Key areas covered

- Glances on history of HSC* transplantation
- Evolution of PBHSC**Mobilization and Collection
- Mobilization impact on related health and economic considerations
- Local Experience in Pitié-Sâlpétrie hospital a living demonstration

*Hematopoietic Stem Cell
**Peripheral blood hematopoietic stem cell
Early allogeneic HSCT

- **1939**: The first HSCT* in a patient with aplastic anemia who received 18ml of her brother’s bone marrow

*Hematopoietic stem cell transplantation
• 1956: Curing mice with induced ALL with irradiation followed by syngeneic bone marrow (BM) infusion (Barnes & al.)

• 1956: Cryopreservation was applied to bone marrow (door was opened to AH SCT*)

*Autologous hematopoietic stem cells transplantation
Early Autologous HSCT

- 1958: Dogs lethally irradiated recovered when their previously aspirated BM was re-infused (Alpen et al)

- Lacking knowledge about chemotherapy and supportive treatment was a major barrier for the development of AHSCT
Human allogeneic BMT* milestones

- 1956: E. Donnall made the 1st twin BMT
- 1958: Jean DAUSSET discovered HLA
- 1968: the first sibling non twin BMT
- 1973: the 1st unrelated BMT for immunodeficiency disorder
- 1979: the 1st unrelated BMT for leukemia

*Bone marrow transplantation
Human allogeneic PBHSC milestones

• 1980: Syngeneic blood mononuclear cells for Ewing sarcoma  ABRAMS et al, September 1980, blood: 56

• 1993: Syngeneic PBHSC from donors under G.CSF  Weaver et al, Oct. 1993, blood

• 1995: Bensinger & al described 8 patients who received PBHSC of their siblings mobilized by G.CSF  Bensinger et al 1995 Mar 15, blood
Human autologous BMT & PBHSC milestones

- Between 1958-1962: many papers described autologous BMT (lacking enough Knowledge about chemo & supportive therapy)
- 1976: Identification of a high level of progenitor cells in the blood of patients treated by CY at the end of nadir  
  Richman, Blood 1976:47
- 1978: the first cured patients of resistant NHL using ABMT  
  Appelbaum & al, Blood. 1978 July;52
• 1977: Cline & al described the mobilization following Cyclophosphamide
• 1979: CML blood progenitors were used as auto-graft
• 1984: Civin identified the CD34 marker on HSC; his discovery opened the doors for an increased understanding and manipulation of HSC
• 1988: G.CSF & GM.CSF mobilization potential alone or after chemotherapy was recognized
Evolution of mobilization & collection
the key to the ASCT process
(before G-CSF & CD34 era)

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

1980s Chemo-mobilization:
• Cy based chemotherapy
• 5 consecutive apheresis made at the end of NADIR
• Waiting 15 days for CFU-GM (collected cells fit AH SCT)
CD34 Identification

• CD34 marker identification by Civin on HSC make their mobilization and collection easier

• CD34 measurement in blood and collection had become the rule to initiate and end apheresis and to evaluate grafts
G-CSF & CD34 era

- Early 1990s, G-CSF after chemotherapy lead to more powerful 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)
Optimal Mobilization (autologous)

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

• Minimal apheresis procedures (1-2)

• Low collection Neutrophiles, Platelets and RBCs

This is closely related to blood CD34+ count
Recommendations & Regulations
International, European & national

Eve of 2000s: Increasing regulations pressure due to higher standard rules of cell therapy, it concerns:

• Structures (space, localization, Physicians & Nurses training, etc.)
• Mobilization rules
• Cytapheresis (patients and donors conditions, number of procedures, labelling, transport, etc.)
• Products quality (Ht, Neutrophils, platelets, CD34, etc.)
• Manipulation and storage
• Delivery
• Administration

Lead to heavy health resources solicitation
Mobilization today

• Today Definition: Increased number of CD34+ cells in the peripheral blood in reaction to medullary stress like some chemotherapies and G-CSF. (lowering of SDF1 in BM)

→ Post chemotherapy (Cy, Cytarabine), 5µg/kg/d of G-CSF (8-10 days) only for autologous patients

→ Steady state: G-CSF alone, 10µg/kg/d (4-6 days) for both autologous patients and healthy donors

Despite, 15-20% of Patients and some Healthy donors failed to Mobilize
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 factors.
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?)

2. Olivieri et al (GITMO) (2011) Bone Marrow Transplantation 1 – 10
Dealing with Mobilization Failure

Re-mobilization

- SCF
- Chemomobilization?
- Steady state after washing out period?
- CXCR4 inhibitor (Plerixafor)?

OR

Pre-emptive CXCR4 inhibitor (Plerixafor)?
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 routinely today
Chemo re-mobilization

- 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)?

Do we need to add Plerixafor?
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?

Is Plerixafor needed?
Pre-emptive Plerixafor Administration

- Easy access, available in the hospital (in pharmacy)?
- Modality of administration (In bed/out bed patient)
- Administration organization in short delay (few hours)?
- Apheresis within appropriate delay (6-11 hours)?
New CXCR4 inhibitors

POL 6326: (Polyphor Ltd)
- Tested in 16 MM German patients
- Evaluated for efficiency and tumor cells contamination
- Tested in healthy donors

Stefan SCMITT & al, international myeloma foundation
Darja Karpova & al, ASH December 5-8, 2015

ALT-1188:
- Successful prolonged mobilization in murine
- More 2.7 folds of cells than Plerixafor

ASH 2013, 891 ALT-1188: A New CXCR4 Antagonist In Development For Mobilization Of HSPCs
A Glance on advances in Collection

- Cells separators are mainly concerned by evolution
- Easier to set up kits (less errors)
- More automated procedures (less variability)
- Continuous evolution of software

Optia resume such evolution, smaller separator, easy guided set up, evolution of kits to fit specific needs, fast adaptation of software
Mobilization Related Health and Economic Considerations

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

• Predictable collection dates
• Low number of apheresis
• High CD34+ number in collection
<table>
<thead>
<tr>
<th>Predictable collection dates</th>
<th>Health Impact</th>
<th>Economic Impact</th>
</tr>
</thead>
</table>
|                             | • Maintaining of chemotherapy scheduling  
  • Minimizing stress  
  • Improving compliance | • Better rationalization of medical resources  
  • Avoid WE collection & processing (increase medical resources use & cost) |

<table>
<thead>
<tr>
<th>Minimal apheresis N°</th>
<th>Health Impact</th>
<th>Economic Impact</th>
</tr>
</thead>
</table>
|                     | • Reduce neutrophils in graft  
  • Less apheresis toxicity  
  • Better patients comfort | • Reduce freezing procedures  
  • Reduce freezing bag  
  • Reduce medical resources solicitation |

<table>
<thead>
<tr>
<th>Maximal CD34+ in graft</th>
<th>Health Impact</th>
<th>Economic Impact</th>
</tr>
</thead>
</table>
|                        | • Faster engraftment  
  • Reduce infectious events  
  • Improve survival | • Reduce hospital stay  
  • Reduce transfusions  
  • Reduce antibiotherapy |
Local Experience in Pitié-Sâlpétrieire hospital

• 1986: Alogeneic BMT

• 1989 Beginning of AHSCT (BM & PBSC, < 12 patients)

• 1991 Chemo-mobilization 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)

• 2009 Plerixafor (in case of mobilization failure ➔ efficient & easy administration)

• 2011 ECP was initiated ➔ Stressing need & abled by freed health resources
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/µl
- Apheresis if CD34 > 15/µl
- CD34 ≥ 4 but < 15 & WBC > 20,000 → Plerixafor
- CD34 < 4 & WBC > 20,000 → remobilization (high dose G-CSF (20-30 µg/kg), chemomobilization & Plerixafor)

**Minimal collection goal is** > 3x10⁶ CD34/kg autologous & 4x10⁶ CD34/kg allogeneic graft
Collection Organization

• Bed occupation based on time slots
• Cytapheresis slot (4 hours), ECP (2 hours)
• Only 2 Slots are booked per patient/donor

Our goal is:
✓ Minimal number of cytapheresis/patient or donor
✓ Decreasing number of lost slots (unused bed)
✓ Satisfy both demands and quality needs
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
In 2015
Pitié-Salpêtrière Hospital

• Autologous PBSC 93 Patients/142 apheresis
  (originating from 4 hospitals)

• Allogeneic PBSC 32 Donors/ 42 apheresis

• Extra corporeal Phototherapy 50 patients/ 735 procedures
Plerixafor Administration

Pitié-Salpêtrière Hospital

- Prescription of Mozobil 24µg/kg of BW (15< CD34+ ≥ 4, 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 Plerixafor
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

≥4 Plerixafor

<4 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)
Plerixafor added if CD34+ ≥4
#### Pitié-Salpêtrière Hospital APBSC

<table>
<thead>
<tr>
<th>Year</th>
<th>2008</th>
<th>2011</th>
<th>2013</th>
<th>2015</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patient N° MM/NHL/Other</td>
<td>127/39/60/28</td>
<td>117/39/56/22</td>
<td>110/25/50/35</td>
<td>93</td>
</tr>
<tr>
<td>Mean Apheresis/patient</td>
<td>2.1 (1-6) 16%</td>
<td>1.8 (1-4) 9%</td>
<td>1.6 (1-5) 7%</td>
<td>1.5 (1-3)</td>
</tr>
<tr>
<td>Lost Slots</td>
<td>146 30%</td>
<td>106 30%</td>
<td>80 30%</td>
<td>25</td>
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<tr>
<td>Definitive failure N°</td>
<td>18 (14%) 7 folds</td>
<td>2 (2%)</td>
<td>0</td>
<td>1 (1%)</td>
</tr>
<tr>
<td>Patients (Plerixafor)</td>
<td>0</td>
<td>21</td>
<td>14</td>
<td>21</td>
</tr>
<tr>
<td>Poor mobilizers</td>
<td>16%</td>
<td>20%</td>
<td>13%</td>
<td>22%</td>
</tr>
</tbody>
</table>
Conclusion

- Mobilization of PBHSC leads to optimization and cost savings

- Optimization is a predictable collection, fewer apheresis 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

- CXCR4 inhibitors could be one of the helpful elements to achieve this goal, their administration should be evaluated & permitted in healthy donors in case of mobilization failure.
Thank You for your attention