Mobilizzazione di cellule staminali emopoietiche "chemo-free" nel Mieloma Multiplo: è tempo di prime time?

Bologna, 16 marzo 2017

REVISIONE CRITICA DELLA LETTERATURA
CHT + G-CSF VS G-CSF +-PLERIXAFOR

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The «ideal collection»

- Large number of CD34+ (>2 ASCT procedures)...
- …in one short LK procedure…
- …withouth need of several days of monitoring…
- …withouth reaching exagerate Leukocyte count…
- …*with low PMN contamination…*
- *…with high immunocompetent cell content…*
- …with low/absent tumor cell contamination…
- …easy to plan (fixed collection day!)…
- …no need of toxic mobilizing agents…
- …no SAE during the mobilization.

Feasibility of ASCT

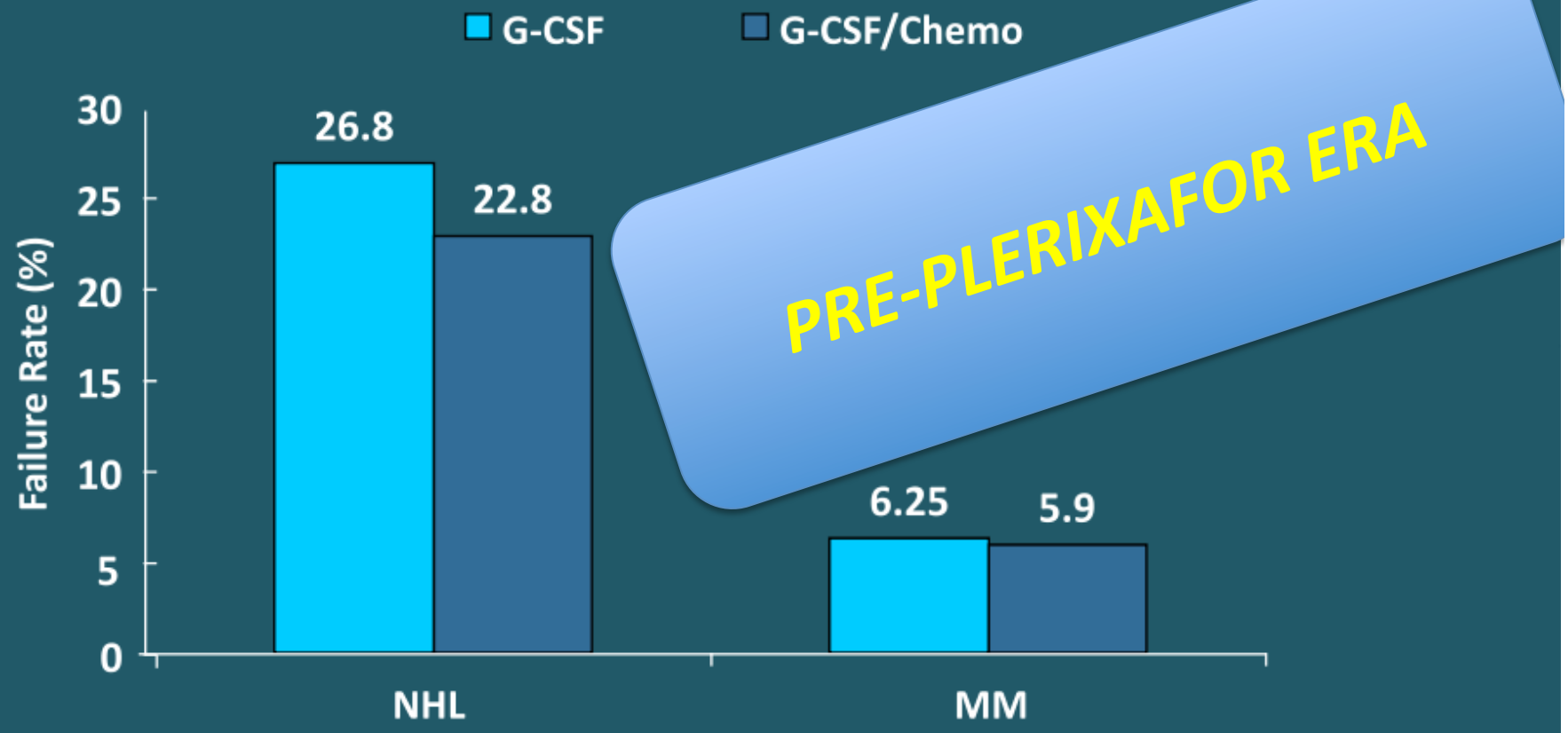
Less costs, better QOL

Minor risk,

Better product

- **Appropriate use of resources**
- **Less morbidity**

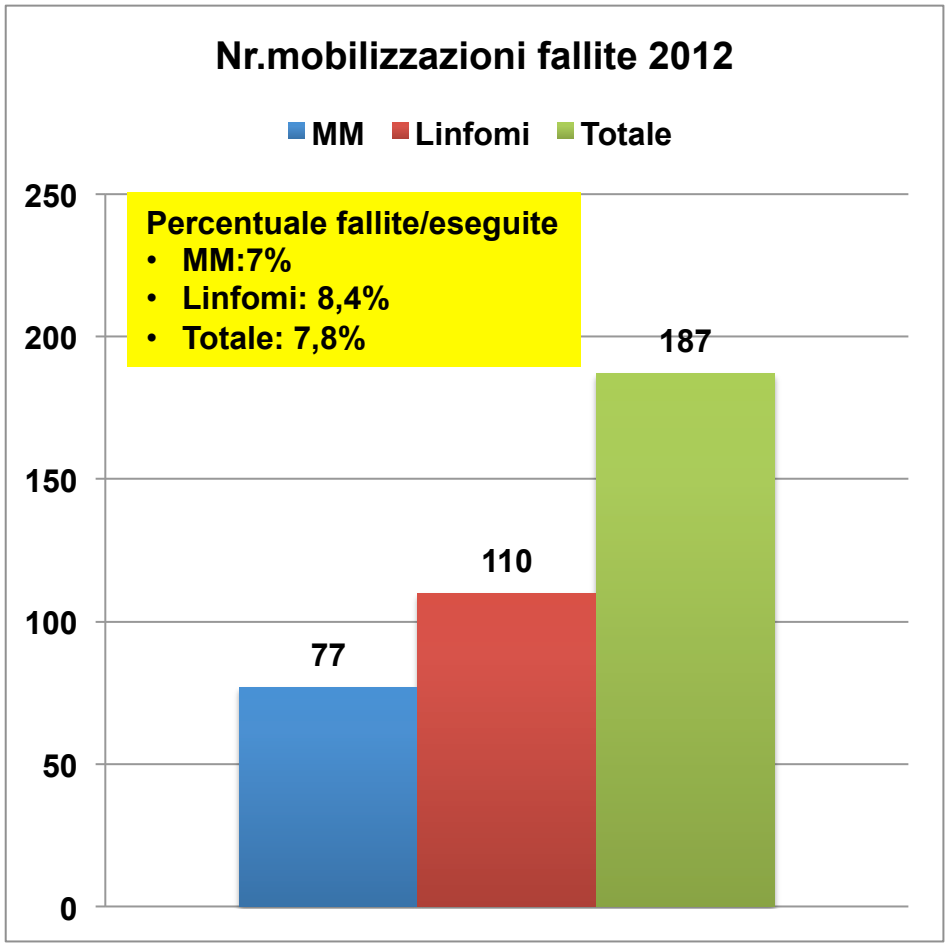
Failure Rates of G-CSF ± Chemotherapy Mobilization Regimens

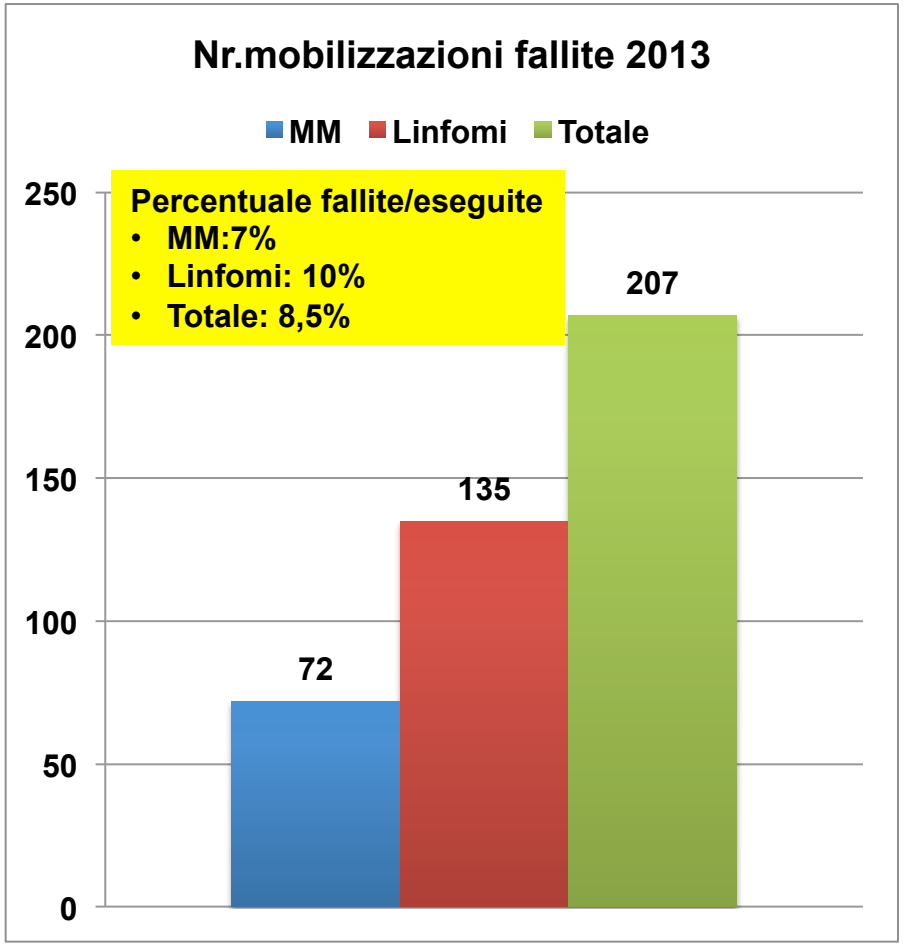


Chemo, chemotherapy; G-CSF, granulocyte colony stimulating factor; MM, multiple myeloma; NHL, non-Hodgkin's lymphoma.

Pusic et al. *Biol Blood Marrow Transplant* 2008;14:1045–1056.

Mobilizzazioni fallite nel 2012 e nel 2013
(aferesi non iniziata o raccolta <2x10^6/Kg di CD34+)





RE-MOBILIZATION RATE

- 1834 patients undergoing autologous PBSC mobilisation at Washington University, St Louis, USA showed that 269 patients (14.7%) required re–mobilisation due to inadequate PBSC dose

Pusic I, Jiang SY, Landua S, Uy GL, Rettig MP, Cashen AF et al. Impact of Mobilization and Remobilization Strategies on Achieving Sufficient Stem Cell Yields for Autologous Transplantation. *Biology of Blood and Marrow Transplantation* 2008;**14**:1045–1056.

RE-MOBILIZATION RESULTS

- Re–mobilisation using conventional approaches failed to mobilise sufficient CD34+ cells for transplant in 29.7% of patients, even when cells obtained at re–mobilisation were pooled with previously cryopreserved PBSC from first mobilisation.

Pusic I, Jiang SY, Landua S, Uy GL, Rettig MP, Cashen AF et al. Impact of Mobilization and Remobilization Strategies on Achieving Sufficient Stem Cell Yields for Autologous Transplantation. *Biology of Blood and Marrow Transplantation* 2008;**14**:1045–1056.

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

Factors That Influence Collection and Engraftment of Autologous Peripheral-Blood Stem Cells

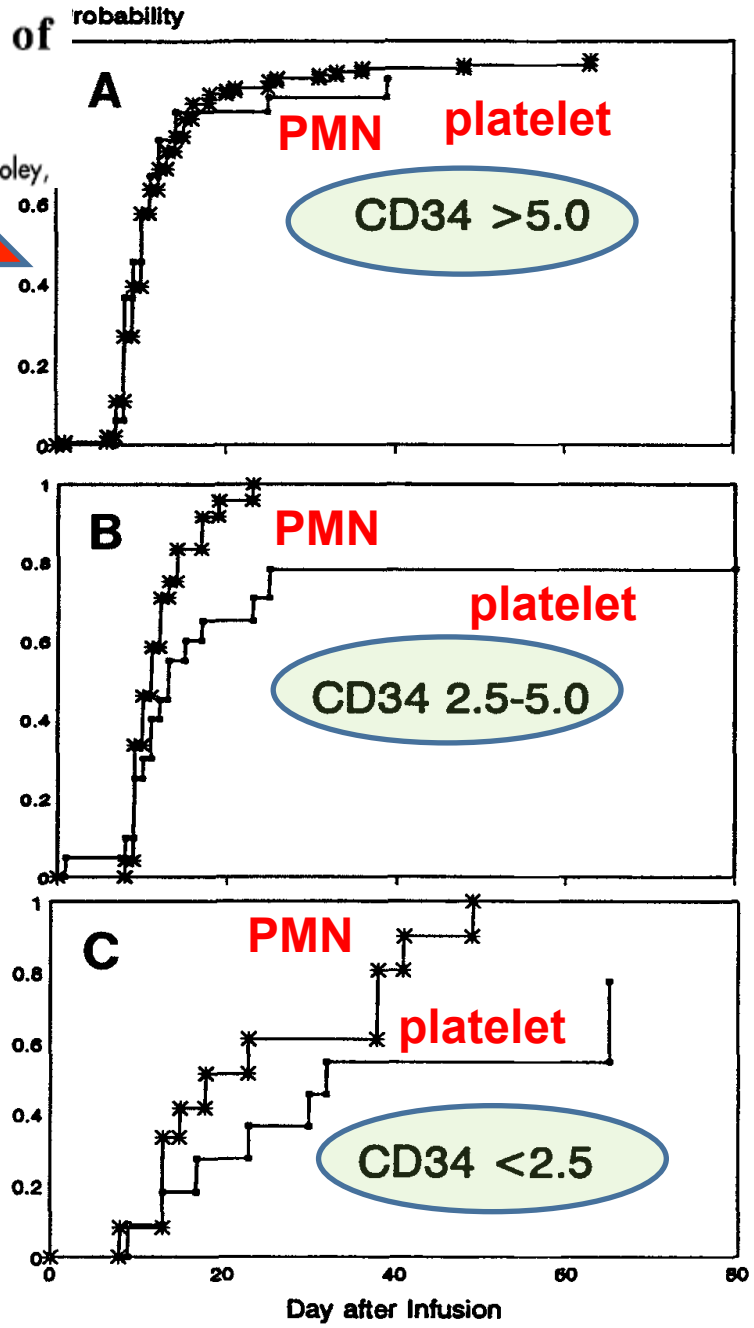
By William Bensinger, Fred Appelbaum, Scott Rowley, Rainer Storb, Jean Sanders, Kathy Lilleby, Ted Gooley,

J Clin Oncol 13:2547-2555. © 1995

tempo of PMN engraftment was indistinguishable between patients who received 2.5 to 5.0 and >5.0 x 10e6 CD34+ cells/kg.

In contrast, the probabilities for achieving platelet independence were distinct for each cell dose level

CD 34+ dose



Target dose of CD34+ cells can be both disease-specific or program-specific

Efficacy outcome measures:

- number of days of apheresis required to mobilize
- the minimum (≥2×106 CD34+ cells/kg)
- and optimum: ≥5×106 CD34+ cells/kg **for NHL and HD**

- ….or ≥6×106 CD34+ cells/kg **for MM**

Plerixafor and granulocyte colony-stimulating factor for first-line steady-state autologous peripheral blood stem cell mobilization in lymphoma and multiple myeloma: results of the prospective PREDICT trial

Nigel Russell,[1] Kenny Douglas,[2] Anthony D. Ho,[3] Mohamad Mohty,[4] Kristina Carlson,[5] G.J. Ossenkoppele,[6] Giuseppe Milone,[7] Macarena Ortiz Pareja,[8] Daniel Shaheen,[9] Arnold Willemsen,[10] Nicky Whitaker,[11] and Christian Chabannon[12]

haematologica | 2013; 98(2)

The GITMO-WG project

GOALS

Make the best decision about definition of poor mobilizer: (proven or predicted PM)

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"

Open

Bone Marrow Transplantation (2011), 1–10

www.nature.com/bmt

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 Olivieri[1], M Marchetti[2], R Lemoli[3], C Tarella[4], A Iacone[5], F Lanza[6], A Rambaldi[7] and A Bosi[8]
on behalf of the Italian Group for Stem Cell Transplantation (GITMO)

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 ≥5μg/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 **if he/she holds at least** **-one major criterion or** **-at least 2 minor criteria**	**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 **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

SHOULD WE ADOPT AN UNIVERSAL SCHEDULE FOR PBSC MOBILIZATION?

- **MOBILIZATION WITH G-CSF ALONE?**
- **CHEMO-MOBILIZATION WITH DISEASE-SPECIFIC SCHEDULES? (E.G. DHAP)**
- **CHEMO-MOBILIZATION WITH CYTOXAN? (2-3 G/M2)**

HOW AND WHEN ADDING PLERIXAFOR?

- *Upfront (always…)*
- *After failure (proven PM)*
- ***On demand (different strategies)***
- ***Pre-emptive (predicted PM:???)***

Do we really need to improve the PBSC harvest in MM?

- Two main options for mobilization : G-CSF alone (10 mcg/kg/day) or intermediate-dose Cyclophosphamide (2-4 g/M2) followed by G-CSF Koc ON, J Clin Oncol. 2000;18:1824-1830; Narayanasami U; Blood. 2001;98:2059-2064.

- *ex vivo* purging of stem cell products (CD34+select) to remove contamination by myeloma cells had no impact on patient outcome . (Vescio R et al Blood 1999;93:1858; Stewart AK et al J Clin Oncol 2001;19:3771–3779); Bourhis JH et al Haematologica 2007; 92(08)

- … however the presence of circulating clonal PCs predicts early relapse after ASCT (Dingli D. et al Flow cytometric detection of circulating myeloma cells before transplantation: a simple risk stratification system. BLOOD,15,2006,107, 8.

International myeloma working group (IMWG) consensus statement and guidelines regarding the current status of stem cell collection and high-dose therapy for multiple myeloma and the role of plerixafor (AMD 3100)

Leukemia (2009), 1–9

S Giralt[1], EA Stadtmauer[2], JL Harousseau[3], A Palumbo[4], W Bensinger[5], RL Comenzo[6], S Kumar[7], NC Munshi[8], A Dispenzieri[7], R Kyle[7], G Merlini[9], J San Miguel[10], H Ludwig[11], R Hajek[12], S Jagannath[13], J Blade[14], S Lonial[15], MA Dimopoulos[16], H Einsele[17], B Barlogie[18], KC Anderson[8], M Gertz[7], M Attal[19], P Tosi[20], P Sonneveld[21], M Boccadoro[4], G Morgan[22], O Sezer[23], MV Mateos[10], M Cavo[24], D Joshua[25], I Turesson[26], W Chen[27], K Shimizu[28], R Powles[29], PG Richardson[8], R Niesvizky[30], SV Rajkumar[7] and BGM Durie[31] on behalf of the IMWG[32]

Table 2 Pros and Cons of commonly used mobilization strategies in patients with myeloma

Strategy	*Frequency used*	*Pros*	*Cons*	*Comments*
Single agent filgrastim	Most common	Ease of use Cost Effective >80% of time Minimal toxicity Predictable	Only moderate CD34 yield No anti-myeloma effect	Current gold standard
Cyclophosphamide plus filgrastim	Most common chemomobilization used	Predictability Overcomes lenalidomide stem cell effect Well tolerated Predictable	Cytopenias and infectious complications Adds costs Minimal anti-myeloma effect Resource utilization	Doses over 4 g/m^2 associated with more toxicity without clear clinical benefit
Combination chemotherapy plus filgrastim	In some selected centers or for patients with high tumor burden	Disease control *In vivo* purging	Toxicity Cytopenias and infectious complications Cost and delays in eventual transplantation	DTPACE and modified CVAD commonly used. No comparative trials
Combination growth factors	Filgrastim and GMCSF explored now rarely used	Theoretical improvement in graft composition	Costs GMCSF not available in Europe	No proven benefit

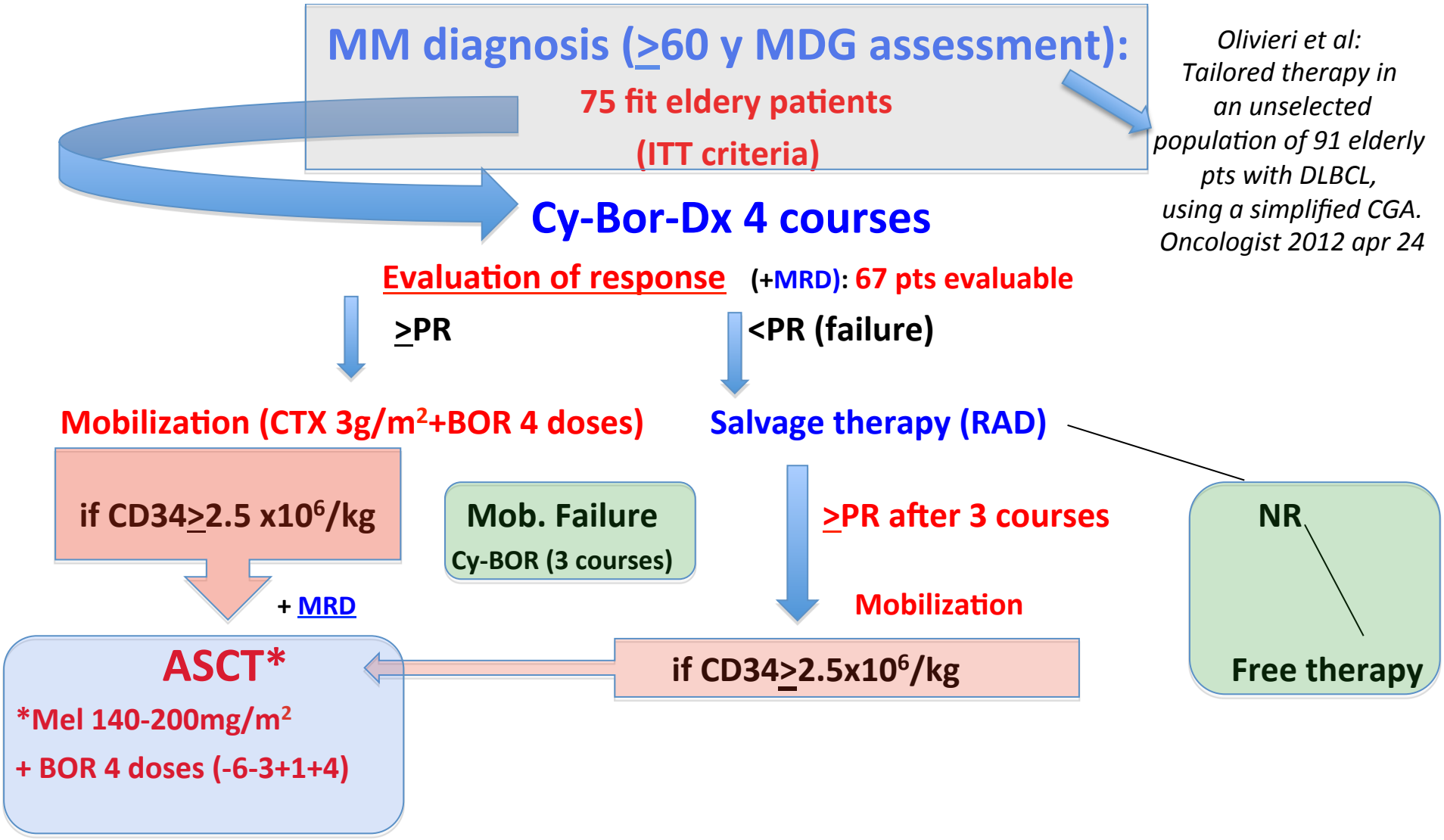
Comparison of high-dose CY and growth factor with growth factor alone for mobilization of stem cells for transplantation in patients with multiple myeloma

MA Gertz[1], SK Kumar[1], MQ Lacy[1], A Dispenzieri[1], SR Hayman[1], FK Buadi[1], D Dingli[1], DA

Patient characteristics ($N = 716$)

Variable	*CY* (n = *370*)	*Growth factor only* (n = *346*)	P-*value*
Men, no. of patients (%)	224 (61)	202 (58)	0.50
Age, median (IQR), years	58 (52–64)	60 (53–65)	0.11
β-2Microglobulin, median (IQR), μg/ml	2.7 (1.9–4.0)	2.3 (1.9–3.2)	0.01
Creatinine, median (IQR), mg per 100 ml	1.1 (0.9–1.3)	1.0 (0.8–1.2)	0.002
Apheresis, median (IQR) collections, no.	2 (1–3)	4 (3–6)	0.001
Marrow plasma cells, %	17 (5–34)	5 (1–13)	0.001
$CD34^+$ cells, median (IQR), cells/kg			
Total collected	10.3×10^6 (7.2×10^6–14.6×10^6)	9.9×10^6 (7.6×10^6–11.9×10^6)	0.01
Infused	5.6×10^6 (4.5×10^6–7.6×10^6)	4.2×10^6 (3.8×10^6–5.0×10^6)	<0.001
Duration of hospitalization, median (IQR), days	4 (0–10)	4 (0–9)	0.92
Nonstaphylococcal bacteremia, no. of patients (%)	48 (13)	25 (7)	0.01

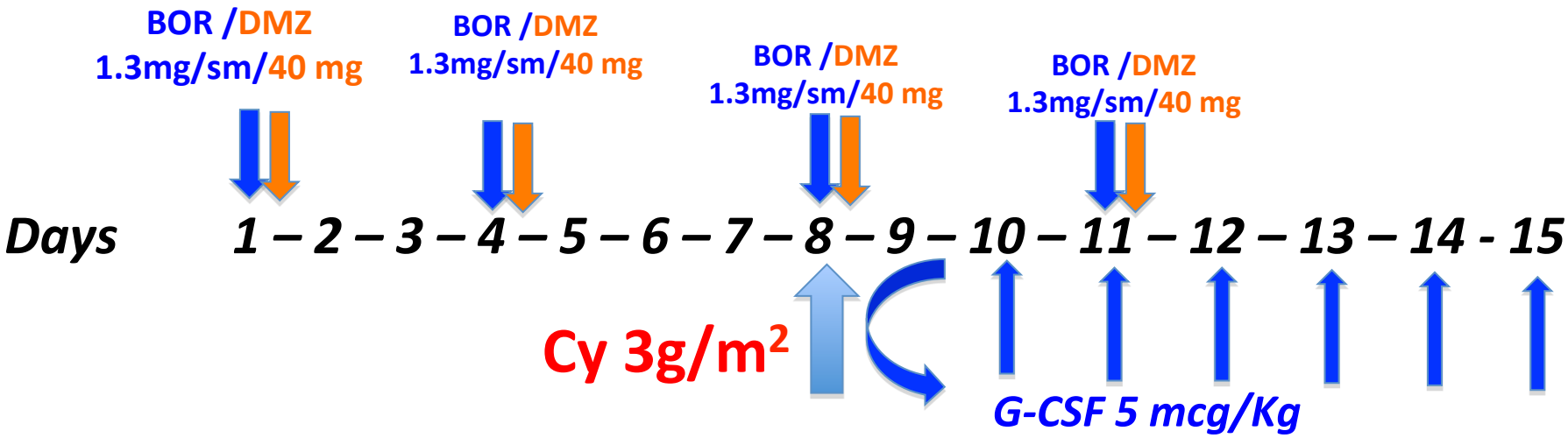
Bone Marrow Transplant. 2009 April ; 43(8): 619–625.



+90 after ASCT: Evaluation of response (+MRD)

F-U

Mobilization strategy *48 pts evaluable*



Days>15 continue G-CSF

WBC

>1000 WBC

CD 34 **> 15/mcl** → **START LK**

<15/mcl → **START Plerixafor**

Plerixafor in proven or predicted PM (4pts) by default+ 2pts on demand

Target >2.5x10e6CD34+/kg

MOBILIZATION RESULTS

- 47/48 (98%) pts successfully mobilized >2.0 CD34+ cells/Kg
  (overall feasibility: 47/69= 75% on ITT basis)

- Median harvested CD34+: $7x10^6$ /Kg (range: 2.75-23)

- In 39/47 (83%) pts PBSC harvest > $4.0x10^6$ /Kg

- Median number of leukaphereses: 2 (range: 1-4)

- 6 (12.5%) pts received Plerixafor (2 proven; 2 predicted PM, 2 on demand): median harvested CD34+/kg with two doses: 6.6 (range: 3.7-11.5)

  Median number of LK: 2

No upgrade of response was observed

MOBILIZATION-RELATED TOXICITY (48pts)

Grade 3-4 Toxicity (NCI-CTCAE)	n.
Gr.3/4 haematologic	2 (neutropenia/thrombocytopenia not requiring hospitalization)
Gr ¾ Cardiac	1 (congestive heart failure requiring hospitalization)
F.U.O.	7
Septic shock (death)	**1**
Gr.3/4 Infections	0
Gr.3/4 Gastrointestinal	0
Gr.3/4 Pulmonary	0
Neurologic (PN)	0
Renal	0

Bone Marrow Transplantation (2016) **51,** 372–376

www.nature.com/bmt

OPEN

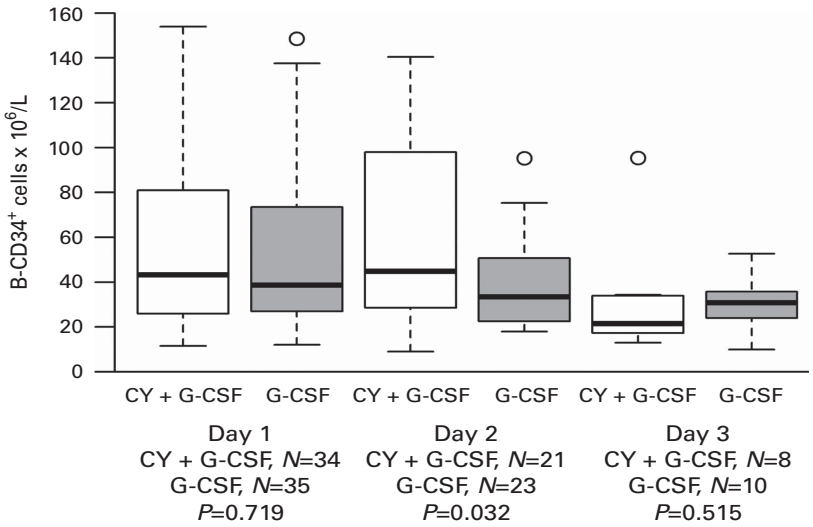
ORIGINAL ARTICLE

A randomized phase II study of stem cell mobilization with cyclophosphamide+G-CSF or G-CSF alone after lenalidomide-based induction in multiple myeloma

Primary End point:
⩾ 3 × 106/kg CD34+
with 1 – 2 LK

R Silvennoinen[1], P Anttila[2], M Säily[3], T Lundan[4], J Heiskanen[2], TM Siitonen[3], S Kakko[3], M Putkonen[5], H Ollikainen[6], V Terävä[7], A Kutila[8], K Launonen[9], A Räsänen[10], A Sikiö[11], M Suominen[12], P Bazia[13], K Kananen[13], T Selander[14], T Kuittinen[1], K Remes[5,15] and E Jantunen[1]

CD34+ cells (×106/L) before first, second and third apheresis.



CD34+ stem cell yields of apheresis on days 1–3

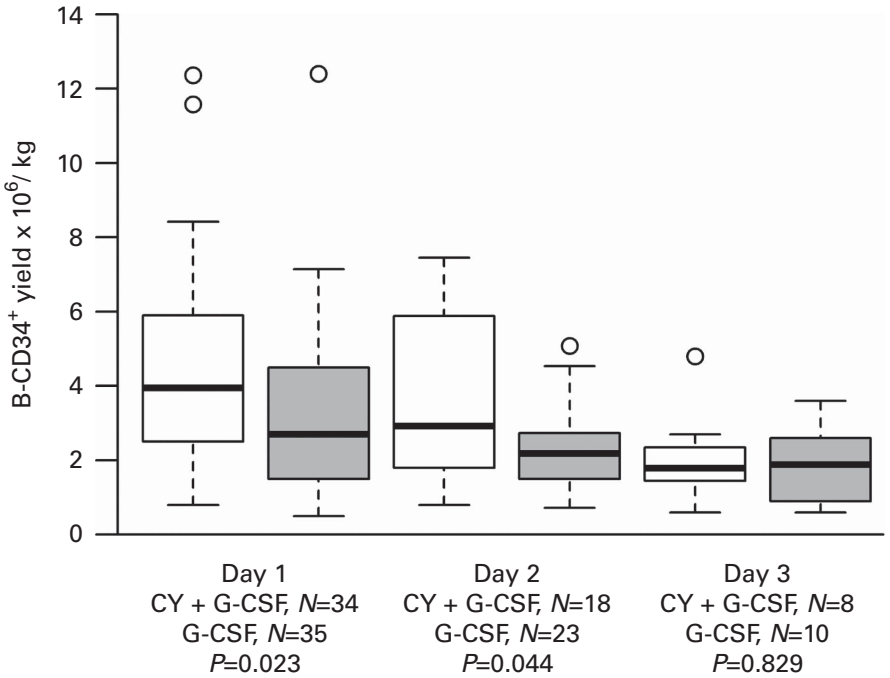


Table 2. Mobilization and harvesting results

	Arm A (CY+G-CSF), N = *34*	*Arm B (G-CSF)*, N = *35*	P
Blood $CD34^+$ cells $\times 10^6$/L at first apheresis, median (range)	43 (12 – 258)	39 (12 – 149)	0.719
$CD34^+$ cell yield $\times 10^6$/kg with first apheresis, median range	4.0 (0.8 – 12.4)	2.7 (0.5 – 12.4)	0.023
Peak blood $CD34^+$ cells $\times 10^6$/L, median (range)	67 (14 – 258)	44 (18 – 149)	0.106
Plerixafor use, *N* (%)	2 (6)	5 (14)	0.428
Primary end point yield $\geqslant 3 \times 10^6$/kg with 1 – 2 harvests, *N* (%)	32/34 (94)	27/35 (77)	0.084
Primary end point yield $\geqslant 6 \times 10^6$/kg for double graft with 1 – 2 harvests, *N* (%)	13/21 (62)	9/18 (50)	0.662
Median no. of aphereses			
$\geqslant 3 \times 10^6$/kg, median (range)	1 (1 – 3)	2 (1 – 3)	0.035
$\geqslant 6 \times 10^6$/kg, median (range)	2 (1 – 3)	3 (1 – 4)	0.241
Total yield harvested $\times 10^6$/kg, median (range)	6.7 (2.2 – 12.4)	5.3 (2.4 – 12.4)	0.012

Table 3. Hospitalization, toxicity and need for supportive care during mobilization and ASCT in myeloma patients according to the mobilization arm

	Arm A (CY+G-CSF), N = *34*	*Arm B (G-CSF)*, N = *35*	P
Days in hospital during mobilization, median (range)	3 (1 – 5)	0 (0 – 2)	< 0.001
Days in hospital during apheresis, median (range)	3 (1 – 11)	3 (1 – 5)	0.228
Fever during mobilization, *N* (%)	4 (12%)	1 (3%)	0.169
IV antibiotics during mobilization, days median (range)	0 (0 – 9)	0 (0 – 12)	0.800
Toxic deaths during mobilization	0	0	
Neutropenic fever during ASCT, *N* (%)	28 (90)	18 (67)	0.049
Platelet infusions during ASCT, units (range)	4 (0 – 24)	8 (0 – 28)	0.516
Red cell infusions during ASCT, units, (range)	0 (0–6)	0 (0 – 10)	0.567
Toxic deaths during ASCT	0	0	
Days in hospital during ASCT, median (range)	21 (14 – 72), *N* = 31	19 (14 – 29), *N* = 27	0.577

COMMENTARY

Mobilization policy in multiple myeloma: minimum target or law of redundancy? Two different approaches by the two sides of the Atlantic Ocean

A Olivieri and F Saraceni

Bone Marrow Transplantation (2016) **51,** 348–350; bmt.2015.317; published online 21 December 2015

The main endpoint was achieved in 94% and 77% of patients of the two arms, respectively, without statistically significant difference ($P=0.084$). All patients (in both arms) reached the secondary endpoint, the minimum safety target of 2×10^6 CD34+ cells/kg with less than three aphereses. However, the median number of aphereses needed to reach the 3×10^6 threshold was significantly higher in patients receiving G-CSF ($P=0.035$); again, more patients needed PLX in this arm, but the difference was not statistically relevant. Finally, a significantly better yield of the first apheresis was observed after CY+G-CSF (median 4×10^6/kg), compared with G-CSF alone (2.7×10^6/kg)

COMMENTARY

Mobilization policy in multiple myeloma: minimum target or law of redundancy? Two different approaches by the two sides of the Atlantic Ocean

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However, it seems quite obvious that the optimal dose of CD34+ cells is better than the minimum target; furthermore the CD34+ target dose defined in this study (3×10^6 CD34+ cells/kg) is appropriate only for MM patients candidate to single ASCT.

Though not statistically different from the G-CSF+CY arm, 23% MM patients mobilized with G-CSF alone did not reach this target and the proportion of patients able to collect the double dose (6×10^6 CD34+ cells/kg) for tandem ASCT was only 51%. Recent data suggest that further ASCT could be beneficial for MM patients in late relapse after a full ASCT program including one or two ASCT,[14] suggesting that a higher target should be desirable.

COMMENTARY

Mobilization policy in multiple myeloma: minimum target or law of redundancy? Two different approaches by the two sides of the Atlantic Ocean

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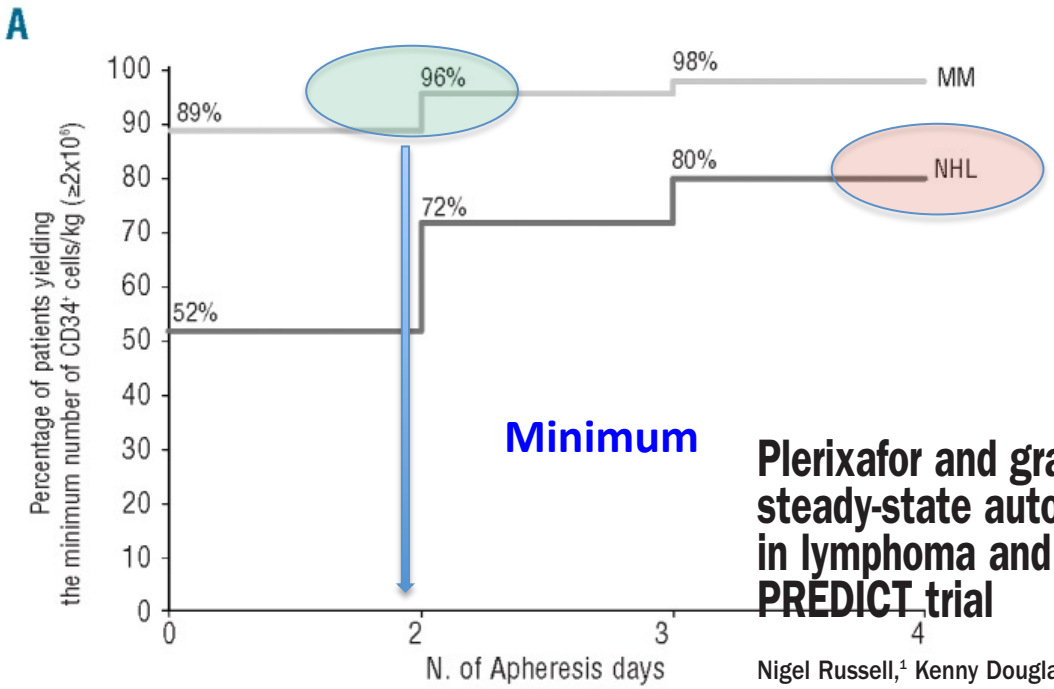
To synthesize, is it better to collect a fixed dose of HPCs for a single ASCT (3×10^6 CD34+ cells/kg or 6×10^6 CD34+ cells/kg, respectively) or rather a larger dose (ideally collected with few aphereses) able to support both a safe tandem ASCT and a subsequent ASCT for late relapsing patients?

If so a dose of 9×10^6 CD34+ cells/kg should be today the optimal target; but in such case, should we consider G-CSF alone as the golden standard? If not, which is the best mobilization policy? G-CSF plus PLX (upfront or on demand) or CY followed by G-CSF plus PLX on demand? New agents are appearing on the

HOW AND WHEN ADDING PLERIXAFOR?

- *Upfront (always…)*
- *After failure (proven PM)*
- ***On demand (different strategies)***
- ***Pre-emptive (predicted PM:???)***

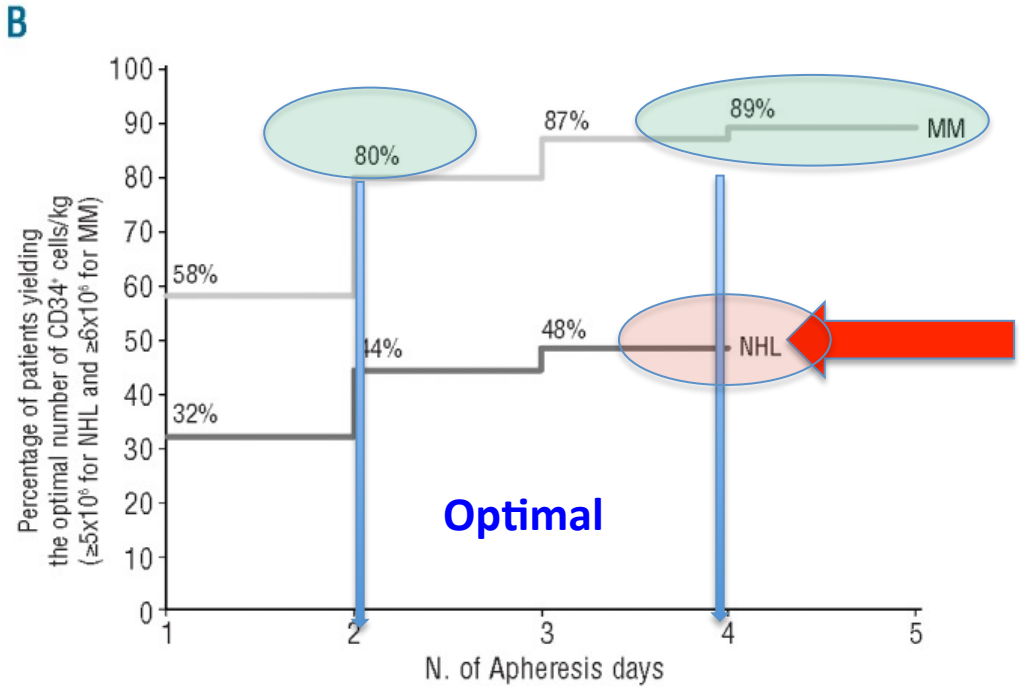
…after G-CSF alone or after CHT+G-CSF?



Plerixafor+G-CSF upfront: updated results..

Plerixafor and granulocyte colony-stimulating factor for first-line steady-state autologous peripheral blood stem cell mobilization in lymphoma and multiple myeloma: results of the prospective PREDICT trial

Nigel Russell,[1] Kenny Douglas,[2] Anthony D. Ho,[3] Mohamad Mohty,[4] Kristina Carlson,[5] G.J. Ossenkoppele,[6] Gius Milone,[7] Macarena Ortiz Pareja,[8] Daniel Shaheen,[9] Arnold Willemsen,[10] Nicky Whitaker,[11] and Christian Chaba



haematologica | 2013; 98(2)

The current practice requires simple and standardized approaches; most proposed algorithms for Plerixafor on demand are difficult to apply!

PLERIXAFOR ON DEMAND OR PRE-EMPTIVE ADMINISTRATION?

Pre-emptive Plerixafor

- Pre–emptive use of P may have advantages in terms of avoidance of cancelled apheresis and/or transplant slots, and also in terms of avoiding the negative quality–of–life impact of failed PBSC mobilisation
- Pre–emptive use of P does not requires complicated agorythms

General rules for pre-emptive P

- Pre–emptive use may be triggered by:
- CD34+ <15/µl at the time of WBC recovery following chemomobilisation
- CD34+ <15 to 20/µl-1 after 4 days of G–CSF without prior mobilising chemotherapy
- 1st day's apheresis yield<1 ×10e6 CD34+ cells/kg
- or <50% the target total CD34+ cell dose

There is a minimum CD34+ count threshold below which Plerixafor should not be attempted, because it is unlikely to be effective?

- In case series from Poland and Croatia, pre–emptive P was found equally effective for patients with CD34+ <3/µl as for patients with higher CD34+ count.
- Similar results in a large series from Barcelona, where P was still effective with CD34+ count < 3.5/µl
- However, this has not always been the UK and Italian experience

CONCLUSIONS

- Although patients with peripheral CD34+ counts below 5 µl-1 do appear to be at higher risk of mobilisation failure despite pre–emptive plerixafor, there is no absolute minimum peripheral CD34+ count threshold below which pre– emptive plerixafor may not be used.

Algorithms for Plerixafor on demand: 3 basic approaches

- CD34-PB kinetics-based: the decision to administer Plerixafor is based on kinetics data of CD34+ count in PB after G-CSF or G-CSF/chemo-based mobilization*
- CD34-PB kinetics and risk factors-based: EBMT algorithm (Jantunen, Lemoli); (Rossi)
- CD34+ kinetics and WBC count or CD34+/WBC ratio (Farina, Sorasio, Milone)

- ** The results of 1st LK harvest <1x10e6 CD34+/kg is a supplementary criterion for Plerixafor addition*

Algorithms for P use: was it worth?

- A plethora of algorithm have been proposed to guide Plerixafor administration and apheresis initiation, but none has succeeded for a widespread use.
- Such algorithms have often been studied in the context of monocentric experiences or have been applied selectively to a single disease or a schedule of mobilization, hindering a wider application of the results.

the decision to administer Plerixafor should be based on a comprehensive evaluation including not only CD 34+/WBC kinetics, but also on the clinical history and the baseline blood count of the patients

The New GITMO study* to validate the definitions of the PM in MM and Lymph pts

- aim of the study: validate the predictive ability of GITMO criteria for pPM, by measuring their diagnostic accuracy for the outcome of PPM;
- to improve their predictive ability by building a model, to establish a clinical tool to identify patients at high risk for mobilization failure before starting the mobilization attempt.

**17 italian GITMO centers for 1318 consecutive Mobilization procedures*

A GITMO retrospective study to validate the definitions of the PM (mobilization outcomes in 1318 consecutive MM and Lymph pts)

GENERAL CHARACTERISTICS	
SEX	753 M / 565 F
AGE	Median 55.6 yrs (range 5 - 76)
DISEASE	600 (46%) MM 554 (42%) NHL 164 (12%) HL
HISTORY – PREVIOUS TREATMENTS	
PREVIOUS MOBILIZATION FAILURE	94 (7.1%)
PREVIOUS CHT LINES	1 LINE: 790 (60%) 2 LINES: 413 (31%) 3 LINES: 93 (7%) ≥ 4 LINES: 22 (2%)
TREATMENTS AT RISK	153 (11.6%) 12 Fludarabine, 121 Lenalidomide, 1 RIC, 27 Melphalan, 9 BCNU
RADIOTHERAPY	122 LIMITED (9%) 32 EXTENSIVE (2%)

Main characteristics of the 1318 pts

STATUS PRE-MOBILIZATION	
DISEASE STATUS BEFORE MOBILIZATION	1066 REMISSION (81%) 242 REFRACTORY (18%) 10 UNKNOWN (1%)
BONE MARROW STATUS BEFORE MOBILIZATION	263 INVOLVED <30% (20%) 35 INVOLVED >30% (3%) 199 NOT DONE / UNKNOWN (15%)
HEMOGLOBIN BEFORE MOBILIZATION	Median 11.8 g/dl (range 7.2 - 18)
LEUKOCYTE COUNT BEFORE MOBILIZATION	Median 5.2 x 10^9/L (range 0 – 426)
NEUTROPHIL COUNT BEFORE MOBILIZATION	Median 3.2 x 10^9/L (range 0 – 282)
PLATELET COUNT BEFORE MOBILIZATION	Median 223 x 10^9/L (range 6 – 1167)

Mobilization outcome in 1318 pts

OUTCOME - COLLECTION	
TOTAL HARVEST (CD34 x 10^6/kg) <2 x 10^6/kg 2 - 5 x 10^6/kg >5 x 10^6/kg	Median 8.9 x 10^6/kg (range 0 – 63.5) 144 (10.9%) 204 (15.5%) 970 (73.6%)
MOBILIZATION FAILURE (PROVEN PM according to GITMO criteria)	180 pts (13.7%) 27 / 254 MM (10.6%) 19 / 258 NHL (7.4%) 2 / 85 HL (2.4%)
DETERMINANTS OF MOBILIZATION FAILURE	163 / 180 due to LOW CD34 PEAK COUNT (91%) 144 / 180 due to INSUFFICIENT HARVEST (80%) 127 / 180 due to BOTH CRITERIA (71%)
APHERESES CD34 PEAK COUNT	Median 1 aph. (range 1 – 6) Median 85 CD34/mcl (range 0 – 1942)

Independent predictive factors for mobilization failure identified by backward variable selection with multiple logistic regression

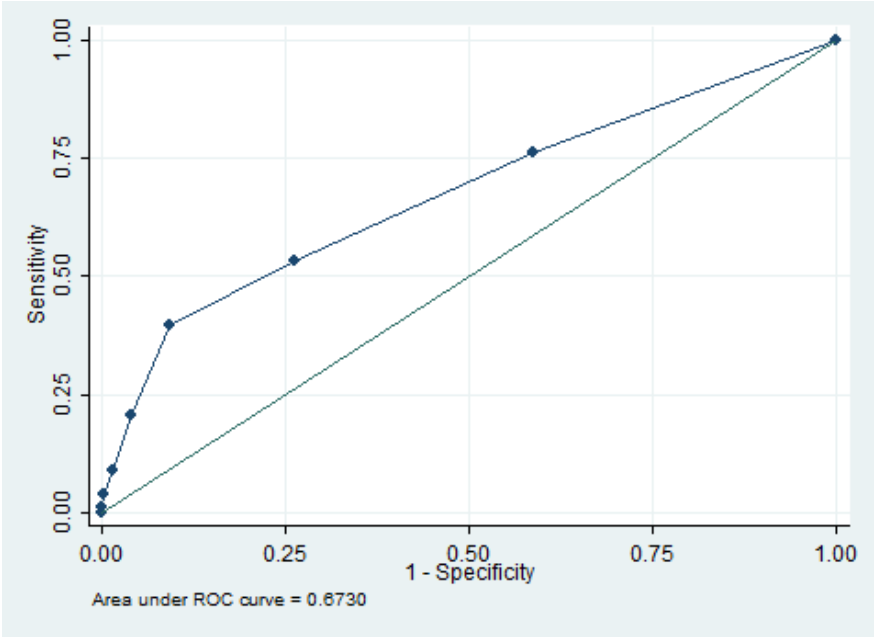
Predictive factor	β	Odds ratio (95% CI)	Probability (Wald test)
Age class (46-60 years = 1; > 60 years = 2)	0.3796	1.46 (1.14 - 1.88)	0.003
Diagnosis = NHL	0.5535	1.74 (1.16 - 2.6)	0.007
Disease infiltration ≥ 30% at the pre-mobilization BMB	1.269	3.56 (1.51 - 8.35)	0.004
Number of full chemotherapy courses	0.5888	1.8 (1.43 - 2.27)	<0.001
At least one previous treatment at risk	0.7739	2.17 (1.28 - 3.67)	0.004
Pre-mobilization Hb value class (<80 g/l = 1; 80 – 130 g/l = 2)	1.1165	3.05 (1.72 - 5.42)	<0.001
Pre-mobilization WBC < 5 x 10^9/L	0.7185	2.05 (1.41 - 2.99)	<0.001
Pre mobilization Plt < 170 x 10^9/L	0.5869	1.8 (1.23 - 2.62)	0.002
Priming with G-CSF alone	2.2513	9.5 (4.75 - 19)	<0.001
Upfront Plerixafor not planned	2.7292	15.32 (5.09 - 46.16)	<0.001
Previous mobilization failure	1.9059	6.73 (3.67 - 12.34)	<0.001

Predictive ability according to the proposed GITMO consensus criteria

Major criteria = 2 POINTS
- Failed previous mobilization attempt, not otherwise specified.
- Previous extensive radiotherapy to marrow bearing tissue.
- Full courses of previous therapy, including melphalan, fludarabine or other therapies potentially affecting stem cell mobilization.

Minor criteria = 1 POINT
- Advanced phase disease (≥2 CHT lines)
- Refractory disease
- Extensive BM involvement at mobilization
- BM cellularity <30% at mobilization
- Age ≥65 years

CUT-OFF=2 (1 Major or 2 Minor)



AUC = 0.673

Sensitivity = 53%

Specificity = 74%

LR+ = 2.04

LR- = 0.63

PPV = 24%

NPV = 91%

ESEMPI DI UTILIZZO DEL PM SCORE

VARIABILE	SCORE
Infiltrazione midollare pre-mobilizzazione >30%	1
Linfoma Non-Hodgkin	0.5
Uso di G-CSF alone	2
Età <45 / 45 – 60 / >60	0.3 x2
Hb pre-mobilizzazione: <8 / 8 – 13 / >13	1
Numero di linee di CHT	0.5 x2
Plt pre-mobilizzazione < 170.000/mmc	0.5
Non uso di PLX upfront	2
Precedente fallimento mobilizzazione	1.5
Almeno 1 trattamento a rischio (Mel/Len/Flu/ BCNU/RIC)	0.5
Leucociti pre-mobilizzazione < 5000/mmc	0.5

CASE 1: A **70 year** old patient undergoing a first attempt of mobilization **with G-CSF alone (no Plx)** for MM after **2 lines** of therapy (1° **R**d; 2° VCD), with 20% plasma cells in the marrow and Hb 13.5 g/dl, WBC 5800/mmc, **Plt 110.000**/mmc before mobilization, **has a PM score of 6.6**

→ **HIGH RISK OF MOBILIZATION FAILURE**

CASE 2: A **58 year** old patient with **NHL** is attempting a second mobilization procedure (DHAP+G-CSF+**Plerixafor**) after a **first failure** (suboptimal G-CSF dose); he has been **treated with R-CHOP x 6, R-DHAP x 2**. He has no BM involvement. Pre-mob CBC: **Hb 12.6, WBC 4600/mmc, Plt 158.000. The PM score is 5.3.**

→ **NOT HIGH RISK**

PLANNING

Stem Cell Mobilization with Cyclophosphamide Overcomes the Suppressive Effect of Lenalidomide Therapy on Stem Cell Collection in Multiple Myeloma

Tomer Mark,[1] Jessica Stern,[1] Jessica R. Furst,[1] David Jayabalan,[1] Faiza Zafar,[1] April LaRow,[1] Roger N. Pearse,[1] John Harpel,[1] Tsiporah Shore,[1] Michael W. Schuster,[1] John P. Leonard,[1] Paul J. Christos,[2] Morton Coleman,[1] Ruben Niesvizky[1]

TRANSPLANTATION AND CELLULAR ENGINEERING

CME Second time a charm? Remobilization of peripheral blood stem cells with plerixafor in patients who previously mobilized poorly despite using plerixafor as a salvage agent

Shan Yuan, Auayporn Nademanee, Amrita Krishnan, Neil Kogut, Sepideh Shayani, and Shirong Wang

MONITORING
ADAPTING

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

Vox Sanguinis (2006) **91**, 126–134

ORIGINAL PAPER

DOI: 10.1111/j.1423-0410.2006.00796.x

Accurate prediction of autologous stem cell apheresis yields using a double variable-dependent method assures systematic efficiency control of continuous flow collection procedures

L. Pierelli,[1] M. Maresca,[2] N. Piccirillo,[2] S. Pupella,[3] M. Gozzer,[3] M. L. Foddai,[4] M. Vacca,[5] G. Adorno,[6] U. Coppetelli[7] & U. Paladini[8]

RISK-STRATIFIED APPROACH

- Low-risk → G-CSF alone
- Int-risk
  - → G-CSF + CHT
  - → G-CSF + PLX upfront
- High-risk → G-CSF ± CHT + PLX upfront

PLX on demand

RINGRAZIAMENTI

- Jacopo Olivieri[1], Immacolata Attolico[2], Francesco Saraceni, Roberta Nuccorini[2], Sara Pasquina Pascale[2], Martina Chiarucci[1], Monica Poiani[1], Maria Gozzer[3], Saveria Capria[4], Giuseppe Mele[5], Angela Melpignano[5], Paolo Perseghin[6], Pietro Pioltelli[6], Massimo Martino[7], Tiziana Moscato[7], Pellegrino Musto[8], Giuseppe Pietrantuono[8], Paolo Corradini[9], Lucia Farina[9], Luca Nassi[10], Gloria Margiotta Casaluci[10], Annalia Di Marco[11], Andrea Spadaro[11], Svitlana Gumenyuk[12], Francesco Marchesi[12], Francesco Lanza[13], Paola Brambilla[13], Massimo Pini[14], Francesco Zallio[14], Sarah Marktel[15], Salvatore Gattillo[15], Simona Sica[16], Giuseppe Ausoni[16], Francesco Merli[17], Katia Codeluppi[17], Giorgina Specchia[18], Domenico Pastore[18], Michele Pizzuti[2], Elvira Di Nardo[19]

Il mondo sta diventando una piatta società di vegetariani, astemi e puritani. Io credo nella carne rossa, nel vino e nelle donne."