Definizione e gestione del “predicted e proven poor mobilizer”

Attilio Olivieri
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
tempo of PMN engraftment was indistinguishable between patients who received 2.5 to 5.0 and >5.0 x 10^6 CD34+ cells/kg.

In contrast, the probabilities for achieving platelet independence were distinct for each cell dose level.
Poor mobilization is an independent prognostic factor in patients with malignant lymphomas treated by peripheral blood stem cell transplantation.

V Pavone\textsuperscript{1,2}, F Gaudio\textsuperscript{1}, G Console\textsuperscript{3}, U Vitolo\textsuperscript{4}, P Iacopino\textsuperscript{3}, A Guarini\textsuperscript{1}, V Liso\textsuperscript{1}, T Perrone\textsuperscript{1}

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%
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 $2 \times 10^6$/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>
<thead>
<tr>
<th>Risk factor</th>
<th>Patients over 60 years of age have inferior stem cell mobilization</th>
<th>Consider plerixafor mobilization</th>
</tr>
</thead>
<tbody>
<tr>
<td>Melphalan exposure</td>
<td>Melphalan exposure has traditionally been associated with poor stem cell collection</td>
<td>Observation needs to be confirmed in the context of novel therapies. Current practice of avoiding melphalan should continue until studies performed</td>
</tr>
<tr>
<td>Extensive prior therapy or prolonged disease duration</td>
<td>Collection failures are associated with disease duration and extent of prior therapy</td>
<td>Consider harvesting early in the course of the disease even in patients opting out of early high-dose therapy consolidation</td>
</tr>
<tr>
<td>Extensive radiotherapy to marrow bearing tissue</td>
<td>Collection failures increase</td>
<td>Consider collection before radiotherapy</td>
</tr>
</tbody>
</table>

Giralt S.
Leukemia 2009
Rescue Procedure with Plerixafor: when and for who?

- Patients who failed to collect $\geq 0.8 \times 10^6$ CD34$^+$ cells/kg after 2 days of apheresis (??)

- or $<2 \times 10^6$ CD34$^+$ cells/kg in 4 apheresis days

- or patients planned for tandem ASCT and did not collect $\geq 4 \times 10^6$ CD34$^+$ cells/kg in $\leq 4$ apheresis days

  - ....were given the option to participate in an open-label rescue procedure

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

mean predicted values

individual predicted values.
Impact of Mobilization and Remobilization Strategies on Achieving Sufficient Stem Cell Yields for Autologous Transplantation


• 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 \(10^6\) CD34+ cells/kg after ≥ 5 aphaereses

• Only 23% of remobilized patients achieved ≥2 \(10^6\) CD34+ cells/kg and 30% failed to pool sufficient number of stem cells from both collections.
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)

- Increase ASCT feasibility
- Avoid delay to transplantation
- Avoid side effects of remobilization
- Reduce time to engraftment
- Optimizing resource use

**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”

**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 Olivieri¹, M Marchetti², R Lemoli³, C Tarella⁴, A Iacone⁵, F Lanza⁶, A Rambaldi⁷ and A Bosi⁸ 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).
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

The Analytic Hierarchy Process (AHP)

- Disease status
- BM involv
- N° prior lines
- Myelotoxic
- Prior RT
- BM cell
- Age
- Mobiliz therapy
- Peak CD34
- Apher procedure
- Harvest CD34

From conceptual criteria, to the operational 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......

<table>
<thead>
<tr>
<th>Criteria</th>
<th>Cost</th>
<th>Efficiency</th>
<th>Power (KW)</th>
<th>Delivery</th>
<th>Priority</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cost</td>
<td>1</td>
<td>3</td>
<td>2</td>
<td>2</td>
<td>0.398</td>
</tr>
<tr>
<td>Efficiency</td>
<td>-</td>
<td>1</td>
<td>1/4</td>
<td>1/4</td>
<td>0.085</td>
</tr>
<tr>
<td>Power (KW)</td>
<td>-</td>
<td>-</td>
<td>1</td>
<td>1/2</td>
<td>0.218</td>
</tr>
<tr>
<td>Time to delivery</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>1</td>
<td>0.299</td>
</tr>
</tbody>
</table>
Pairwise comparison allows to build a quantitative hierarchy of conceptual criteria

<table>
<thead>
<tr>
<th></th>
<th>Harvest</th>
<th>Peak34</th>
<th>Prior CT</th>
<th>Prior RT</th>
<th>Dis status</th>
<th>BM</th>
<th>Age</th>
</tr>
</thead>
<tbody>
<tr>
<td>Harvest</td>
<td>1-9/;</td>
<td>1/9-1</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Peak34</td>
<td></td>
<td></td>
<td>5……</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Prior CT</td>
<td></td>
<td></td>
<td>3……</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Prior RT</td>
<td></td>
<td></td>
<td></td>
<td>etc</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dis status</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>BM</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>5……</td>
<td></td>
</tr>
<tr>
<td>Age</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>5……</td>
<td></td>
</tr>
</tbody>
</table>
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 1]

- A list of conceptual criteria was built based on literature and further integrated by criteria proposed by the experts.
<table>
<thead>
<tr>
<th>Conceptual Criteria</th>
<th>Percentage of agreement</th>
</tr>
</thead>
<tbody>
<tr>
<td>Harvested CD34&lt;sup&gt;+&lt;/sup&gt; cells</td>
<td>86%</td>
</tr>
<tr>
<td>Harvested CD34&lt;sup&gt;+&lt;/sup&gt; cells per planned SCT</td>
<td>100%</td>
</tr>
<tr>
<td>Number of planned ASCT</td>
<td>57%</td>
</tr>
<tr>
<td>Overall harvested CD34&lt;sup&gt;+&lt;/sup&gt; cells after 2 aphereses</td>
<td>71%</td>
</tr>
<tr>
<td>Harvested CD34&lt;sup&gt;+&lt;/sup&gt; cells at 1&lt;sup&gt;st&lt;/sup&gt; apheresis</td>
<td>57%</td>
</tr>
<tr>
<td>Pre and post-apheresis CD34&lt;sup&gt;+&lt;/sup&gt; cell count</td>
<td>57%</td>
</tr>
<tr>
<td>Absolute number of circulating CD34&lt;sup&gt;+&lt;/sup&gt; cells/µL</td>
<td>100%</td>
</tr>
<tr>
<td>Overall number of nucleated cells harvested</td>
<td>14%</td>
</tr>
<tr>
<td>Overall number of nucleated cells harvested per planned SCT</td>
<td>14%</td>
</tr>
<tr>
<td>Planned volumes of apheresis</td>
<td>57%</td>
</tr>
<tr>
<td>Chemo-mobilization</td>
<td>71%</td>
</tr>
<tr>
<td>Mobilizing G-CSF dose</td>
<td>71%</td>
</tr>
<tr>
<td>Diagnosis of underlying disease</td>
<td>71%</td>
</tr>
<tr>
<td>Age</td>
<td>100%</td>
</tr>
<tr>
<td>Disease status</td>
<td>100%</td>
</tr>
<tr>
<td>Bone marrow involvement</td>
<td>86%</td>
</tr>
<tr>
<td>Pre-mobilization BM cellularity</td>
<td>86%</td>
</tr>
<tr>
<td>Conceptual Criteria</td>
<td>Percentage of agreement</td>
</tr>
<tr>
<td>-----------------------------------------------------------------------------------</td>
<td>-------------------------</td>
</tr>
<tr>
<td>Number of previous cytotoxic therapy lines</td>
<td>100%</td>
</tr>
<tr>
<td>Duration of prior chemotherapy</td>
<td>71%</td>
</tr>
<tr>
<td>Interval elapsed since previous chemotherapy</td>
<td>29%</td>
</tr>
<tr>
<td>Prior extensive radiotherapy</td>
<td>100%</td>
</tr>
<tr>
<td>Prior alkylating therapy</td>
<td>86%</td>
</tr>
<tr>
<td>Prior therapy with lenalidomide</td>
<td>86%</td>
</tr>
<tr>
<td>Prior therapy with fludarabine</td>
<td>86%</td>
</tr>
<tr>
<td>Platelet count at 1st apheresis</td>
<td>29%</td>
</tr>
<tr>
<td>Time to platelet recovery after chemo-mobilization</td>
<td>57%</td>
</tr>
<tr>
<td>Pre-mobilization WBC/PLT count</td>
<td>14%</td>
</tr>
<tr>
<td>Circulating CD34+ cells in steady state prior PBSC mobilization</td>
<td>14%</td>
</tr>
<tr>
<td>Fold-increase of circulating CD34+ cells/µL respect to baseline</td>
<td>43%</td>
</tr>
<tr>
<td>Absolute number of circulating CD34+ cells/µL at a predetermined timing after start of mobilization</td>
<td>86%</td>
</tr>
<tr>
<td>Kinetics of mobilization of CD34+ cells</td>
<td>43%</td>
</tr>
<tr>
<td>Time to reach the CD34+ cell peak</td>
<td>57%</td>
</tr>
<tr>
<td>Kinetics of mobilization of MNC cells</td>
<td>43%</td>
</tr>
</tbody>
</table>
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 ≥2.0 x10^6 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.
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
<table>
<thead>
<tr>
<th>Conceptual Criteria (10)</th>
<th>Operational Criteria</th>
<th>Rank (1-9)</th>
<th>Pairwise comparison</th>
<th>Variability</th>
</tr>
</thead>
<tbody>
<tr>
<td>Harvested CD34⁺ cells</td>
<td>less than $2.0 \times 10^6$ harvested CD34⁺ cells/Kg per planned SCT by no more than 3 apheresis</td>
<td>8.7</td>
<td>0.26</td>
<td>47%</td>
</tr>
<tr>
<td>Peak CD34⁺ cells</td>
<td>peak CD34⁺ cell count &lt;20/µl on day 4-6 after start of mobilization with G-CSF alone or up to 20 days after chemotherapy and G-CSF</td>
<td>8.0</td>
<td>0.25</td>
<td>36%</td>
</tr>
<tr>
<td>Refractory disease</td>
<td>RISK FACTORS</td>
<td>6.0</td>
<td>0.08</td>
<td>74%</td>
</tr>
<tr>
<td>Advanced disease</td>
<td>advanced disease, i.e. at least two prior cytotoxic lines</td>
<td>5.8</td>
<td>0.12</td>
<td>38%</td>
</tr>
<tr>
<td>Extensive radiotherapy</td>
<td>extensive radiotherapy to marrow bearing tissue</td>
<td>7.2</td>
<td></td>
<td>54%</td>
</tr>
<tr>
<td>Prior exposure to fludarabine, melphalan, lenalidomide</td>
<td></td>
<td>6.6</td>
<td>0.06</td>
<td>47%</td>
</tr>
<tr>
<td>Prior exposure to other therapies potentially affecting SC mobilization</td>
<td></td>
<td>4.8</td>
<td>0.03</td>
<td>67%</td>
</tr>
<tr>
<td>Extensive BM involvement at mobilization</td>
<td></td>
<td></td>
<td>0.04</td>
<td>47%</td>
</tr>
<tr>
<td>Poor BM cellularity at mobilization</td>
<td>BM cellularity &lt;30% at mobilization</td>
<td>4.8</td>
<td>0.04</td>
<td>42%</td>
</tr>
<tr>
<td>Old age</td>
<td>Age older than 65 years</td>
<td>5.1</td>
<td>0.02</td>
<td>50%</td>
</tr>
</tbody>
</table>
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 refractory 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 ≥ 5 µg/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 | **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 |

| if he/she holds at least - one major criterion or - at least 2 minor criteria |
| **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 |
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

Mobilize

CD34+ HSC

CXCR4

SDF-1α

plerixafor binds to CXCR4 on HSC

Blood

Vascular Endothelial Cell Layer

Stromal Cell

Bone
Molecules involved in stem cell-stromal interactions

- **Endothelial Cells**
- **Stromal Cells**

**VEGFC**

**Sorafenib**

**FLT4**

**Notch**

**Extracellular matrix**
- Osteopontin
- Fibronectin
- Collagen
- Hyaluronin

**Cytokine & Chemokine reservoirs**

**HSC**

- ↓ Cell cycling, ↑ p27^{kip1}
- ↑ PI3K/Akt & MAPK signaling
- mTOR (S6 kinase)
- ↑ Bcl-2 expression

**AMD3100**

**AMD3465 “070”**

**SDF-1**

**Sorafenib**

**FLT3**

**KIT**

**CD44**

**CD62L**

**VLA-4**

**VCAM-1**

**GMI-1070**

**Natalizumab**

**BIO5192**

**Osteoblasts**

**Tight junctions**
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.
Dose-response analysis of AMD3100-induced mobilization of CD34 cells into peripheral blood
Table 2. Toxicities of AMD3100

<table>
<thead>
<tr>
<th>Toxicity</th>
<th>No. of Affected Patients (N = 13)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Injection site erythema or edema</td>
<td>10</td>
</tr>
<tr>
<td>Abdominal bloating or cramping</td>
<td>5</td>
</tr>
<tr>
<td>Flatulence</td>
<td>3</td>
</tr>
<tr>
<td>Diarrhea or soft stools</td>
<td>3</td>
</tr>
<tr>
<td>Nausea</td>
<td>2</td>
</tr>
<tr>
<td>Facial paresthesias</td>
<td>3</td>
</tr>
<tr>
<td>Lightheadedness</td>
<td>2</td>
</tr>
<tr>
<td>Warm sensation, “fuzzy” vision, eyelid heaviness, neck rash, petechiae, hypotension</td>
<td>1</td>
</tr>
</tbody>
</table>

*All toxicities encountered were grade 1 only.*
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

**Plerixafor Phase III Trials – Study Design**

**Study 3101**
NHL patients (n=300)

- G-CSF (10 ug/kg/day) + placebo
- G-CSF (10 ug/kg/day) + plerixafor (240 ug/kg)

**Endpoint:**
≥ 5 million CD34+ cells/kg in 4 or fewer apheresis

**Study 3102**
MM patients (n=300)

- G-CSF (10 ug/kg/day) + placebo
- G-CSF (10 ug/kg/day) + plerixafor (240 ug/kg)

**Endpoint:**
≥ 6 million CD34+ cells/kg in 2 or fewer apheresis

Successful and durable engraftment
Proportion of patients reaching $5 \text{ or } 2 \times 10^6$ CD34 cells/kg

Median number of apheresis days required to achieve $5\times10^6$ 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.
Study 3102
MM patients (n=300)

Kinetics of collections
% of patients reaching 2.6 x 10^6 CD34+/kg

Median CD34+ cells collected on each apheresis day
Compassionate use programs with Plerixafor
Compassionate Use Protocols (CUP)

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 Calandra¹, J McCarty², J McGuirk³, G Tricot⁴, S-A Crocker¹, K Badel¹, B Grove¹, A Dye¹ and G Bridger¹

66% of these patients collected ≥2e06 CD34+/kg after Plerixafor
A cohort of 115 data-audited poor mobilizers was assessed in the CUP study. Success rates (harvest > $2 \times 10^6$ CD34+/kg) for patients who previously failed mobilization were 65, 75 and 75% for NHL, MM and HD, respectively. 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

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

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

Calandra et al, BMT 2008
### Collections and Engraftment

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.

<table>
<thead>
<tr>
<th>Disease</th>
<th>NHL*§</th>
<th>MM</th>
</tr>
</thead>
<tbody>
<tr>
<td>Previous mobilization regimen</td>
<td>Cytokines</td>
<td>Chemotherapy</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Patients collecting $\geq 2 \times 10^6$ CD34+ cells per kg (%)</th>
<th>NHL*§</th>
<th>MM</th>
</tr>
</thead>
<tbody>
<tr>
<td>Proportion proceeded to transplantation (%)</td>
<td>38 (60.3)</td>
<td>7 (63.6)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Days to PMN engraftment</th>
</tr>
</thead>
<tbody>
<tr>
<td>$N$</td>
</tr>
<tr>
<td>Median</td>
</tr>
<tr>
<td>M.n, Max</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Days to PLT engraftment</th>
</tr>
</thead>
<tbody>
<tr>
<td>$N$</td>
</tr>
<tr>
<td>Median</td>
</tr>
<tr>
<td>M.n, Max</td>
</tr>
</tbody>
</table>

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 $\geq 3x$ the blood volume instead of $2x$)
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

<table>
<thead>
<tr>
<th>Patient Number</th>
<th>Patient Age</th>
<th>Day 1</th>
<th>Day 2</th>
<th>Day 3</th>
<th>Day 4</th>
<th>Total</th>
<th>PMN</th>
<th>PIT</th>
<th>12-Month Graft Durability</th>
</tr>
</thead>
<tbody>
<tr>
<td>01-101</td>
<td>49</td>
<td>0.65</td>
<td>0.63</td>
<td>0.80</td>
<td>0.66</td>
<td>2.74</td>
<td>11</td>
<td>33</td>
<td>Durable</td>
</tr>
<tr>
<td>01-102</td>
<td>63</td>
<td>1.81</td>
<td>0.90</td>
<td>1.69</td>
<td>2.24</td>
<td>3.66</td>
<td>10</td>
<td>21</td>
<td>Durable</td>
</tr>
<tr>
<td>01-103</td>
<td>57</td>
<td>2.66</td>
<td>1.16</td>
<td>0.43</td>
<td>0.39</td>
<td>1.06</td>
<td>10</td>
<td>19</td>
<td>Dead at 6 months</td>
</tr>
<tr>
<td>01-104</td>
<td>55</td>
<td>1.40</td>
<td>1.02</td>
<td>1.32</td>
<td>1.06</td>
<td>4.80</td>
<td>11</td>
<td>23</td>
<td>Not evaluable*</td>
</tr>
<tr>
<td>03-105</td>
<td>63</td>
<td>1.37</td>
<td>1.01</td>
<td>0.69</td>
<td>0.75</td>
<td>1.82</td>
<td>11</td>
<td>21</td>
<td>Durable</td>
</tr>
<tr>
<td>03-106</td>
<td>74</td>
<td>1.85</td>
<td>1.59</td>
<td>1.55</td>
<td>—</td>
<td>4.99</td>
<td>10</td>
<td>23</td>
<td>Durable</td>
</tr>
<tr>
<td>03-107</td>
<td>70</td>
<td>0.50</td>
<td>0.59</td>
<td>0.67</td>
<td>0.51</td>
<td>2.27</td>
<td>11</td>
<td>NA†</td>
<td>Dead at 6 months</td>
</tr>
<tr>
<td>03-108</td>
<td>58</td>
<td>0.47</td>
<td>0.60</td>
<td>0.68</td>
<td>0.92</td>
<td>2.67</td>
<td>10</td>
<td>15</td>
<td>Durable</td>
</tr>
<tr>
<td>03-109</td>
<td>69</td>
<td>0.88</td>
<td>0.76</td>
<td>0.95</td>
<td>1.07</td>
<td>3.66</td>
<td>11</td>
<td>17</td>
<td>Durable</td>
</tr>
</tbody>
</table>

Possible option in case of G-CSF contra-indication?
Adverse factors for PBSC mobilization:

- Advanced disease
- Prior treatment with extensive radiotherapy
- Prolonged chemotherapy (>2 courses)
- Exposure to stem cell poisons (e.g., Fluda, Lena, and alkylating agents)
- Advanced age (>65 years old)
- Extensive BM involvement (>30%) before mobilization
- Previous failure of mobilization attempt

27 of the 37 patients (73%) rescued with CHT*G-CSF+P collected ≥2 × 10^6 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.

Current indication in Europe for Plerixafor is ‘in combination with G-CSF patients with lymphoma and MM, whose cells mobilize poorly………………
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)
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 Renfro, 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 (>5x10^6/kg in Lymphoma and 10x10^6/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 ≥2x10^6 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 Pritchard, Darlene Anderson, Charise Gleason, Sagar Lonial, Christopher R. Flowers, Jonathan L. Kaufman, and Edmund K. Waller
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, Rosette Vaughn, Michael Graiser, Heather Renfroe, Mary Jo Lechowicz, Amelia Langston, Jefferson Mark Prichard, Darlene Anderson, Charise Gleason, Sagar Lontal, Christopher R. Flowers, Jonathan L. Kaufman, and Edmund K. Waller

<table>
<thead>
<tr>
<th>Patient characteristics</th>
<th>2008 (before plerixafor approval)</th>
<th>Good mobilizer nonplerixafor</th>
<th>Poor mobilizer nonplerixafor</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of patients</td>
<td>148</td>
<td>112</td>
<td>36</td>
</tr>
<tr>
<td>Myeloma patients</td>
<td>92</td>
<td>66</td>
<td>27</td>
</tr>
<tr>
<td>Lymphoma patients</td>
<td>56</td>
<td>46</td>
<td>9</td>
</tr>
<tr>
<td>Percentage of patients with CD34+ count ( \geq 15 \times 10^6 ) cells/L and WBC count ( \geq 10 \times 10^9 ) cells/L after at least 5 days of G-CSF administration</td>
<td>76</td>
<td>100</td>
<td>0</td>
</tr>
<tr>
<td>Percentage of patients with CD34+ cell count ( \geq 15 \times 10^9 ) /L and WBC count ( \geq 10 \times 10^9 )/L by more days of G-CSF or G-CSF plus plerixafor treatment</td>
<td>80</td>
<td>100</td>
<td>17</td>
</tr>
<tr>
<td>Percentage of patients who collected target cell dose of CD34+ cells (( \geq 5 \times 10^6 ) cells/kg for lymphoma, ( \geq 10 \times 10^6 ) cells/kg for myeloma)</td>
<td>61</td>
<td>73</td>
<td>22</td>
</tr>
<tr>
<td>Percentage of patients collected a minimum transplant dose of CD34+ cells (( \geq 2 \times 10^6 ) cells/kg)</td>
<td>93</td>
<td>100</td>
<td>72</td>
</tr>
<tr>
<td>Percentage of patients collected a minimum transplant dose of CD34+ cells (( \geq 2 \times 10^6 ) cells/kg) on Day 1 of apheresis</td>
<td>84</td>
<td>99</td>
<td>39</td>
</tr>
<tr>
<td>Median (range) number of CD34+ cells collected (( \times 10^6 ) cells/kg)</td>
<td>8.8 (0.6-72.3)</td>
<td>10.4 (2.8-72.3)</td>
<td>4.4 (0.6-14.9)</td>
</tr>
</tbody>
</table>
### Transfusion 2011

<table>
<thead>
<tr>
<th>Pts number</th>
<th>Good mobilizer nonplerixafor</th>
<th>High-risk patients plerixafor</th>
<th>Poor mobilizer just-in-time plerixafor</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total</td>
<td>188</td>
<td>124</td>
<td>23</td>
</tr>
<tr>
<td>MM</td>
<td>138</td>
<td>97</td>
<td>20</td>
</tr>
<tr>
<td>Lymph</td>
<td>50</td>
<td>28</td>
<td>3</td>
</tr>
<tr>
<td>&gt;15 CD34+/mcl (%) after G-CSF 5 days</td>
<td>70</td>
<td>100 %</td>
<td>30 %</td>
</tr>
<tr>
<td>&gt;15 CD34+/mcl (%) after &gt;5 days of G-CSF+/-P</td>
<td>69</td>
<td>100 %</td>
<td>63 %</td>
</tr>
<tr>
<td>&gt;5x10⁶/kg CD34</td>
<td>64</td>
<td>70</td>
<td>70</td>
</tr>
<tr>
<td>&gt;2x10⁶/kg 1°aph</td>
<td>98</td>
<td>100 %</td>
<td>96</td>
</tr>
<tr>
<td>&gt;2x10⁶/kg 1°aph</td>
<td>86</td>
<td>94</td>
<td>83</td>
</tr>
</tbody>
</table>

Median CD34+ (range):
- Good mobilizer nonplerixafor: 8.2 (0.6-135.3)
- High-risk patients plerixafor: 10.9 (2.7-135.3)
- Poor mobilizer just-in-time plerixafor: 11.7 (1.8-43.3)
- Median CD34+ (range): 6.8 (0.6-13.8)
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%.

*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 Oszan,1 Ivana N. Micalef,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. Gertz2

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 × 10⁶ CD34/kg), suboptimal (2–5 × 10⁶ CD34/kg) and poor (<2 × 10⁶/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 × 10⁹/L, addition of plerixafor may be helpful to salvage the mobilization attempt. Am. J. Hematol. 00:000–000, 2011. © 2011 Wiley-Liss, Inc.
benefits and limitations of plerixafor

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