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Mobilization of HSC: History, evolution & impact

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Key areas covered

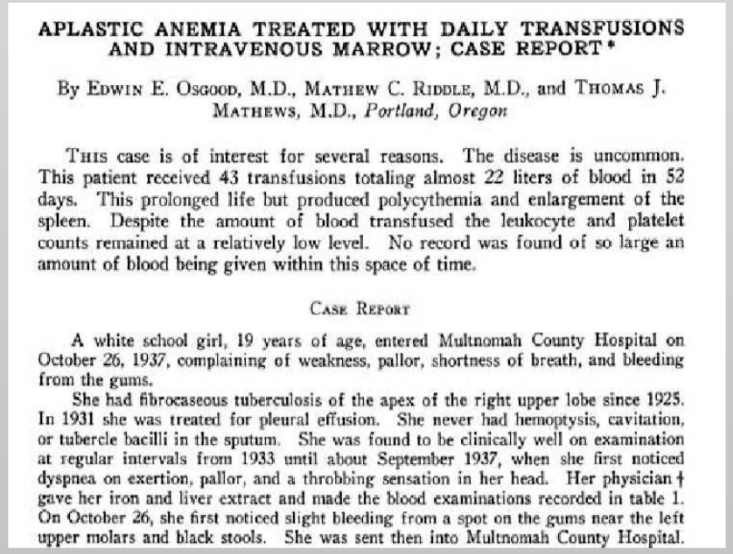
- Glances on history of HSC* transplantation
- Evolution of PBHSC**Mobilization and Collection
- Mobilization impact on related health and economic considerations
- Local Experience in Pitié-Sâlpétriere hospital a living demonstration

*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



APLASTIC ANEMIA TREATED WITH DAILY TRANSFUSIONS AND INTRAVENOUS MARROW; CASE REPORT*

By Edwin E. Osgood, M.D., Mathew C. Riddle, M.D., and Thomas J. Mathews, M.D., *Portland, Oregon*

This case is of interest for several reasons. The disease is uncommon. This patient received 43 transfusions totaling almost 22 liters of blood in 52 days. This prolonged life but produced polycythemia and enlargement of the spleen. Despite the amount of blood transfused the leukocyte and platelet counts remained at a relatively low level. No record was found of so large an amount of blood being given within this space of time.

Case Report

A white school girl, 19 years of age, entered Multnomah County Hospital on October 26, 1937, complaining of weakness, pallor, shortness of breath, and bleeding from the gums.

She had fibrocaseous tuberculosis of the apex of the right upper lobe since 1925. In 1931 she was treated for pleural effusion. She never had hemoptysis, cavitation, or tubercle bacilli in the sputum. She was found to be clinically well on examination at regular intervals from 1933 until about September 1937, when she first noticed dyspnea on exertion, pallor, and a throbbing sensation in her head. Her physician † gave her iron and liver extract and made the blood examinations recorded in table 1. On October 26, she first noticed slight bleeding from a spot on the gums near the left upper molars and black stools. She was sent then into Multnomah County Hospital.

*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 AHSCT*)

*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,..Blood1976 :47
- 1978: the first cured patients of resistant NHL using ABMT Appelbaum & al, Blood. 1978 Jul;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 AHSCT)

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 Neutophiles, 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?)

1 J Hematother Stem Cell Res. 2003 Aug;12(4):425-34,

2 Olivieri et al (GITMO) (2011) *Bone Marrow Transpla*ntation 1 – 10

3 Costa et al (2011a) *Bone Marrow Transplant* 46 (1):64-69

4 Douglas K et al (2011) (abstract #P1080). EBMT, Paris April 5.

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 programed 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?

Dawson MA et al Bone Marrow Transplant. 2005 Sep;36(5):389-96

- 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 in16 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

	Health Impact	Economic Impact
Predictable collection dates	• Maintaining of chemotherapy scheduling • Minimizing stress • Improving compliance	• Better rationalization of medical resources • Avoid WE collection & processing (increase medical resources use & cost)
Minimal apheresis N°	• Reduce neutrophils in graft • Less apheresis toxicity • Better patients comfort	• Reduce freezing procedures • Reduce freezing bag • Reduce medical resources solicitation
Maximal CD34+ in graft	• Faster engraftment • Reduce infectious events • Improve survival	• Reduce hospital stay • Reduce transfusions • Reduce antibiotherapy

Local Experience in Pitié-Sâlpétriere 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-CSF10µg/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 > $3x10^6$ CD34/kg autologous & $4x10^6$ 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

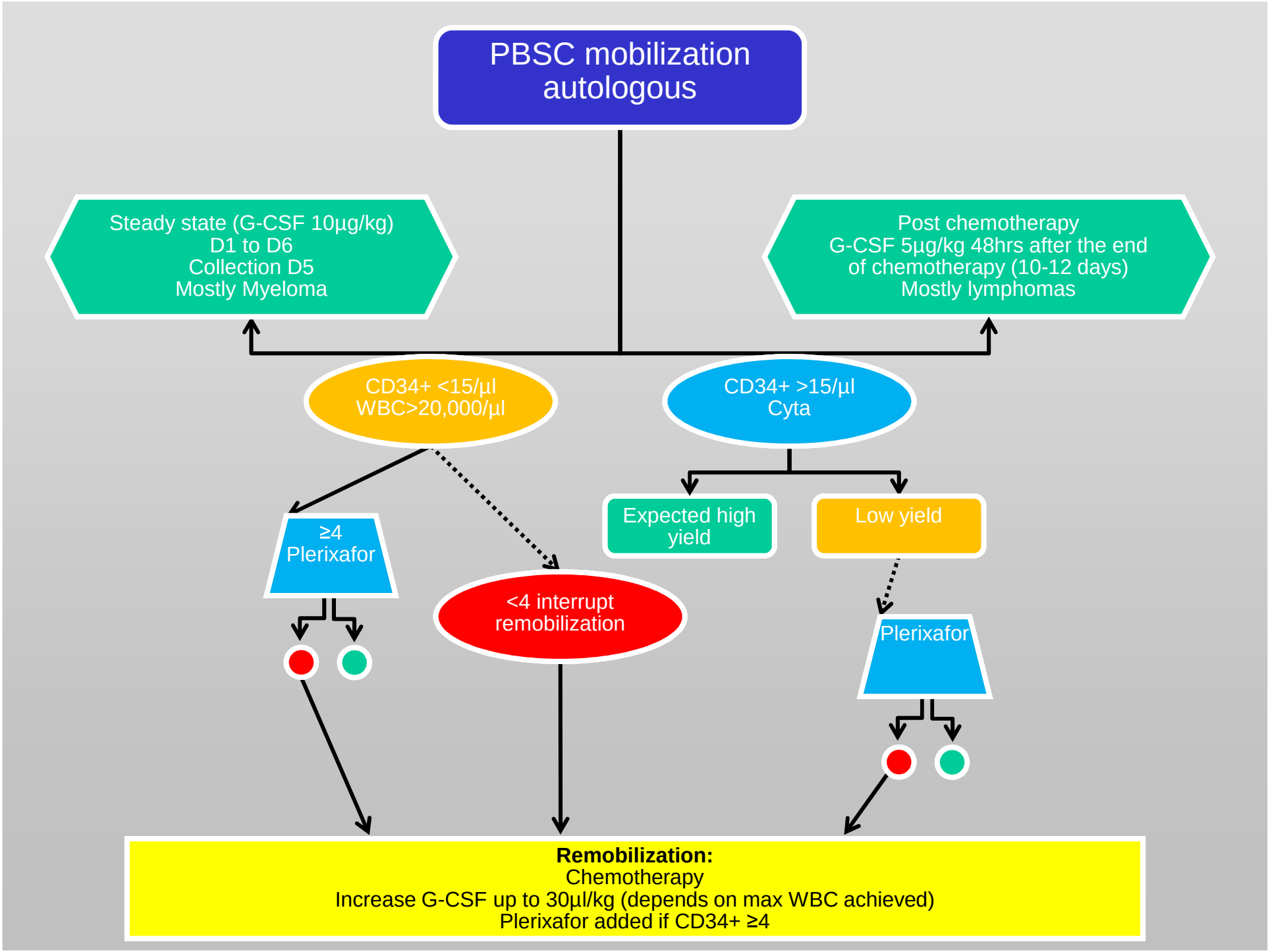
Pitié-Salpêtrière Hospital

- Autologous PBSC 93 Patients/142 apheresis
  (originating from 4 hospitals)
- Allogeneic PBSC 32 Donors/ 42 apheresis
- Extra corporal 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
CD34+ >15/µl
Cyta
≥4
Plerixafor
<4 interrupt remobilization
Expected high yield
Low yield
Plerixafor
Remobilization:
Chemotherapy
Increase G-CSF up to 30µl/kg (depends on max WBC achieved)
Plerixafor added if CD34+ ≥4

Evolution 2008 -2011-2013-2015 Pitié-Salpêtrière Hospital APBSC

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

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