STEM CELL COLLECTION IN MOBILIZATION FAILURE

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Department of Hematology and Bone Marrow Transplantation Unit
• 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
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.

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

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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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

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.

MOBILIZATION FAILURE
What’s a Poor Mobilizer?

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

- L. Bik To, et al. How I treat patients who mobilize hematopoietic stem cells poorly. BLOOD 2011; 118(17): 4530-4540
<table>
<thead>
<tr>
<th>Author</th>
<th>Patient Population</th>
<th>Regimen</th>
<th>CD34+ Yield, × 10^6/kg</th>
<th>FD</th>
<th>Failure Rate, %</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>n = 119 G-CSF</td>
<td>5.21</td>
<td></td>
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<tr>
<td></td>
<td></td>
<td>n = 976 G-CSF</td>
<td>3.36</td>
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<td>18.6</td>
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<td>n = 64 CM + G-CSF</td>
<td>5.43</td>
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<td>n = 1775 G-CSF ± Cy</td>
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<td>47</td>
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<tr>
<td>Pusic et al. [20]</td>
<td>MM, lymphoma</td>
<td>n = 97 Cy + G-CSF</td>
<td>28.8 (median for all</td>
<td>O</td>
<td>17.9</td>
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<tr>
<td></td>
<td></td>
<td>n = 87 DHAP + G-CSF</td>
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<td></td>
<td></td>
<td>n = 83 MAD + G-CSF</td>
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<tr>
<td>Gertz et al. [73]</td>
<td>MM, lymphoma</td>
<td>n = 97 Cy + G-CSF</td>
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<tr>
<td>Pavone et al. [72]</td>
<td>Lymphoma</td>
<td>n = 87 DHAP + G-CSF</td>
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<tr>
<td></td>
<td></td>
<td>n = 83 MAD + G-CSF</td>
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<tr>
<td>Roberts et al. [75]</td>
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<td>n = 97 CM + G-CSF</td>
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<td>O</td>
<td>29.9</td>
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<td></td>
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<td>n = 155 G-CSF</td>
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<td>38.1</td>
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<tr>
<td>Alegre et al. [21]</td>
<td>MM</td>
<td>n = 18 Cy + GM-CSF</td>
<td>6.8</td>
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<td>NR</td>
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<tr>
<td>Narayanasami et al. [100]</td>
<td>Lymphoma</td>
<td>n = 22 G-CSF</td>
<td>4.9</td>
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<td>NR</td>
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<tr>
<td>Desikan et al. [23]</td>
<td>MM</td>
<td>n = 22 G-CSF</td>
<td>2.5</td>
<td>M</td>
<td>4.5</td>
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<td></td>
<td></td>
<td>n = 24 Cy + G-CSF</td>
<td>7.2</td>
<td></td>
<td>4.2</td>
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<tr>
<td>Dazzi et al. [101]</td>
<td>NHL</td>
<td>n = 22 G-CSF</td>
<td>5.8</td>
<td>O</td>
<td>23</td>
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<td></td>
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<td>n = 22 Cy + G-CSF</td>
<td>33.4</td>
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<td>18</td>
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<td>Schiller [191]</td>
<td>MM</td>
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<td></td>
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<td>n = 12 Cy + G-CSF</td>
<td>6.41</td>
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<td>n = 37 Cy + G-CSF</td>
<td>4.65</td>
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### Factors described to be predictive of poor PBSC collection

<table>
<thead>
<tr>
<th>Factors</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (older patients)</td>
<td>1. Olivieri et al. Bone Marrow Transplant 2012;47:342-51.</td>
</tr>
<tr>
<td>Disease (more advanced stage)</td>
<td>1-3</td>
</tr>
<tr>
<td>Prior chemotherapy</td>
<td>• Higher no. of prior treatment lines 1-4</td>
</tr>
<tr>
<td></td>
<td>• Type of chemotherapy (fludarabine, lenalidomide [controversial] or melphalan) 1-5</td>
</tr>
<tr>
<td>Prior irradiation</td>
<td>1,2</td>
</tr>
<tr>
<td>Low CD34⁺ cell count in PB before apheresis</td>
<td>3,4,7</td>
</tr>
<tr>
<td>Low platelet count before mobilisation (controversial)</td>
<td>8,9</td>
</tr>
</tbody>
</table>

CD34⁺ cell count in PB before apheresis is presumably the most robust predictor for poor PBSC collection 1,3,4,7
Factors Associated With Poor Mobilization

Predicting the successful peripheral blood stem cell harvesting

İtir Şirinoğlu Demiriz*, Sinem Civriz Bozdağ, Emre Yılmaz, Bilge Uğur, Gamze Durgun, Şerife Koçubaba, Fevzi Altuntaş

Ankara Oncology Education and Research Hospital, Hematology and Hemotherapy Education and Research Clinic, Ankara, Turkey

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Article history:
Available online xxxx

Previously defined factors affecting the mobilization success include age, prior chemotherapy 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
  - Increased need for transfusions

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

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

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Current PBSC mobilization strategies:  
Chemo-mobilization*

<table>
<thead>
<tr>
<th>Disease-specific chemo-mobilization</th>
<th>Separate mobilization chemotherapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>MM:</td>
<td>Cyclophosphamide-based</td>
</tr>
<tr>
<td>DPACE, VDT-PACE, CAD</td>
<td>Etoposide-based</td>
</tr>
<tr>
<td>(Relapsed) lymphoma:</td>
<td></td>
</tr>
</tbody>
</table>
| ABVD, BEACOPP, (R)-CHOP, (R)-DA-EPOCH, (R)-DHAP, carbo-DHAP, dexta-BEAM, (R)-mini-BEAM, (R)-ICE, IVE, R-AVGBP, R-Bendamustine, VIM | • Cy (range of 1.5–4.0 g/m² 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
Disease-specific chemotherapy protocols such as ASHAP and NGEPP are safe and similar mobilization capacity as cyclophosphamide alone. Chemo-mobilization.
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

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

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


Kinetics of Mobilization After Plerixafor + GCSF

Day 5 administration after 4 days of G-CSF was randomized to:
- Efficacy as single agent
- Synergistic with G-CSF
- Increases likelihood of successful CD34+ cell mobilization

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

Efficacy – Phase III Trials in MM and NHL

NHL patients\(^1\)  
(n = 298)

Myeloma patients\(^2\)  
(n = 302)

<table>
<thead>
<tr>
<th>Group</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>G-CSF (10 μg/kg/day) + Plerixafor (0.24 mg/kg)</td>
<td></td>
</tr>
<tr>
<td>G-CSF (10 μg/kg/day) + placebo</td>
<td></td>
</tr>
</tbody>
</table>

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Efficacy – Phase III Trials in MM and NHL

**PB CD34+ Cell Levels with G-CSF + Plerixafor**

- **Placebo + G-CSF**
- **Plerixafor + G-CSF**

**Median PB CD34+ cell count (cells/µL)**
- **NHL Study**: 1.4-fold
  - Day 4: 5.0-fold
  - Day 5: 4.8-fold (p < 0.001)

**Myeloma Study**: 1.7-fold
- Day 4
- Day 5

**References**
Efficacy – Phase III Registration Trials in MM and NHL

Efficacy and Safety in Optimal Conditions

FDA Approval

Efficacy – Phase III Trials in MM and NHL

**Patients with Myeloma**

- Placebo + G-CSF
  - n = 154
  - 7 entered rescue
  - 100% achieved $\geq 2 \times 10^6$ cells/kg
  - 100% underwent transplant
  - 57% underwent tandem transplant

**Patients with NHL**

- Placebo + G-CSF
  - n = 148
  - 52 entered rescue
  - 63.5% achieved $\geq 2 \times 10^6$ cells/kg
  - 88% underwent transplant

Micallef et al. *Biol Blood Marrow Transplant* 2009
66% of cases collected ≥2 × 10^6 CD34+ Cells/kg

Comparison by Disease Type

- **NHL**: 60% (N=63)
- **HD**: 76% (N=17)
- **MM**: 71% (N=35)

80% of patients were able to proceed to ASCT
• 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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The rational use of preemptive plerixafor depends on identifying potential poor mobilizers.

PB day 4 CD34 level-based Preemptive Model

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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.
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 x10⁶ 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.
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.

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• 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 **will define the next era of mobilization strategy.**

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### Efficient Mobilization Strategies and Algorithms using Plerixafor

<table>
<thead>
<tr>
<th>Risk-Adapted Algorithm</th>
<th>Based on CD34 targets and daily yield of CD34</th>
</tr>
</thead>
<tbody>
<tr>
<td>• They monitor CD34 levels in PB on days 4 or 5 of steady state GCSF mobilization and the daily yield of CD34+cells.</td>
<td></td>
</tr>
<tr>
<td>• Patients get plerixafor <strong>on day 5</strong></td>
<td></td>
</tr>
<tr>
<td></td>
<td>if low CD34 (&lt;10 cells/μL) or</td>
</tr>
<tr>
<td></td>
<td><strong>1st day collection &lt;0.5 x10⁶/kg</strong></td>
</tr>
<tr>
<td>• Failure rates, days of apheresis, and total days of mobilization/collection are lower.</td>
<td></td>
</tr>
<tr>
<td>• However, per-patient costs of PBSC mobilization increases.</td>
<td></td>
</tr>
</tbody>
</table>

Efficient Mobilization Strategies and Algorithms using Plerixafor

<table>
<thead>
<tr>
<th>Risk-Adapted Algorithm</th>
<th>Based on CD34 targets and daily yield of CD34</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Pre-collection PB CD34(^+) count on day 5 of G-CSF</strong></td>
<td></td>
</tr>
</tbody>
</table>
| - If CD34\(^+\) count is <10 cells/μL and patient needs a minimum CD34\(^+\) cell dose of 2.5 \(\times\) 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 \(\times\) 10\(^6\)/kg | • 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 \(\times\) 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 \(\times\) 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 |

<table>
<thead>
<tr>
<th>Lymphoma</th>
<th>Based on CD34 targets and daily yield of CD34</th>
</tr>
</thead>
<tbody>
<tr>
<td>For steady state disease;</td>
<td>• G-CSF 10 μg/kg sq; single dose 4 d.</td>
</tr>
<tr>
<td>• On Day 4, check PB CD34+. If &lt;10/μL, add plerixafor 240 μg/kg. Collect on Day 5</td>
<td></td>
</tr>
<tr>
<td>For active relapse;</td>
<td>• Salvage chemotherapy + G-CSF.</td>
</tr>
<tr>
<td>• When WBC recovers &gt;1x10⁹/L check PB CD34+. If CD34+ &lt;10/μL continue to check daily. If after 3 d CD34+ &lt;10/μL, add plerixafor.</td>
<td></td>
</tr>
<tr>
<td>Myeloma</td>
<td></td>
</tr>
<tr>
<td>For steady state disease;</td>
<td>• G-CSF 10 μg/kg single dose x 4 d.</td>
</tr>
<tr>
<td>• If collecting for 1 transplant: if CD34+ &lt;10/μL, add plerixafor.</td>
<td></td>
</tr>
<tr>
<td>• If collecting for &gt;1 transplant: if CD34+ &lt;20/μL, add plerixafor.</td>
<td></td>
</tr>
<tr>
<td>If myeloma relapse or refractory to induction;</td>
<td></td>
</tr>
<tr>
<td>• Cy 1.5 g/m² x 2 d, begin G-CSF 5 μg/kg on Day 3, check PB CD34+ when WBC &gt;1x10⁹/L.</td>
<td></td>
</tr>
<tr>
<td>• If CD34+ &lt;10/μL continue to check for three consecutive days. If PB CD34 remains &lt;10/μL begin plerixafor.</td>
<td></td>
</tr>
<tr>
<td>Lymphoma Myeloma mobilization</td>
<td>• If day 1 yield &lt;1.5 x10⁶ CD34+/kg, add plerixafor.</td>
</tr>
<tr>
<td>• If yield beyond day 1&lt;0.5x10⁶ CD34+/kg, add plerixafor.</td>
<td></td>
</tr>
<tr>
<td>• If plerixafor is added and CD34+ cell yield &lt;0.5x10⁶ CD34+/kg on 2 consecutive days, patient is a collection failure and all therapy ceases.</td>
<td></td>
</tr>
<tr>
<td>Study</td>
<td>Target CD34+Cell Yield, cells/kg</td>
</tr>
<tr>
<td>------------------</td>
<td>----------------------------------</td>
</tr>
<tr>
<td>Costa et al. [95]</td>
<td>6 x 10⁶ (some MM)</td>
</tr>
<tr>
<td></td>
<td>3 x 10⁶ (all others)</td>
</tr>
<tr>
<td>Costa et al. [138]</td>
<td>6 x 10⁶ (some MM)</td>
</tr>
<tr>
<td></td>
<td>3 x 10⁶ (all others)</td>
</tr>
<tr>
<td>Abhyankar et al. [96]</td>
<td>2.5 - 3.5 × 10⁷ cells/kg</td>
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</table>

<table>
<thead>
<tr>
<th></th>
<th>Study Target</th>
<th>CD34⁺Cell Yield, cells/kg</th>
<th>Criteria for Plerixafor Administration</th>
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<tbody>
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<td></td>
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### Algorithms for Preemptive Plerixafor Use in Stem Cell Mobilization

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### Failure rate was 2-5% with preemptive plerixafor use

### Algorithms for Preemptive Plerixafor Use in Stem Cell Mobilization

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<td>PEP U 6</td>
</tr>
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<td>LaPorte et al. [83]</td>
<td>2 × 10⁶ (minimum)</td>
<td>Day 5 PB CD34⁺ &lt; 1 × 10⁶ or ≤ 50% of previous day’s yield</td>
</tr>
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*FD, Failure Rate, %*

Failure rate was 1-6% with preemptive plerixafor use.
• 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.


OTHER OPTIONS IN MOBILIZATION FAILURE
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.

Experimental agents

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

GUIDES FOR STEM CELL COLLECTION IN MOBILIZATION FAILURE

EBMT
European Group for Blood and Marrow Transplantation

ASBMT
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/m² 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

CD34+ cell count prior to apheresis

- >20 cells/μL*
- 10–20 cells/μL
- <10 cells/μL

Dynamic approach based on patients’ disease characteristics and treatment history

Apheresis (target = 2x10⁶ CD34+ cells/kg BW)

Preemptive plerixafor

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

✓ 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.

Recommendations for algorithm development

✓ 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.

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
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,
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