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Advances in Mobilization of Hematopoietic Stem Cells (HSC)

Pitié-Sâlpétrieère Hospital-Paris- France
University of Paris-VI

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PBHSC* Mobilization

Key subjects:

- History glances
- Evolution of mobilization
- Experience of Pitié-Sâlpétrière Hospital
- Mobilization related health and economic considerations

*Peripheral blood hematopoietic stem cell
Benchmarks & Facts

- Early autologous bone marrow transplantation in late 1940s of Dogs lethally irradiated recovered when their previously aspirated BM was re-infused

- The challenge was identifying how to keep BM alive over an extended time period
1949 Polge et al. developed a method of freezing bull sperm with glycerol

1956 the technique was applied to BM successfully

Lacking knowledge about chemotherapy and supportive treatment was a major barrier for the development of AHSCT*

*Autologous hematopoietic stem cells transplantation
• 1970s: Description of a high level of progenitor cells in the peripheral blood of patients suffering from myelo-proliferative disorders

• 1970s: Identification of a high level of progenitor cells in the blood of patients treated by CY at the end of nadir
• 1970s: Re-emergence of ABMT*

• 1980s: First autologous PBHSC* transplant in a patient with leukemia using leukapheresis made at the end of nadir after CY-based chemotherapy

*Autologous bone marrow transplantation
*Peripheral blood hematopoietic stem cell
Evolution of mobilization
the key to the ASCT process

Early Definition: Increased number of progenitor cells in the peripheral blood sufficiently to make their collection feasible (after CY based chemotherapy)

1980s Chemomobilization: (before G-CSF era)

- Cy based chemotherapy
- 5 consecutive apheresis made at the end of NADIR
- Waiting 15 days for CFU-GM (collected cells fit AHSCT)
CD34 Identification

- 1984: Civin identified the CD34 marker on HSC; his discovery opened the doors for an increased understanding and manipulation of HSC*

- Mobilization and AHSCT has been continually advancing since the discovery of CD34

* Hematopoietic stem cell
G-CSF Era

- Early 1990s, G-CSF after chemotherapy lead to more important increase of PB CD34 count.
- Late 1990s GM-CSF was tested efficient, but many side effects.
- In 1995, G-CSF higher dose alone prove to be a good mobilization drug (steady state)
Mobilization today

Today Definition: Increased number of CD34+ cells in the peripheral blood in reaction to medullary stress like some chemotherapies, major surgery, hepatitis, etc. (lowering of SDF1 in BM)

- Post chemotherapy (Cy, Cytarabine), 5µg/kg/d of G-CSF (8-10 days)

- Steady state: G-CSF alone, 10µg/kg/d (4-6 days)

Despite, 15-20% of Patients failed to Mobilize
Optimal Mobilization

• Collection of high number of CD34 (> 5x10^6/kg)

• Minimal apheresis procedures (1-2)

This is closely related to blood CD34+ count
Goals of AHSCT

Administer high-dose chemotherapy with curative intent or survival benefit

Mobilize and collect sufficient cells capable of prompt and durable hematopoietic reconstitution
  • Minimize apheresis time\(^1\)
  • Optimize total CD34+ cell collection\(^2\)
  • Minimize toxicity\(^3\)

Achieve adequate neutrophil and platelet engraftment
  • Neutrophil engraftment: first of 3 consecutive days where the absolute neutrophil count is \(> 0.5 \times 10^9/L\)\(^4-6\)
  • Platelet engraftment: first of 3 consecutive days where the platelet count is \(> 20 \times 10^9/L\) without platelet transfusion\(^4,5\)

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Mobilization & Collection Failure

• Mobilization failure is defined as insufficient blood CD34+ count to carry out apheresis: < 15/µl (20-10?), it takes place in about 15% of patients (10-20%)

• Collection failure is defined as collected CD34+ number lower than the minimum estimated results, depending on CD34+ PB count (low yield) due to biological or/and technical origin.
Factors Affecting Mobilization

They can be classified into 5 groups:

1. Age (elderly people mobilize poorly)
2. Disease (type; bone marrow involvement)
3. Past history of irradiation
4. Past history of chemotherapy, length of treatment, Thalidomide, Fludarabine, etc.
5. Unidentified factors (Low blood SDF1?, high CXCR4 on cells surface?)

1 J Hematother Stem Cell Res. 2003 Aug;12(4):425-34,
2 Olivieri et al (GITMO) (2011) Bone Marrow Transplantation 1 – 10
3 Costa et al (2011a) Bone Marrow Transplant 46 (1):64-69
Dealing with Mobilization Failure

Re-mobilization

- SCF
- Chemomobilization?
- Steady state after washing out period?
- Mozobil?

OR

Pre-emptive Mozobil?
SCF
at the end of 1990s

- With G-CSF alone
- With chemomobilisation

Highly allergic
Long hospitalization
Limited efficiency
Not worthy to use

Ancestim (recombinant human stem cell factor, SCF) in association with filgrastim does not enhance chemotherapy and/or growth factor-induced peripheral blood progenitor cell (PBPC) mobilization in patients with a prior insufficient PBPC collection, da Silva MG et al., BMT, 2004 Oct;34(8):683-91.

Not any more used today
Chemomobilization

• Next chemotherapy is scheduled routinely for the malignancy treatment, what is the probability of success?

• CY-based chemotherapy is programmed for the only purpose of mobilization (side effects)?
Steady State after Washing Out Delay

- What is the necessary delay?
- Which dose of G-CSF?
- What is the impact on the scheduled treatments?
- What are the risks/benefits?

Dawson MA et al Bone Marrow Transplant. 2005 Sep;36(5):389-96
Mozobil in France since 2009

Mozobil reversibly binds to the CXCR-4 receptor, blocks SDF-1 interaction and thus allows a more potent liberation of hematopoietic stem cells
Mozobil

- A bicyclam molecule\(^1\)
- Reversibly binds to CXCR4 receptor and blocks SDF-1 interaction\(^2\)
- Very water soluble\(^1\)
- Highly charged\(^3\)
- Low molecular weight (MW = 502.79g/mol)\(^1\)
- Rapidly increases mobilization of CD34+ hematopoietic stem cells\(^1\)

CXCR4, chemokine receptor 4; SDF-1 stromal cell-derived factor-1.
Mozobil
How Mozobil is used?
Re-mobilization or Pre-emptive

- In association with G-CSF only? Approved
- In association with chemomobilization? Widely used
Pre-emptive Mozobil Administration

- Mozobil readily available in the hospital (in pharmacy)?
- Modality of retribution (In bed/out bed patient)
- Administration organization in short delay (few hours)?
- Apheresis within appropriate delay (6-11 hours)?
<table>
<thead>
<tr>
<th>Patient Segments</th>
<th>Adequate Mobilizers</th>
<th>Poor Mobilizers</th>
<th>Previous Failed Mobilizers</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Definition</strong></td>
<td>No patient or disease characteristics associated with poor mobilization</td>
<td>Baseline patient or disease characteristics associated with poor mobilization exist</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Advanced age</td>
<td>• Low CD34+ peripheral counts e.g., &lt;20 circulating CD34+ cells/mcL(^1)</td>
<td>Failed first mobilization attempt; require remobilization</td>
</tr>
<tr>
<td></td>
<td>• Heavy pretreatment</td>
<td>• Do not achieve adequate cells on day 1 of apheresis</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Previous treatment with lenalidomide, fludarabine, or XRT</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>How Mozobil is Used</strong></td>
<td>For all mobilizations</td>
<td>Proactively in first-line setting</td>
<td>For remobilization</td>
</tr>
<tr>
<td>Mozobil® Value Proposition</td>
<td>• Optimize efficacy and efficiency</td>
<td>Enhanced efficacy and predictability to proactively avoid complications and clinical and economic costs of poor mobilization</td>
<td>Improves efficacy and predictability</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>• Lessens patient burden</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>• Reduces mobilization failures</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Enables failures to proceed to transplant</td>
</tr>
</tbody>
</table>

1- Olivieri et al (2011) *Bone Marrow Trans* 1 – 10
Specificity of Collection under Mozobil

- More lymphocytes B and T (4 fold)
- Increased dendritic cells
- Increased NK

Gaugler B Abstract 4045 Blood 2011

✓ Progenitors are more primitive  (more likely those of BM)

Rettig MP et al. Abstract Blood 2008;112

- Better engraftment and survival?
- Higher apheresis yield of CD34 (40-45% vs. 55-60%)

(non published data of our center)
Experience of Pitié-Salpêtrière Hospital
Paris Mobilization & Collection Unit
Landmarks

- 1989 Beginning of AHSCT (BM & PBSC, < 12 patients)
- 1991 Chemomobilization standards (5 cytapheresis at the end of nadir, results confirmed 2 weeks later)
- 1995 G-CSF (remodelling of hospitalization and collection timing)
- 1998 CD34 counts (introduced as a part of routine quality control)
- 2000 SCF (in case of mobilization failure → deceiving results & complex manipulation)
- 2002 HD G-CSF (in case of previous failure, ½ of failed patients are collected)
- 2008 Mozobil (in case of mobilization failure → efficient, easy administration & few side effects)
IN 2012
Pitié-Salpêtrière Hospital

- Autologous PBSC* 130 Patients
- Allogeneic PBSC 45 Donors
- Allogeneic Bone Marrow 25 donnors
- Extracorporal Photo-Therapy (225 procedures made possible since MOZOBIL introduction)

* Peripheral blood stem cell
Mobilization rules
Pitié-Salpêtrière Hospital

- **Steady state** (G-CSF 10µg/kg, D1-D6, collection D5-D7)
- **Chemomobilization** (G-CSF 5µg/kg, 48 hr after the end of chemotherapy, collection at D12 after chemotherapy)
- **CD34 count if WBC > 5,000**
- **Apheresis if CD34 > 15**
- **CD34 > 4 but < 15 & WBC > 20,000 ➔ Mozobil**
- **CD34 < 4 & WBC > 20,000 ➔ remobilization** (high dose G-CSF, chemomobilization & Mozobil)
- **Minimal collection goal is > 3x10^6 CD34/kg/Graft**
PBSC mobilization autologous

Steady state (G-CSF 10µg/kg)
- D1 to D6
- Collection D5
- Mostly Myeloma

Post chemotherapy
- G-CSF 5µg/kg 48hrs after the end of chemotherapy (10-12 days)
- Mostly lymphomas

CD34+ <15/µl
- WBC>20,000/µl
- >3 Mozobil
- <3 interrupt remobilization

CD34+ >15/µl
- Cyta
- Expected high yield
- Low yield

Remobilization:
- Chemotherapy
- Increase G-CSF up to 30µl/kg (depends on max WBC achieved)
- Mozobil added if CD34+ > 3
Mozobil Mode of Administration

Pitié-Salpêtrière Hospital

- Prescription of Mozobil 24µg/kg of BW (CD34+ > 3, WBC > 20,000/l)
- Administration made at home at midnight
- CETIRIZINE 10mg (anti-histaminic) 1hr before injection
- Apheresis at 08:30
- To be repeated once more if necessary (third injection is rarely needed)
- In case of failure, remobilization with Mozobil
Remobilization

Pitié-Salpêtrière Hospital

**Steady state**
7-10 days of washing out then high dose G-CSF 20-30µg/kg/d (depending on WBC at the time of failure) from D1 to D6
→ collection D5-D7 + Mozobil if needed

**Chemomobilization** (scheduled chemotherapy)
G-CSF 10µg/kg/d to begin 48 hr after the end of chemotherapy
→ collection around D12 after the end of chemotherapy + Mozobil if needed
Apheresis

Pitié-Salpêtrière Hospital

- COBE & OPTIA cell separators
- ACD* 1/12 anticoagulant
- Three blood masses treated limited to 12 liters
- Time limited to maximum 4 hours
- Peripheral access used (warming covers, anxiolytic 1/2 hours before, local anesthetic cream 1/2 hours before)
- Central access in case of needs (average 1 every 18 months)

* Anticoagulant citrate dextrose
## Evolution 2008 - 2011
**APBSC Pitié-Salpêtrière Hospital**

<table>
<thead>
<tr>
<th>Year</th>
<th>2008</th>
<th>2011</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Patient N°</strong>&lt;br&gt;MM/NHL/Other</td>
<td>127&lt;br&gt;39/60/28</td>
<td>117&lt;br&gt;39/56/22</td>
</tr>
<tr>
<td><strong>PB CD34+ N°</strong></td>
<td>385</td>
<td>316</td>
</tr>
<tr>
<td><strong>Apheresis N°</strong></td>
<td>239</td>
<td>210</td>
</tr>
<tr>
<td><strong>Mean</strong>&lt;br&gt;Apheresis/patient</td>
<td>2.1 (1-6)</td>
<td>1.8 (1-4)</td>
</tr>
<tr>
<td><strong>Lost Slots</strong></td>
<td>146</td>
<td>106</td>
</tr>
<tr>
<td><strong>Definitive Failure N°</strong></td>
<td>18 (14%)</td>
<td>2 (2%)</td>
</tr>
<tr>
<td><strong>Patients (Mozobil)</strong></td>
<td>0</td>
<td>21</td>
</tr>
<tr>
<td><strong>Poor mobilizers</strong></td>
<td>16%</td>
<td>20%</td>
</tr>
<tr>
<td>Sex F/M</td>
<td>9/12</td>
<td></td>
</tr>
<tr>
<td>---------</td>
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<td></td>
</tr>
<tr>
<td>Age</td>
<td>55 (30-68)</td>
<td></td>
</tr>
<tr>
<td>Disease</td>
<td>8NHL, 5MM, 4HD, 3W, 1POEMS</td>
<td></td>
</tr>
<tr>
<td>CD34+ PB count mean (before Mozobil)</td>
<td>7 (3-12)</td>
<td></td>
</tr>
<tr>
<td>Mozobil vials mean</td>
<td>1.5 (1-3)</td>
<td></td>
</tr>
<tr>
<td>CD34+ PB count mean (after Mozobil)</td>
<td>57 (6-129)</td>
<td></td>
</tr>
<tr>
<td>CD34+ mean collection</td>
<td>4.47x10^6/kg (2.03-7.26)</td>
<td></td>
</tr>
</tbody>
</table>
Mobilization Related Health and Economic Considerations

The following elements have important impacts on both health and economic aspects of mobilization:

- Predictable collection dates
- Number of apheresis
- CD34+ number in collection
<table>
<thead>
<tr>
<th>Predictable collection dates</th>
<th>Health Impact</th>
<th>Economic Impact</th>
</tr>
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<tbody>
<tr>
<td></td>
<td>• Maintaining of chemotherapy scheduling</td>
<td>• Better rationalization of medical resources</td>
</tr>
<tr>
<td></td>
<td>• Minimizing stress</td>
<td>• Avoid WE collection &amp; processing (increase medical resources use &amp; cost)</td>
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<td></td>
<td>• Improving compliance</td>
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<td>• Reduce neutrophils in graft</td>
<td>• Reduce freezing procedures</td>
</tr>
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<td></td>
<td>• Less apheresis toxicity</td>
<td>• Reduce freezing bag</td>
</tr>
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<td>• Better patients comfort</td>
<td>• Reduce medical resources solicitation</td>
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<td></td>
<td>• Faster engraftment</td>
<td>• Reduce hospital stay</td>
</tr>
<tr>
<td></td>
<td>• Reduce infectious events</td>
<td>• Reduce transfusions</td>
</tr>
<tr>
<td></td>
<td>• Improve survival</td>
<td>• Reduce antibiotherapy</td>
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Pitié-Salpêtrière Hospital APBSC

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Conclusion

• Mobilization of PBHSC leads to optimization and cost savings
• Optimization is a predictable collection, fewer aphereses and a higher number of collected CD34
• Reduction of health cost becomes central task for European Health insurance systems to be considered during mobilization and collection
• Mozobil the most recent advance in mobilization could be one of the major helpful elements to achieve this goal
Thank You