Managing suboptimal CD34 Mobilisation

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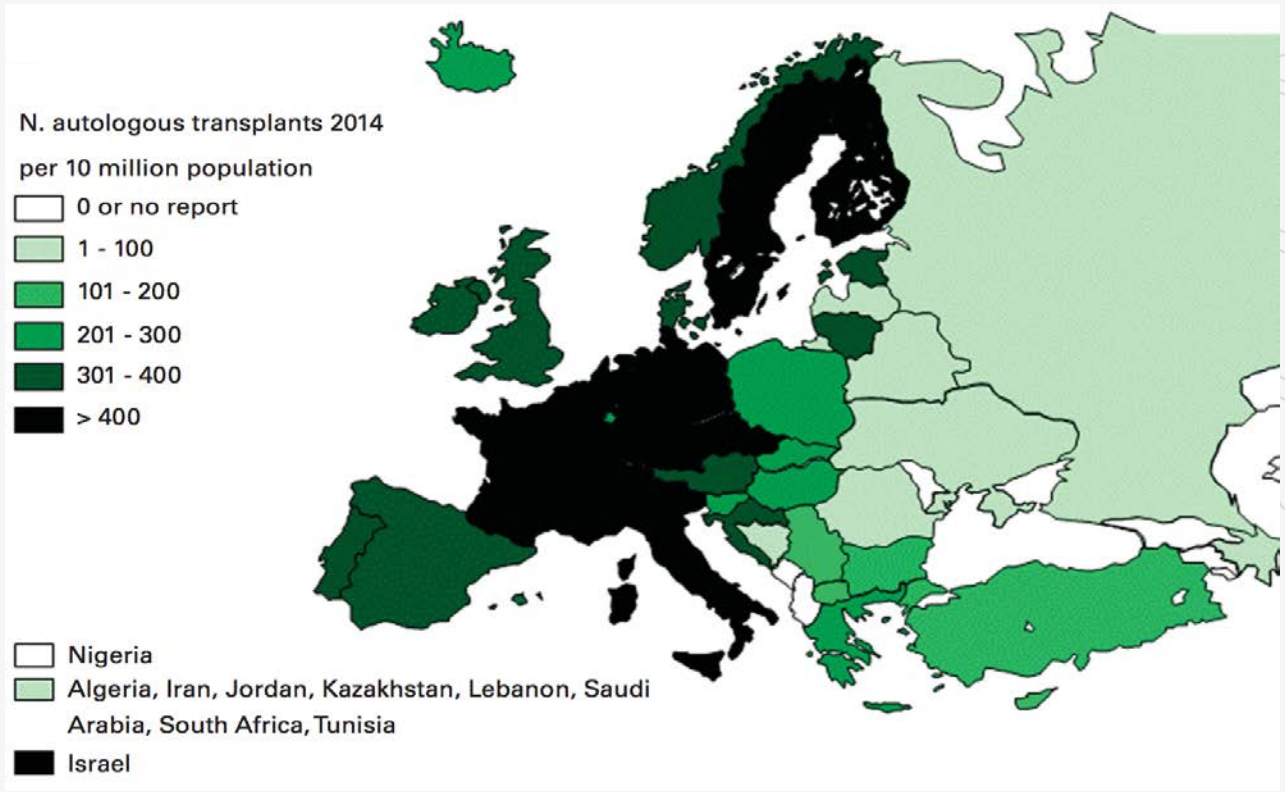
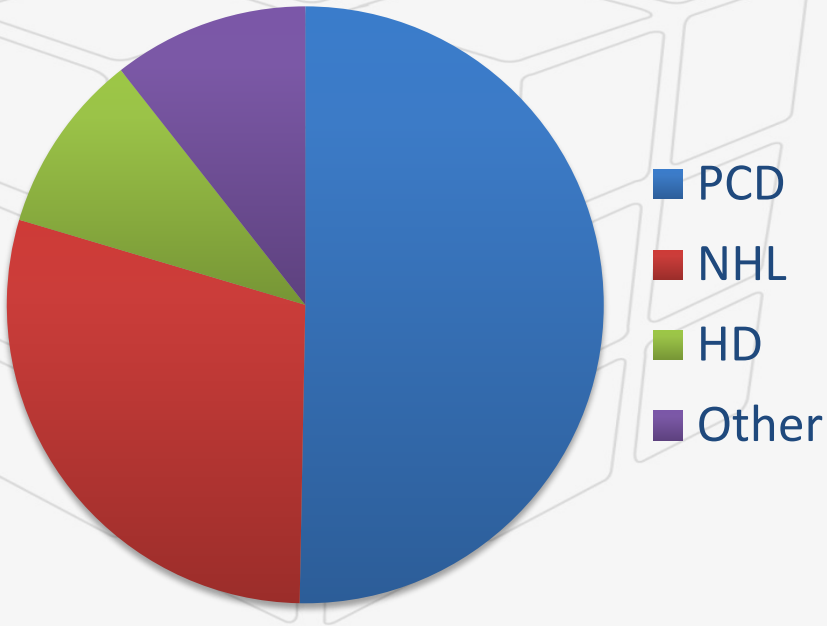
- Conflicts of Interest
  - Consultancy fees from Sanofi

AUTOLOGOUS STEM CELL TRANSPLANTATION

- Use of high dose chemotherapy is the standard of care in “fit” patients with multiple myeloma and in certain patients with NHL and HL
- Myeloma patients will usually have at least 2 procedures
- Following chemotherapy patients require an infusion of stem cells to rescue them from chemotherapy-induced aplasia

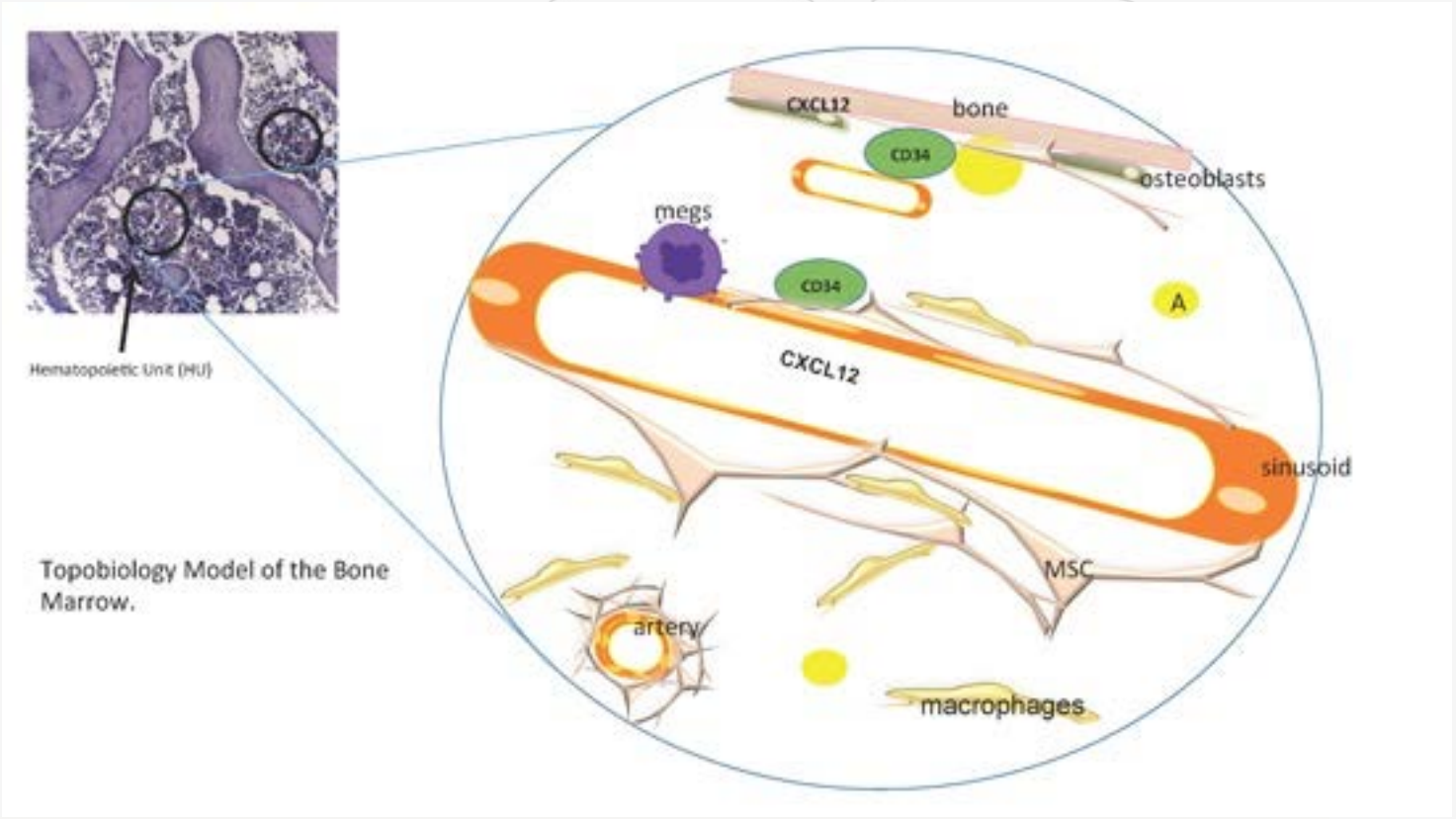
- 23,883 autografts 2014





Cell source

- Stem cells found primarily in paratrabecular space in bone marrow (BM)
- Either
  - Harvest BM directly
  - Cause release of stem cells into blood and collect, peripheral blood stem cell (PBSC) collection



Topobiology Model of the Bone Marrow.

- What yield target?
- Defining and predicting poor mobilisation
- Available options
- Cases
- Unanswered Questions

WHAT YIELD TARGET?

- Minimum recommended dose 2 x 10^6 $CD34^+$ cells/kg
- Consider accepting 1-2 x 10^6 $CD34^+$ cells/kg
- Higher target doses may result in faster engraftment times, the recommended stem cell collection target is 3-5 x 10^6 $CD34^+$ cells/kg. Weigh up against number of apheresis sessions.
- 5 x 10^6 $CD34^+$ cells/kg may lead to improved platelet recovery and less resource utilization compared with doses of 3 x 10^6 $CD34^+$ cells/kg, provided it is collected in a few apheresis sessions.

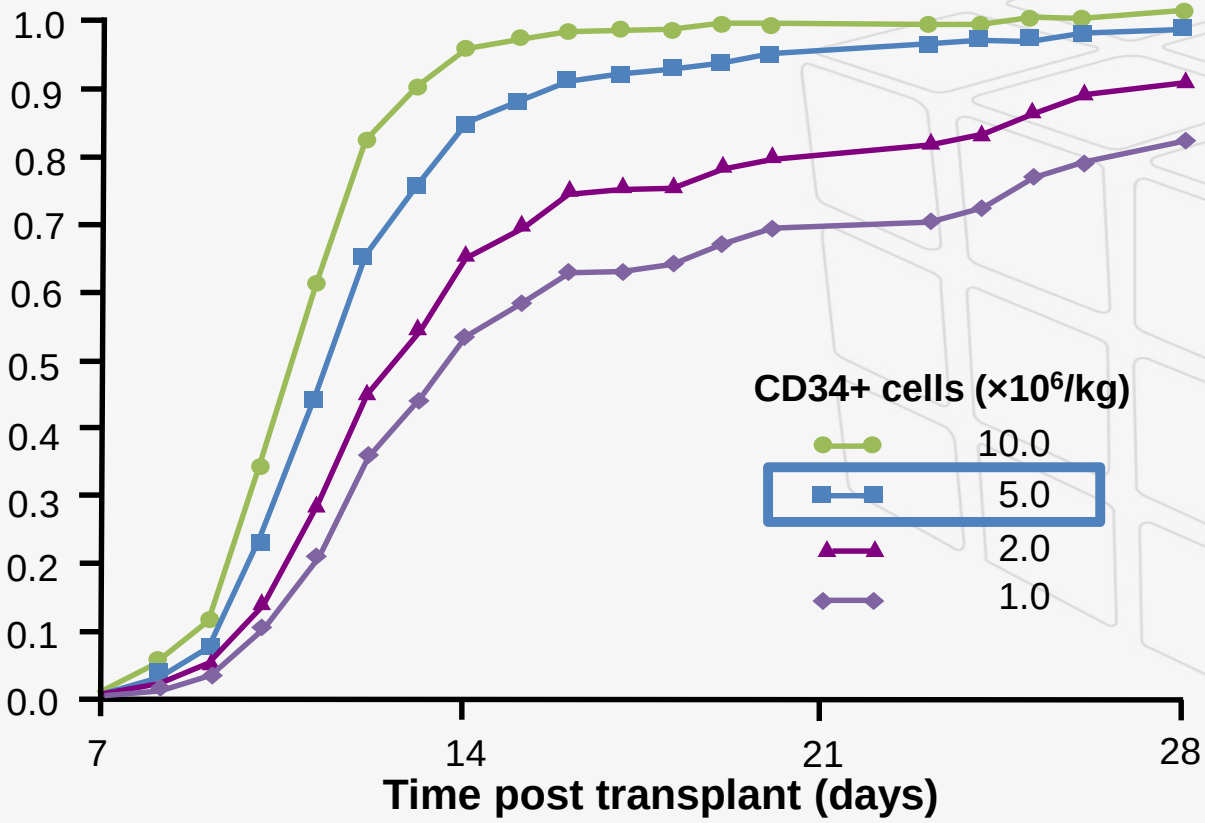
Review

Optimizing Autologous Stem Cell Mobilization Strategies to Improve Patient Outcomes: Consensus Guidelines and Recommendations

ASBMT American Society for Blood and Marrow Transplantation

Giralt et al., Biology Blood Marrow Transplant 20 (2014) 295-308

- Why is yield important?



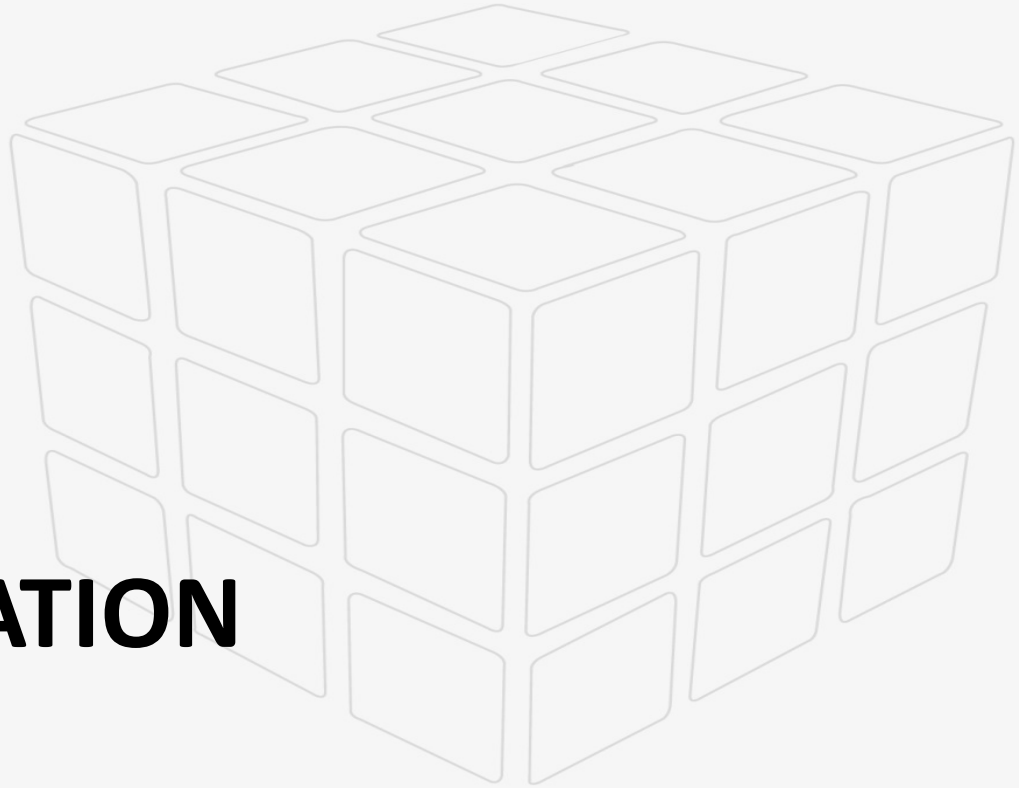
Platelet recovery

Siena et al. J Clin Oncol 2000;18:1360–77

DOES FAILED MOBILISATION MATTER

- Delay or Inability to proceed to high dose therapy → worse clinical outcome
- Cost of re-mobilisation (hospitalisation, drugs and apheresis)

- Failure rate upto 30% of cases



DEFINING POOR MOBILISATION

- Prediction from pre-known factors
- At the point of collection
  - Pre-apheresis peripheral blood CD34+
- During or after collection
  - CD34+ Yield result

Prediction

- Patient factors
  - Age (58 years in one study, 70 in another)
  - Co-morbidities - DM
- Disease factors
  - NHL
  - Bone marrow involvement
- Preceding treatment
  - Number of previous chemotherapy regimens (>3)
  - Radiotherapy to BM
  - Alkylators, Lenalidomide, platinum

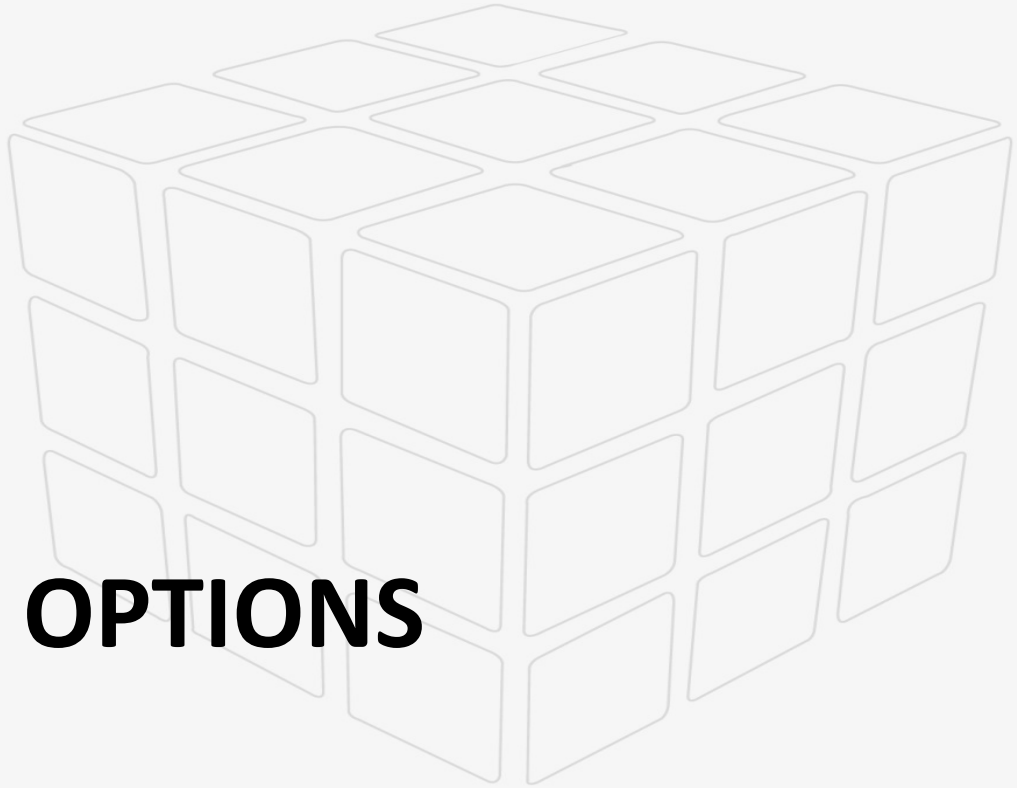
During

- At the time of mobilisation
  - Low steady state peripheral blood CD34 count
  - Steady state thrombocytopenia (<150 x 10^9/l)
  - Low yield day one
  - Recent Sepsis

GITMO definition

- Proven poor mobilizing capacity
  - Peak peripheral CD34 <20 /µl up to 6 days post GCSF primed or 20 days post chemo GCSF prime
  - Yield <2 x 10^6/kg in 3 apheresis sessions
- Predicted poor mobilizing capacity
  - Failed previous attempt
  - Previous extensive radiotherapy or chemotherapy affecting PBSC mobilization
  - Two of the following
    - Advanced disease(≥2 lines of therapy)
    - Refractory disease
    - Extensive BM involvement
    - Celluarity <30% at time of mobilization
    - Age >65

Olivieri *et al* Bone Marrow Transplantation (2012) 47, 342–351

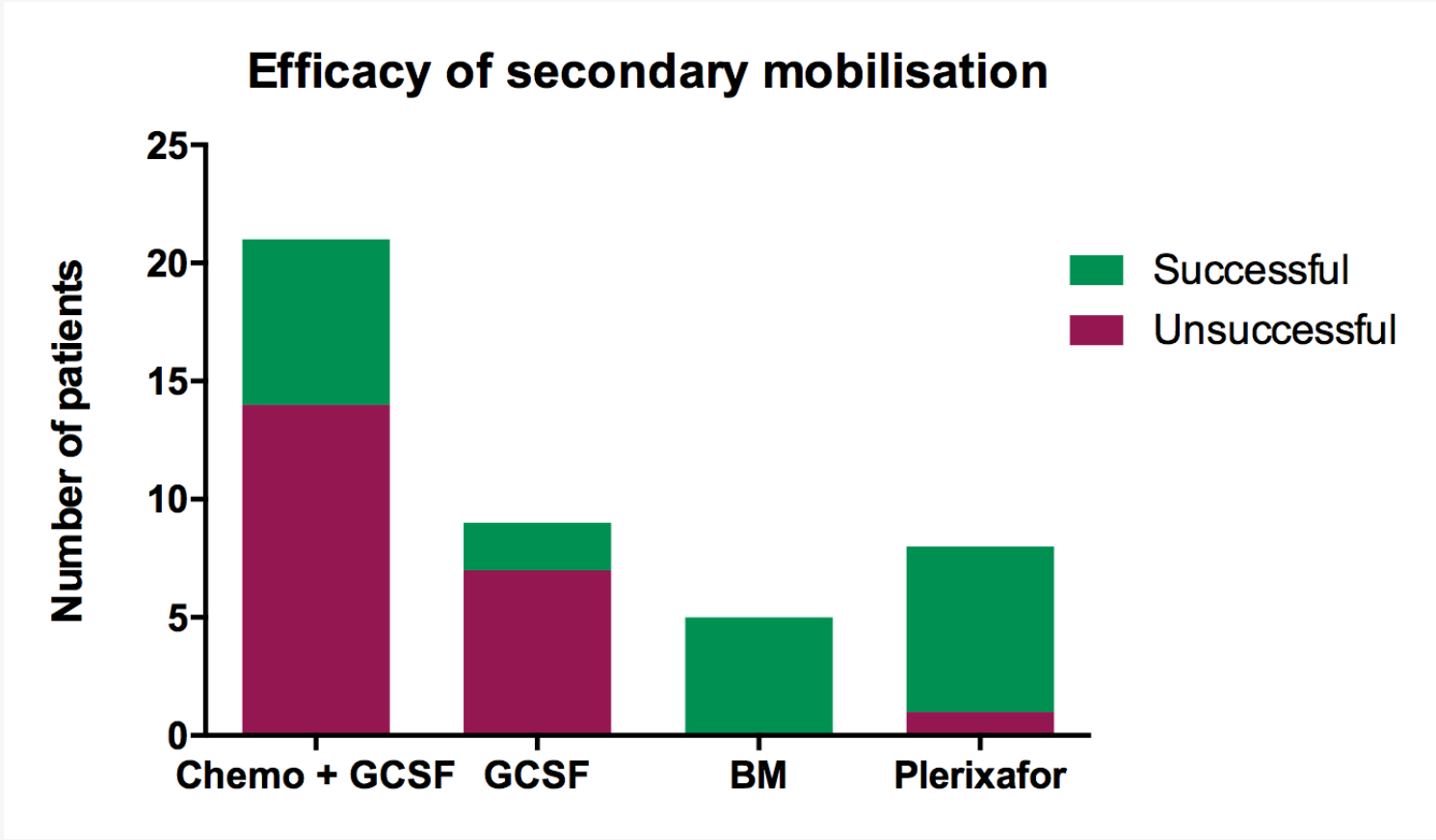


AVAILABLE MOBILIZATION OPTIONS

- Increase length of collection, or number of days

- Granulocyte colony stimulating factor - GCSF
- (Chemotherapy)
- CXCR4 agonist

- Bone marrow harvest



Wuchter *et al* Biol Blood Marrow Transplant 16:490-499, 2010

GCSF

- GCSF is the main drug used in mobilisation
- Filgrastim now has biosimilar agents
- Lenograstim only choice for allogeneic donors as concerns over long-term safety of biosimilars highlighted by EBMT and WMDA

- Recommended dose 5-16µg/kg/day

GCSF

- In mobilisation
  - Promotes CD34 proliferation
    - CD34 retained by local adhesion molecules VCAM-1/VLA-4 and SDF-1/CXCR4
  - Increased neutrophils → increased protease release (Elastase, Cathepsin G, MMPs)
    - which degrades VCAM-1/VLA-4
  - SDF-1 retention signals degraded → release of interaction stem cells from the paratrabecular space

Chemotherapy

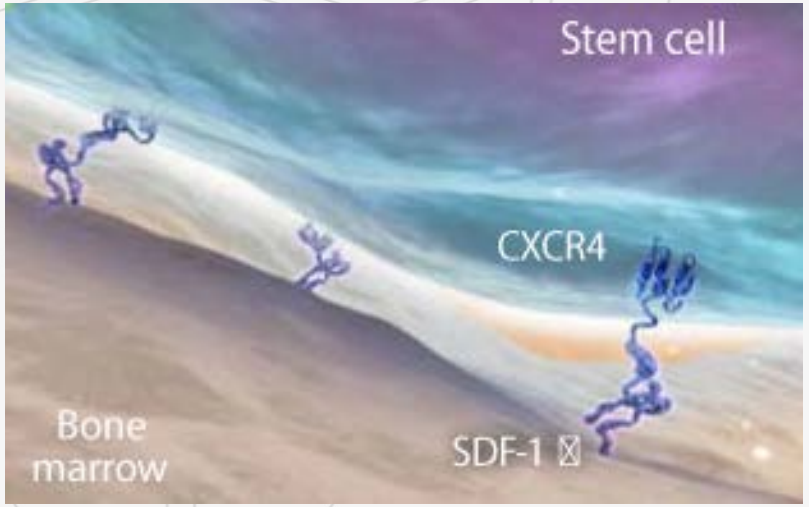
- On recovery following chemotherapy, there is an increased rate of cellular proliferation and when given in combination with GCSF, stem cells are released into the blood

- Will not work in the acute rescue setting but may be used for secondary mobilisation

CXCR 4 inhibition

Plerixafor (selective, reversible CXCR4 inhibitor)

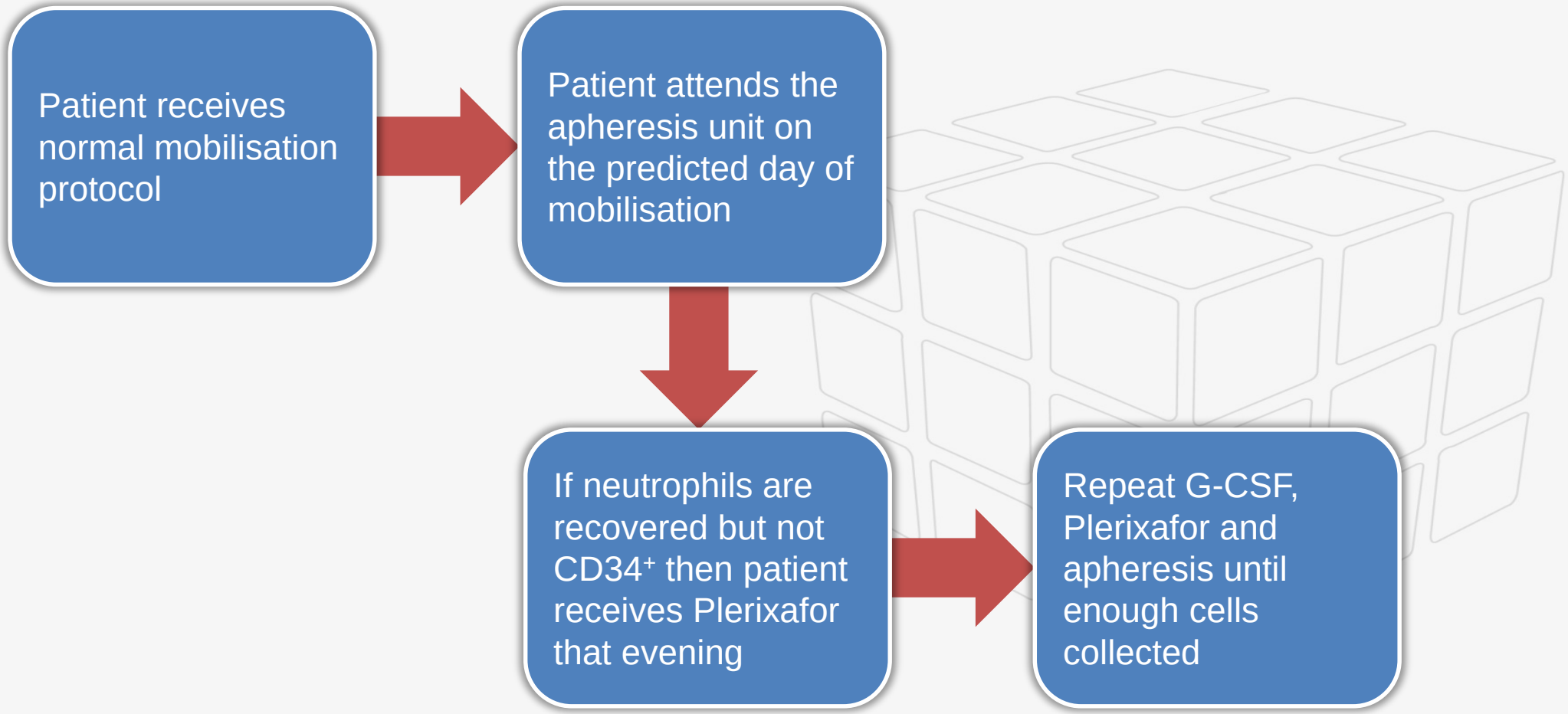
- CXCR4 is surface molecule found on stem cells.
- ligand CXCL12 (aka SDF1) results chemotaxis (homing) to bone marrow and retention in the paratrabecular space
- Plerixafor synergises with GCSF →release of stem cells from the bone marrow



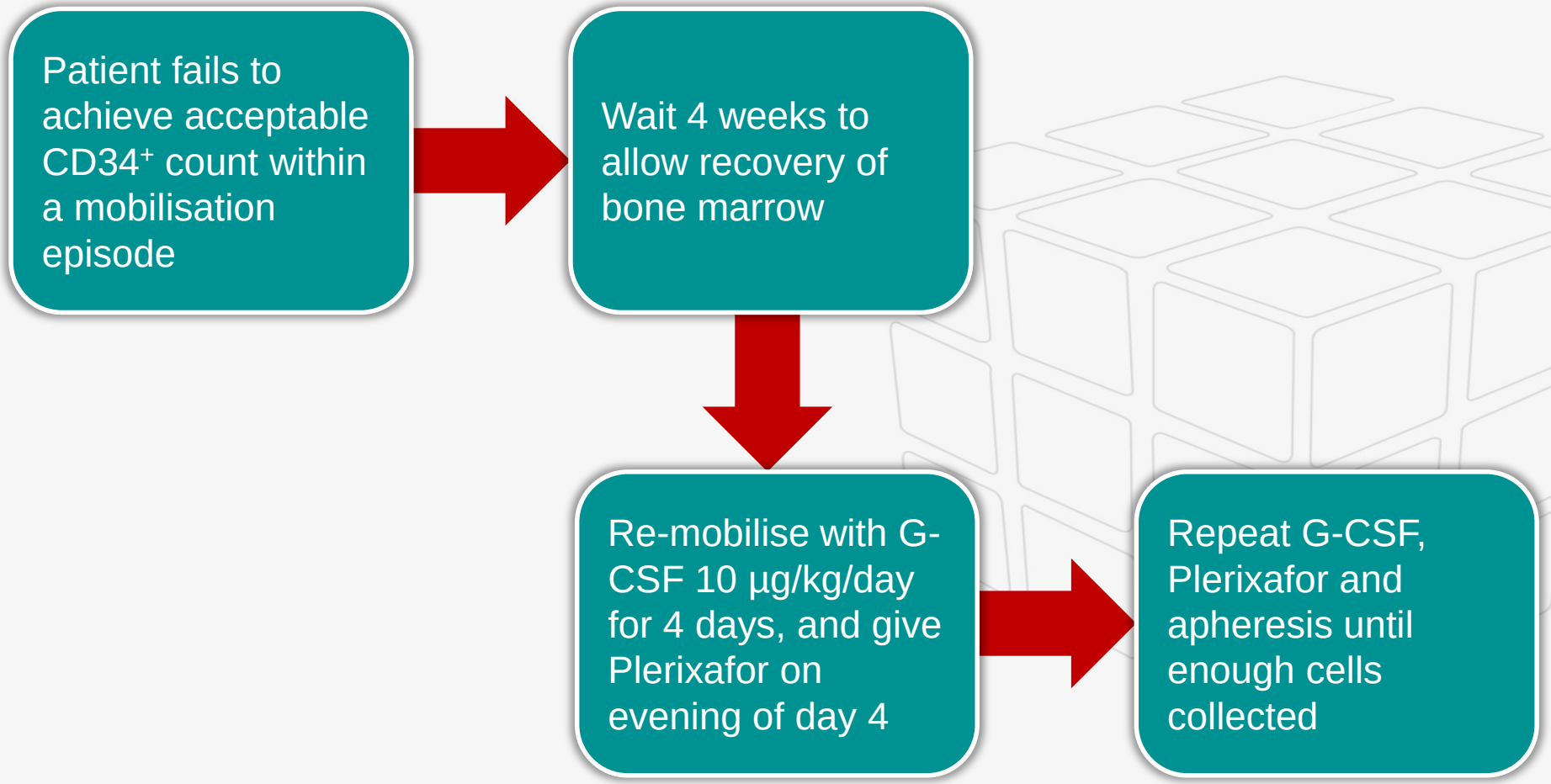
- When to intervene?

1. Pre-mobilisation
2. If failing
3. After failing

Rescue/Pre-emptive



Delayed remobilisation



Cochrane Library

Cochrane Database of Systematic Reviews

Additional plerixafor to granulocyte colony-stimulating factors for haematopoietic stem cell mobilisation for autologous transplantation in people with malignant lymphoma or multiple myeloma (Review)

Hartmann T, Hübel K, Monsef I, Engert A, Skoetz N

- AMD3100-3101 NHL
- AMD3100-3102 MM

Evaluating the Use of Plerixafor in Stem Cell Mobilisation – An Economic Analysis of the PHANTASTIC Trial

Antony P. Martin,[1]* Sarah Richards,[1] Alan Haycox,[1] Rachel Houten,[1] Claire McLeod,[1] Barbara Braithwaite,[2] Jack O. Clark,[2] Joanne Bell,[2] and Richard E. Clark[2]

[1]Liverpool Health Economics, Department of Economics, University of Liverpool Management School, Liverpool, United Kingdom
[2]Haematology Department, Royal Liverpool University Hospital, Liverpool, United Kingdom

Outcome Comparison of Lymphoma and Myeloma Patients after Autologous Stem Cell Transplantation (ASCT) with Peripheral Blood Stem Cell Mobilization Between Plerixafor (P) Mobilized in Poor Mobilizer Patients and Non–Plerixafor Mobilized Patients

Shahbaz A. Malik, Saul Yanovich, Aaron P. Rapoport, Ashraf Z Badros, Nancy M. Hardy, Mehmet H. Kocoglu, Alison Duffy, Kathleen Ruehle, Jennifer Nishioka, Olga Goloubeva, Jean Yared

Blood 2015 126:5507;

< Previous Article | March 2016 Volume 22, Issue 3, Supplement, Page S126 | Next Article >

Plerixafor Used in a "Just in Time" Fashion Allows Timely Autologous Hematopoietic Cell Transplant (HCT) in Patients Who Are at High Risk for Inadequate Apheresis

Jack W. Hsu, MD, Randall Brown, MD, Myron Chang, PhD, John W. Hiemenz, MD, William S. May, Jan S. Moreb, MD, Maxim Norkin, MD, John R. Wingard, MD

TRANSPLANTATION AND CELLULAR ENGINEERING

Plerixafor is effective given either preemptively or as a rescue strategy in poor stem cell mobilizing patients with multiple myeloma

Jian Cheng,[1,2] Michael Schmitt,[1] Patrick Wuchter,[1] Eike C. Buss,[1] Mathias Witzens-Harig,[1] Kai Neben,[1] Michael Hundemer,[1] Jens Hillengass,[1] Renate Alexi,[1] Hartmut Goldschmidt,[1] Bao-an Chen,[2] Anthony D. Ho,[1] and Anita Schmitt[1]

Inclusion of Plerixafor Increases the Efficacy of Stem Cell Harvesting in Poorly Mobilizing Patients with Multiple Myeloma and Lymphoma

Madlen Jentzsch, Elena Ruschpler, Sabine Leiblein, Yvonne Remane, Jan-Phillip Stümpel, Georg-Nikolaus Franke, Simone Heyn, Nadja Jaekel, Susann Schulze, Song-Yau Wang, Wolfram Poenisch, Claudia Nehring, Sebastian Schwind, Dietger Niederwieser, Vladan Vucinic

Blood 2015 126:5439;

TRANSFUSION AABB

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TRANSPLANTATION AND CELLULAR ENGINEERING

A nationwide survey of the use of plerixafor in patients with lymphoid malignancies who mobilize poorly demonstrates the predominant use of the "on-demand" scheme of administration at French autologous hematopoietic stem cell transplant programs

Christian Chabannon ✉, Fontanet Bijou, Jean-Michel Miclea, Noel Milpied, Jean-Marie Grouin, Mohamad Mohty

First published: 13 May 2015 Full publication history

DOI: 10.1111/trf.13141 View/save citation

UHBristol Plerixafor usage 2016

- Total 34 auto mobilisations to end August
- 80% reached yield without additional action (mean 1.55 days)
- 7 used plerixafor with 1million units/kg Zarzio filgrastim
  - 4 as rescue (all reached target with 1 dose plerixafor)
  - 3 planned as previous failure (all reached yield target)

CASES

Case 1

- 28 year old woman with MCL
- R-CHOP / R-DHAP 6 cycles in total
- CR by PET CT
- Mobilised of last cycle with 5µg/kg lenograstim for 6 days
- Day 1 - CD34 = 0.12

- What information is required?

Case 1

- Despite extensive teaching. Forgot that she needed to reconstitute powder and had been injecting herself with water!

Case 2

- 58 year old woman
- NDMM entered into Myeloma XI+ trial
- Received 4 cycles of CCRD chemotherapy to complete response
- Attended for Cyclophosphamide and GCSF primed collection
- Planned day 1 of collection peripheral CD34 = 1.5/µl (Neutrophil count 38.21 x 10^6/l)

Case 2

Questions

- What factors did she have that may have predicted poor mobilisation?
- Had she received appropriate mobilisation?
- What to do next?

Case 2

Prediction of poor mobilisation

- She had neither advanced or refractory disease
- While extensive BM involvement at diagnosis, this had now cleared
- Under 65
- No sepsis

Case 2

- As she had received lenalidomide, we gave chemo + GCSF rather than GCSF alone priming
- Cyclophosphamide 1.5g/m^2 and GCSF (Zarzio) 1 million units/kg for 4 days

- Continued GCSF → Next day CD34 2.4
- Mobilisation abandoned and rebooked

Case 2

- GCSF and plerixafor mobilisation planned
  - Day 1 CD34 1.6
  - Day 2 CD34 1.6

- Bone marrow 20% cellularity
- Repeat organ function – LVEF 20%
- High dose therapy abandoned – Still in CR at 2 years

Case 3

- 65 year old woman with myeloma
- VGPR after RCD x 8
- Cyclophosphamide-GCSF mobilisation
- Day 1 CD34 = 7

- What to do next?

Case 3

- Did not go on machine
- Given GCSF and Plerixafor at 1800
- Day 2 CD34 = 48 → yield 3.40
- Developed a fever an hour after collection with coryzal symptoms, did not receive further GCSF or plerixafor

Case 4

- Male 52 years old
- Relapsed follicular lymphoma
- VGPR after R-GDP salvage
- Day 1 = 10.4

Case 4

- Collection of 1.1 x 10^6 CD34/kg
- Received plerixafor
- Collected a further 2.6 CD34/kg on day 2

Case 5

- 36 year old male (86kg)
- Relapsed HL
- Previous treatment
  - 8 cycles ABVD
  - 4 cycles ESHAP (mobilising off fourth)
- Day one collection peripheral CD34 = 15.6/µl

Case 5

What is the likely yield?

- Average collection efficiency (CE2) = 58%
- Total volume processed 13430
- Expected yield ~1.3 x 10^6/kg

- Give GCSF and collect for a second day

- Total yield 2.9 x 10^6/kg

SWSCN Protocol

Peripheral Blood CD34 count (/µl)

<5	5-10	10-15	>15
No collection		Collection Insert Vascath if needed	
Consider plerixafor	Plerixafor		Plerixafor if previous failed collection only

UNANSWERED QUESTIONS

- Overweight and Obese patients
- Timing
- (Use in healthy donors)

Overweight patient

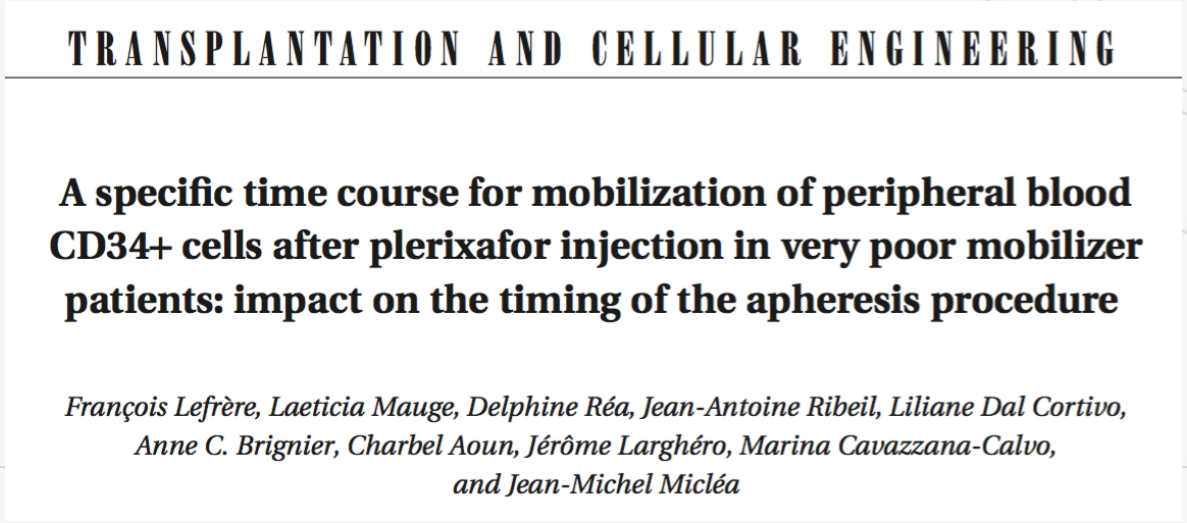
- What dosing of GCSF should be used?
  - Peak levels appear important

- If ideal weight used to calculate yield upto 16% would have 1 less apheresis

Optimal Timing

- Plerixafor SPC – give 6-11 hours prior to apheresis procedure

- In reality, usually given in the early evening prior to day units closing



TRANSPLANTATION AND CELLULAR ENGINEERING

A specific time course for mobilization of peripheral blood CD34+ cells after plerixafor injection in very poor mobilizer patients: impact on the timing of the apheresis procedure

François Lefrère, Laeticia Mauge, Delphine Réa, Jean-Antoine Ribeil, Liliane Dal Cortivo, Anne C. Brignier, Charbel Aoun, Jérôme Larghéro, Marina Cavazzana-Calvo, and Jean-Michel Micléa