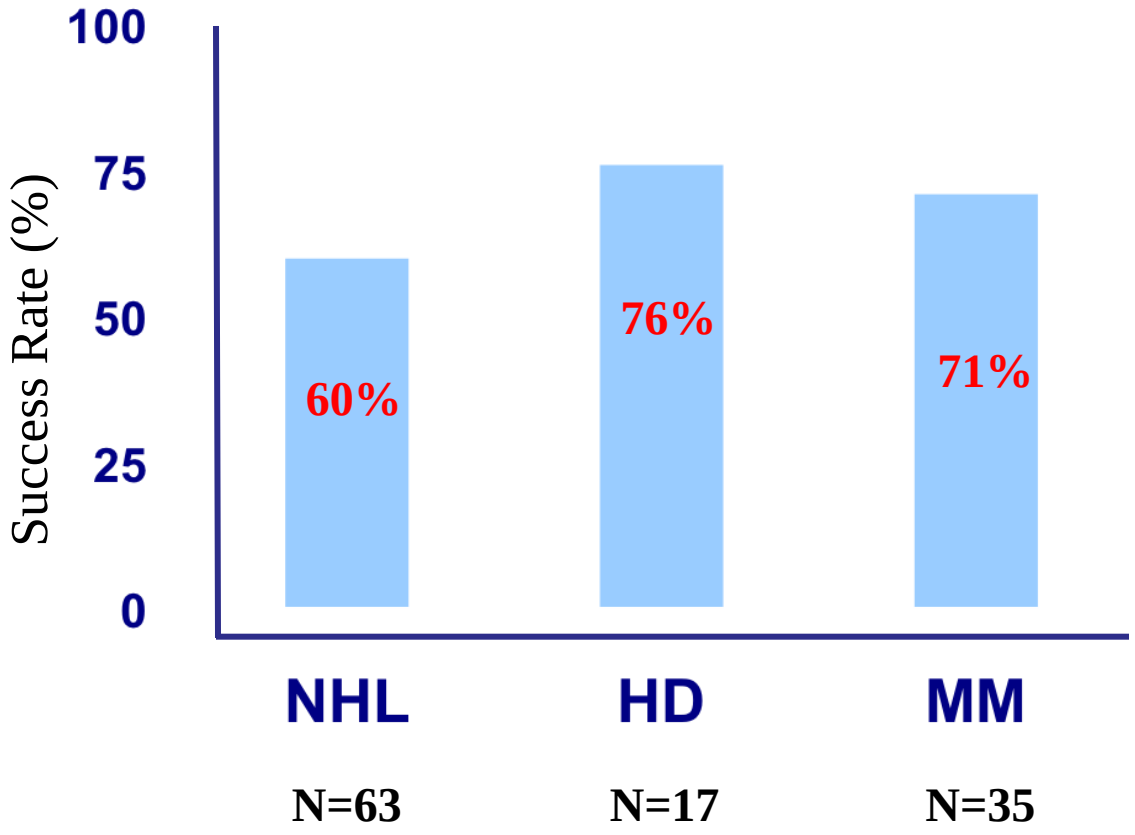


Micallef et al. *Biol Blood Marrow Transplant* 2009

Effectiveness – American Compassionate Use Program

66% of cases collected ≥2 ×10^6 CD34+ Cells/kg

Comparison by Disease Type



Calandra G, et al. *Bone Marrow Transplant* 2008;41:331-338.

Effectiveness – Turkish Study

Transfusion and Apheresis Science 47 (2012) 77–80

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Plerixafor use in patients wit multicenter experience

Emre Tekgündüz [a], Fevzi Al ıkı [c], Ayhan Dönmez [d], Pervin Topçuoğlu [e], Rab yıldız [e], Meltem Kurt Yüksel al [b], Osman İlhan [e]

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[c] Medical Faculty, y, Turkey
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[f] Medi mukkale University, Turkey

T R A C T

Pl
Ste
Mobi
Chemot

Plerixafor in conjunction with G-CSF (G–P) is an effective strategy for hematopoietic stem cell mobilization in patients with previously failed mobilization attempt. Here we report our results with G–P among patients with at least one mobilization failure with G-CSF alone (G) or G-CSF plus chemotherapy (G–C). The study included 20 consecutive patients with lymphoma and myeloma from five centers. In 14 (70%) patients, a minimum of 2×10^6/kg CD34+ stem cells were collected and 16 out of 20 patients (80%) were able to proceed to ASCT. Our study indicates that plerixafor can safely rescue patients with a history of mobilization failure.

80% of patients were able to proceed to ASCT

Efficient Mobilization Strategies and Algorithms

- Risk-adapted algorithms have been proposed:

  1. Preemptive plerixafor in predicted poor mobilizers
  2. Immediate salvage plerixafor for patients with suboptimal mobilization
  3. Remobilization with plerixafor in failed mobilizers.

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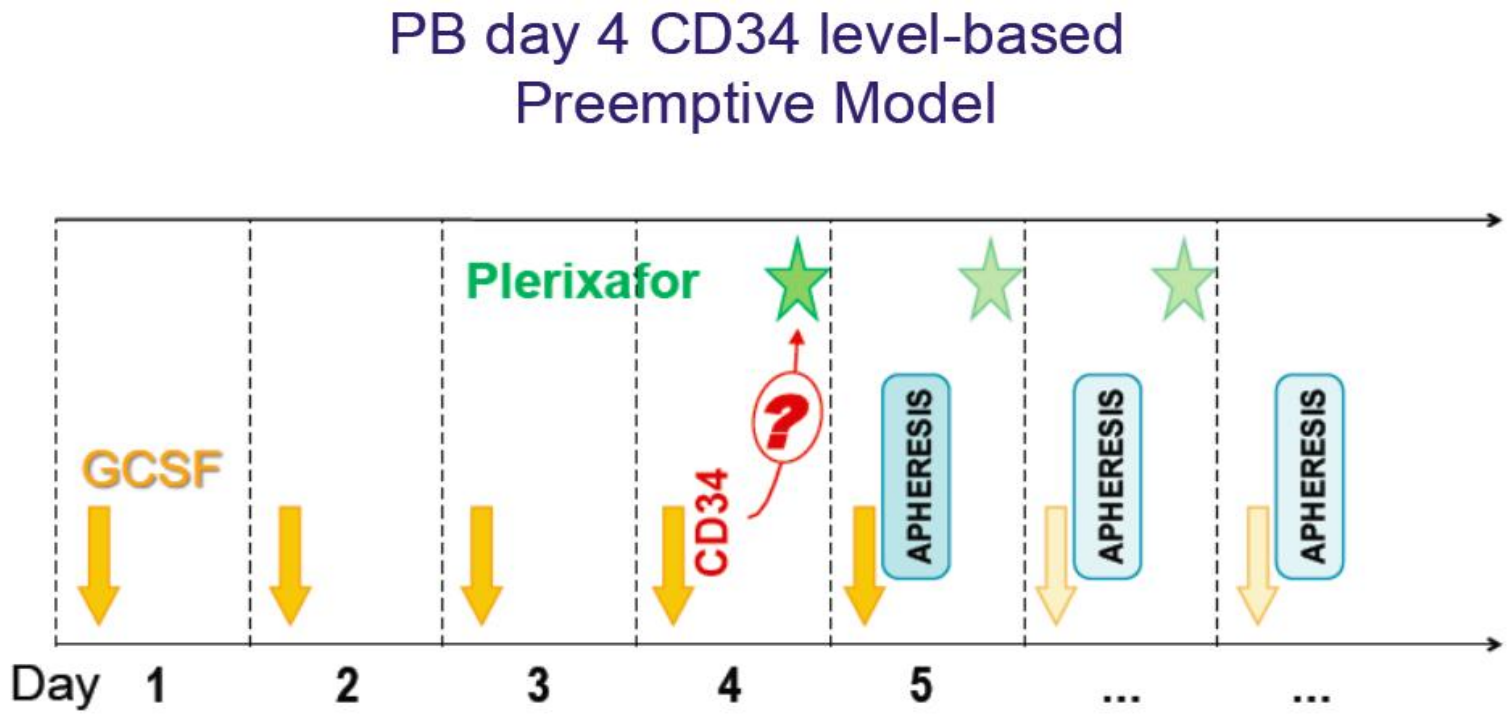
Efficient Mobilization Strategies and Algorithms using Plerixafor

Preemptive plerixafor

- The rational use of preemptive plerixafor **depends on identifying potential poor mobilizers.**



L. Bik To, et al. How I treat patients who mobilize hematopoietic stem cells poorly. BLOOD 2011; 118(17): 4530-4540

Efficient Mobilization Strategies and Algorithms using Plerixafor

Immediate salvage plerixafor

- Immediate salvage plerixafor for patients with suboptimal mobilization;
  - The rational use of immediate salvage plerixafor **depends on real-time indicators to define "poor" and "slow" mobilizers during a mobilization attempt.**
  - These include a **suboptimal PB CD34 cell level** or **suboptimal apheresis yield or both** at the expected first day of apheresis which predicts failure to collect the target yield within an acceptable number of apheresis days.

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Immediate salvage plerixafor

- Immediate salvage plerixafor
  - There is no validated data to define cutoffs for the addition of plerixafor;
  - However, one published algorithm prescribes **the addition of plerixafor on day 5 of G-CSF if the PB CD34 level is 10/μL when collecting cells for 1 transplantation, and 20/μL when collecting cells for 2 transplantations**.
  - **A first-day apheresis yield of 0.5 x10^6 CD34 cells/kg** indicates need for salvage, although higher cutoffs such as a **first-day apheresis of 50% of the target yield are also used**.

L. Bik To, et al. How I treat patients who mobilize hematopoietic stem cells poorly. BLOOD 2011; 118(17): 4530-4540

Remobilization with plerixafor

- Remobilization with plerixafor in failed mobilizers;
  - In failed mobilizers, a remobilization regimen with the addition of plerixafor enables reaching the CD34 cell target in 70% of patients so there is little doubt about its efficacy.
  - One should ensure that there is 4 weeks of break before remobilization.
  - Concerns have been raised about the higher nucleated cell content in the apheresis product affecting apheresis and increasing the infusion volume.
  - This may be overcome by modifying the apheresis Software.

L. Bik To, et al. How I treat patients who mobilize hematopoietic stem cells poorly. BLOOD 2011; 118(17): 4530-4540

Efficient Mobilization Strategies and Algorithms using Plerixafor:
Remobilization with plerixafor

- **Remobilization with plerixafor in failed mobilizers;**
  - Plerixafor-containing regimens have a 30% failure rate among prior failed mobilizers
    - It could not restore low or defective HSC reserve or niche.

✓ Understanding how these factors operate at the molecular level

✓ Steering the development of targeted approaches

✓ Alternative mobilization algorithms **<u>will define the next era of mobilization strategy.</u>**

L. Bik To, et al. How I treat patients who mobilize hematopoietic stem cells poorly. BLOOD 2011; 118(17): 4530-4540

Efficient Mobilization Strategies and Algorithms using Plerixafor

Risk-Adapted Algorithm	Based on CD34 targets and daily yield of CD34

- They monitor CD34 levels in PB on days 4 or 5 of steady state GCSF mobilization and the daily yield of CD34+cells.
- Patients get plerixafor **on day 5**

  if low CD34 (<10 cells/µL) or

  1st day collection <0.5 x10^6/kg
- Failure rates, days of apheresis, and total days of mobilization/collection are lower.
- However, per-patient costs of PBSC mobilization increases.

I.N.M. Micallef et al. Cost-Effectiveness Analysis of a Risk-Adapted Algorithm of Plerixafor Use for Autologous Peripheral Blood Stem Cell Mobilization. Biol Blood Marrow Transplant 2013:87-93.

Efficient Mobilization Strategies and Algorithms using Plerixafor

Risk-Adapted Algorithm	Based on CD34 targets and daily yield of CD34
Pre-collection PB $CD34^+$ count on day 5 of G-CSF	
· If $CD34^+$ count is<10 cells/μL and patient needs a minimum $CD34^+$ cell dose of 2.5 × 10^6/kg	• Administer plerixafor at 5 pm • Continue G-CSF (10 μg/kg) • Perform collection of stem cells next morning (day 6) and assess need for more plerixafor doses based on the collection
· If $CD34^+$ count is 10 cells/μL and patient needs a minimum $CD34^+$ cell dose of 2.5 × 10^6	• No plerixafor given • Perform a large-volume collection (approximately 4–6 BV)
· If $CD34^+$ is >10 but <20 cells/μL and patient needs a minimum $CD34^+$ cell dose of 5.0 × 10^6/kg	• Perform a large-volume collection (approximately 4–6 BV) • Administer plerixafor that evening • Continue G-CSF • Continue collection the following morning and assess need for more plerixafor doses
· If $CD34^+$ count is 20 cells/μL and patient needs a minimum $CD34^+$ cell dose of 5.0 × 10^6/kg	• No plerixafor to be given • Perform a large-volume collection (approximately 4–6 BV)
Day 1 collection product $CD34^+$ count/kg	
· If on the first day of collection the collected product contains less than one-half of the desired dose	• Administer plerixafor that evening • Continue G-CSF • Perform collection the following morning • Assess need for repeating plerixafor

S Abhyankar et al. A risk-based approach to optimize autologous HSC collection with the use of plerixafor. Bone Marrow Transplantation 2012; 47: 483-487.

Efficient Mobilization Strategies and Algorithms using Plerixafor

	Based on CD34 targets and daily yield of CD34
Lymphoma	For steady state disease; •G-CSF 10 μg/kg sq; single dose 4 d. •On Day 4, check PB CD34+. If <10/μL, add plerixafor 240 μg/kg. Collect on Day 5 For active relapse; •Salvage chemotherapy + G-CSF. •When WBC recovers >1x10^9/L check PB CD34+. If CD34+ <10/μL continue to check daily. If after 3 d CD34+ <10/μL, add plerixafor.
Myeloma	For steady state disease; •G-CSF 10 μg/kg single dose x 4 d. •If collecting for 1 transplant: if CD34+ <10/μL, add plerixafor. •If collecting for >1 transplant: if CD34+ <20/μL, add plerixafor. If myeloma relapse or refractory to induction; •Cy 1.5 g/m^2 x 2 d, begin G-CSF 5 μg/kg on Day 3, check PB CD34+ when WBC >1x10^9/L. •If CD34+ <10/μL continue to check for three consecutive days. If PB CD34 remains <10/μL begin plerixafor.
Lymphoma Myeloma mobilization	• If day 1 yield <1.5 x10^6 CD34+/kg, add plerixafor. • If yield beyond day 1<0.5x10^6 CD34+/kg, add plerixafor. • If plerixafor is added and CD34+ cell yield <0.5x10^6 CD34+/kg on 2 consecutive days, patient is a collection failure and all therapy ceases.

Gertz Morie A. Current status of stem cell mobilization. Br J Haematol 2010;150(6):647-62.

Algorithms for Preemptive Plerixafor Use in Stem Cell Mobilization

Study	Target CD34+ Cell Yield, cells/kg	Criteria for Plerixafor Administration			Failure rate, %
Costa et al.[95]	6 × 10⁶ (some MM) 3 × 10⁶ (all others)	Preestablished PB CD34+ [illegible] derived from cost sim[illegible] example, threshol[illegible] target of 3 × 1[illegible] of 25 for[illegible]			
Costa et al.[138]	6 × 10⁶ (some MM) 3 × 10⁶ (all others)	Pre[illegible]	[illegible]M + G-	M	2 22
Abhyankar et al. [96]	2.5 [illegible]	[illegible]esis on [illegible]0 but < 20 [illegible]get is 2.5, begin [illegible]without P; if target is 5, [illegible]apheresis but administer P [illegible]at night Day 5 PB CD34+ ≥20 cells/μL: Begin apheresis without P Apheresis day 1 cell yield <50% of desired collection: Administer P	n = 159 PEP (n = 104 G-CSF alone, n = 55 P + G-CSF)	M	5

Failure rate was 2-5% with premptive plerixafor use

Girald S, et al. Optimizing Autologous Stem Cell Mobilization Strategies to Improve Patient Outcomes: Consensus Guidelines and Recommendations. Biol Blood Marrow Transplant 2013.

Algorithms for Preemptive Plerixafor Use in Stem Cell Mobilization

Study	Target CD34+ Cell Yield, cells/kg	Criteria for Plerixafor Administration		FD	Failure Rate, %
Micallef et al.[99]	2 × 10⁶ (minimum)	Day 5 PB CD34+ daily apher… <0.5 × 1…			5
Micallef et al.[98]	2 × 10⁶ (minimum)	P…	…16 PEP1 + G-CSF	M	19
					5
			n = 98 PEP2 + G-CSF		1
LaPorte et al…		…<12 …or daily apheresis …<1 × 10⁶ or ≤50% of …evious day's yield	n = 68 PEP (n = 38 G-CSF alone, n = 30 P + G-CSF)	M	1
	…s)	Day 4 PB CD34+ <7 cells/μL, give P; day 5 PB CD34+<10/L, give P, begin apheresis on day 6 or day 1 yield <50% target collection	PEP	U	6

Failure rate was 1-6% with preemptive plerixafor use

Girald S, et al. O… …g Autologous Stem Cell Mobilization Strategies to Improve Patient Outcomes: Consensus Guidelines and Recommendations. …Biol Blood Marrow Transplant 2013.

Economic Evaluation of Algorithms including Plerixafor

- Investigations on both clinical effectiveness and cost-effectiveness are needed for chemomobilization versus steady-state mobilization with Plerixafor + G-CSF, for preemptive plerixafor versus upfront plerixafor, and for the role of chemomobilization + G-CSF + Plerixafor in first-line and secondary mobilization.
- Pharmacoeconomics and cost endpoints should be incorporated into all future plerixafor trials, and are warranted for existing trial data.

- P. Shaughnessy et al. Pharmacoeconomics of Hematopoietic Stem Cell Mobilization: An Overview of Current Evidence and Gaps in the Literature. Biol Blood Marrow Transplant 2013:1301-1309.
- Girald S, et al. Optimizing Autologous Stem Cell Mobilization Strategies to Improve Patient Outcomes: Consensus Guidelines and Recommendations. Biol Blood Marrow Transplant 2013.

OTHER OPTIONS IN MOBILIZATION FAILURE

Salvage BM harvest

- Salvage BM harvests:

✓ may be attempted in rare circumstances:

(1) Refractory poor mobilization despite novel agents,

(2) When these agents are unavailable, or

(3) In the presence of contraindication to apheresis or stem cell mobilization regimens.

✓ It is more advisable:

- to seek enrollment on a clinical trial
- a compassionate use program of a novel mobilization agent before resorting to salvage BM harvest.

- L. Bik To, et al. How I treat patients who mobilize hematopoietic stem cells poorly. BLOOD 2011; 118(17): 4530-4540.
- A.S. Kanate et al. Salvage Bone Marrow Harvest in Patients Failing Plerixafor-Based Stem Cell Mobilization Attempt: Feasibility and Autologous Transplantation Outcomes. Biol Blood Marrow Transplant 2013: 1133-1135.
- Girald S, et al. Optimizing Autologous Stem Cell Mobilization Strategies to Improve Patient Outcomes: Consensus Guidelines and Recommendations. Biol Blood Marrow Transplant 2013.

Experimental agents

- Alternative CXCR4 inhibitors
- Inhibitor of VLA4
- Bortezomib
- Parathyroid hormone (PTH)

L. Bik To, et al. How I treat patients who mobilize hematopoietic stem cells poorly. Blood 2011; 118(17): 4530-4540.
Motabi et al. Advances in stem cell mobilization. Blood Review 2012;26:267-78.

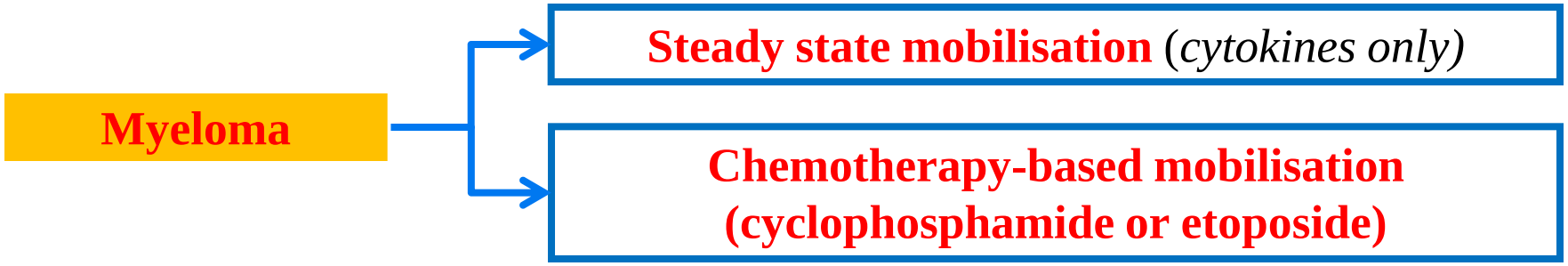
GUIDES FOR

STEM CELL COLLECTION IN

MOBILIZATION FAILURE

Biology of Blood and Marrow Transplantation

Consensus: *PBSC mobilization strategies for MM patients*



- Decision whether to use steady state or chemo-mobilization should be based on local guidelines
- However, it is less likely to obtain sufficient $CD34^+$ cell numbers with steady state mobilization
- Cyclophosphamide monotherapy:
  - range of 1.5–4.0 g/m^2 feasible

Consensus: *PBSC mobilization strategies for lymphoma patients*

- Disease-specific chemotherapy approaches are suggested to avoid the burden of additional chemotherapy cycles

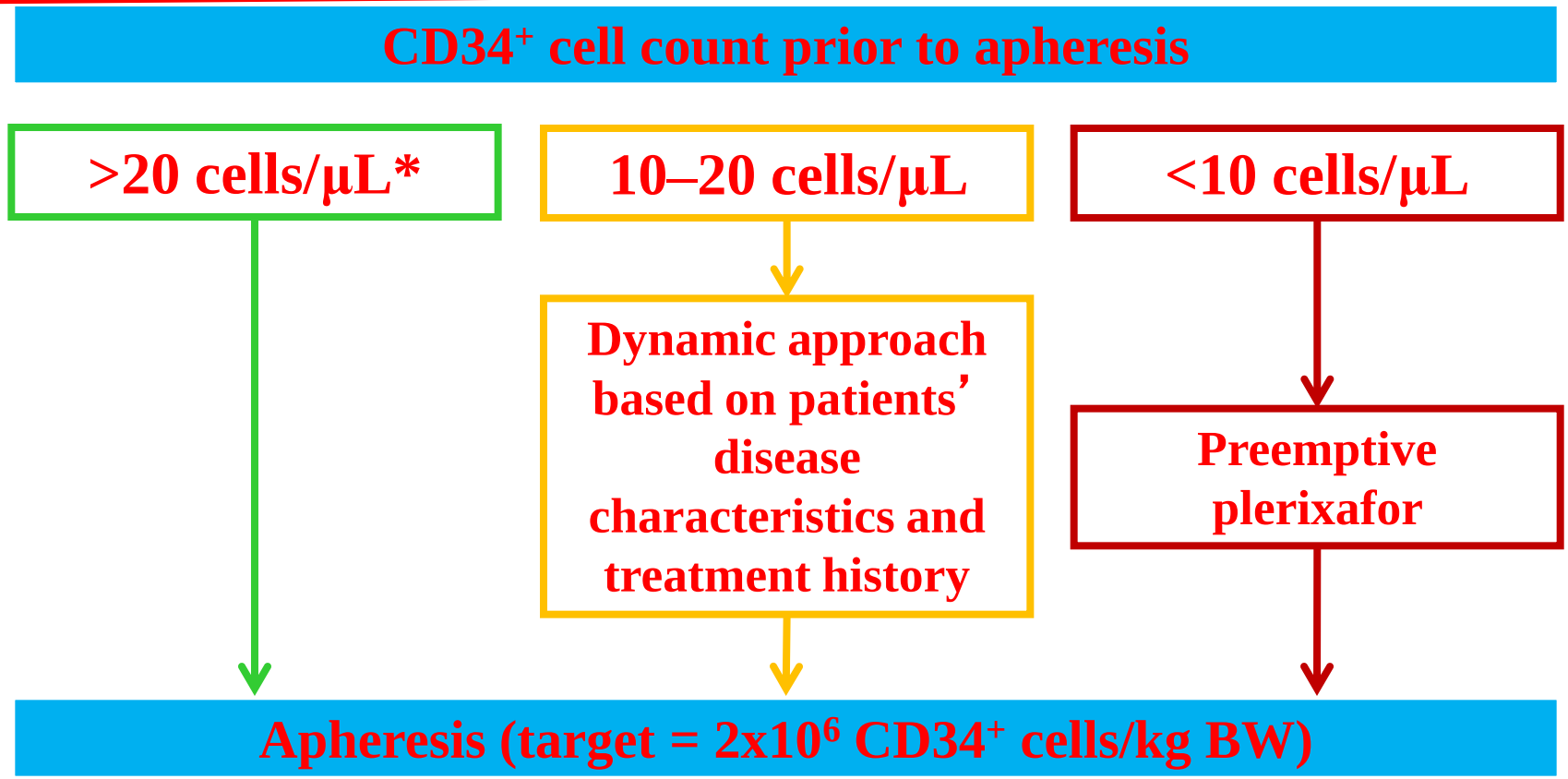
- Steady state mobilization may be an option for selected patients:
  - patients in complete remission
  - patients ineligible for chemo-mobilization

Consensus:
Optimization of mobilization protocols

- Change chemo-mobilisation strategy
  - Steady state → chemo-mobilisation
  - Chemo-mobilization → alternative chemo- mobilisation approach

- Addition of most recent mobilization agents such as plerixafor

Consensus: *Proactive intervention to rescue mobilization failure*



Readily available and robust techniques to determine $CD34^+$ cell counts are needed

*No proactive intervention required.
BW, body weight.

Conclusions

- PBSC mobilization can be optimized with an appropriate strategy adapted to each patient
  - based on disease and treatment features
  - individual collection goal

- A low $CD34^+$ cell count in PB prior to apheresis is a candidate predictor for poor PBSC collection

- Determination of $CD34^+$ cell count is suggested
  - might estimate patients' risk for poor PBSC collection
  - allows proactive intervention to rescue mobilization failure

Recommendations for remobilization

ASBMT
Biology of Blood and Marrow Transplantation

- ✓ Cytokine-alone strategies should not be used for remobilization.
- ✓ Plerixafor should be included in the remobilization regimen for patients failing a non–plerixafor-containing mobilization attempt
- ✓ Remobilization options: P + G-CSF and CM + G-CSF + P.
- ✓ The addition of plerixafor to CM should be explored in prospective trials.
- ✓ CM is an acceptable strategy for patients with failed cytokine-only mobilization.
- ✓ Bone marrow harvest should be reserved as a third-line approach

Girald S, et al. Optimizing Autologous Stem Cell Mobilization Strategies to Improve Patient Outcomes: Consensus Guidelines and Recommendations. Biol Blood Marrow Transplant 2013.

Recommendations for algorithm development

Biology of Blood and Marrow Transplantation

- ✓ Each center should develop and implement its own algorithms
- ✓ Algorithms should include center-specific data regarding:
  - priorities of the transplantation center,
  - priorities of patients and caregivers,
  - relationship of PB $CD34^+$ cell count to collection yield in the center,
  - center-specific cost assessments,
  - minimum and target cell collections.

Girald S, et al. Optimizing Autologous Stem Cell Mobilization Strategies to Improve Patient Outcomes: Consensus Guidelines and Recommendations. Biol Blood Marrow Transplant 2013.

Take Home Massages-1

- ✓ PBSC is the main source of stem cell for HSCT
- ✓ Poor mobilization cannot be completely predicted.
- ✓ Close monitoring of circulating CD34+ cells allows for precise time to harvest.
- ✓ >$2x10^6$ CD 34+ cells/kg is enough to achieve a good engraftment.
- ✓ Mobilization Failure rate is 5-30% with conventional regimens

Take Home Massages-2

- Strategies to manage hard to mobilize patients:
  - ✓ Addition of chemotherapy:
    - Chemotherapy plus growth factor enhances mobilization
    - When the chemotherapy is indicated for treatment of the malignancy.
  - ✓ Harvesting the BM
  - ✓ **Plerixafor in combination with G-CSF,**

Take Home Massages-3

- **Plerixafor in combination with G-CSF,**
  - FDA/EMEA approved for HSC mobilization in NHL and MM
  - Mobilizes HSCs by inhibition of SDF-1 and CXCR4 interaction.
  - Synergistic with G-CSF.
  - The combination with G-CSF:
    - reduce the number of apheresis required for PBPC collection
    - enhance to ability to perform autologous HSCT in “hard to mobilize” patients.
    - may overcome poor mobilization in 60% of the cases.

- Dual inhibitor approach may ultimately provide a more efficient method to collect HSC in a single day