



Plerixafor in Poor Mobilizers with Non-Hodgkin's Lymphoma: Multi-Center Time-Motion Analysis

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Autologous stem cell transplantation (ASCT) in conjunction with high-dose chemotherapy (HDCT) standard treatment approach for non-Hodgkin's lymphoma (NHL) not responding to initial therapy

Successful ASCT requires multiple intervention approach

- | Mobilization of peripheral blood stem cells (PBSC)
- | PBSC collection (apheresis)
- | Cell processing and cryopreservation
- | Conditioning chemotherapy
- | Reinfusion

Insufficient PBSC mobilization directly associated with ASCT failure

- Granulocyte colony Stimulating Factor (G-CSF), with or without chemotherapy, now standard approach for PBSC mobilization



Apheresis initiated when peak CD34+ levels attained, typically:

- Day 4-5 of mobilization with G-CSF only or
- Day 8-12 with G-CSF/chemotherapy mobilization

To proceed to transplantation, generally accepted minimum CD34+ cell yield $\geq 2 \times 10^6$ cells/kg (5) but most organizations target yield 4-5 $\times 10^6$ CD34+ cell/kg

However, even when using G-CSF, 10%-25% of patients fail to obtain sufficient CD34+ cell yields to proceed to ASCT

- Poor mobilizers = poorer prognosis; typically require additional health care resources

To increase PBSC mobilization, plerixafor, a CXCR4 antagonist, in combination with G-CSF introduced into clinical use

- Shown to significantly increase number of peripheral CD34+ cells as compared to G-CSF alone & reducing rate of mobilization failure



Poor Mobilization Associated with Significant Clinical & Cost Impact

Mobilization therapies & apheresis contribute substantially to ASCT overall procedure costs

Transfusion with suboptimal CD34+ cell doses, typical with poor mobilizers, associated with:

- | Longer hospitalizations
- | Increased number PTL & RBC transfusions
- | Longer duration of anti-infective therapy

Studies support current recommendation use of plerixafor in poor mobilizers but do not address specific impact of plerixafor on poor mobilizers in terms of costs and time-effort spent on apheresis



Multi-country, multi-center evaluation of resource utilization (resources, costs, time) associated with PBSC mobilization in management of NHL patients undergoing ASCT in era prior to and following approval of plerixafor



Non-interventional study, consisting of a retrospective and prospective components, in which patients were evenly divided between two eras:

- “Pre-P” era through June 1, 2009
- “P” era from July 1, 2010 onwards; respectively

Conducted at 10 European centers

- France, Italy, Germany



Patients ≥ 18 years

Diagnosis of NHL and candidate for ASCT

Failed to achieve target CD34+ count > 20 cells/ μ L before or on first day of apheresis

- Focus on poor mobilizers, i.e. those with low CD34+ count, for whom plerixafor shown to increase CD34+ collection if used with conventional mobilization regimen

Patients with history of previous ASCT and/or diagnosis other than NHL excluded



Retrospective Component (Pre-P era)

- Patient eligible for enrollment: 6/1/2007-6/1/2009

Prospective Component (P era)

- Patient eligible for enrollment 7/1/2010-7/1/2014

Each P era patient matched on 1:1 basis to Pre-P patient, based on CD34+ target levels

- If no CD34+ target level match found, plerixafor patient excluded from evaluation

Cost of apheresis included:

- personnel labor time, equipment, stem cell collection, cell processing, cryopreservation thawing.

Cost estimates derived from:

- adjusted hospital costs, review of hospital data, physician interviews



Primary endpoint: time and resources for PBSC mobilization, using two main variables

- Mean time to perform apheresis & mean cost per patient
- Findings from prospective costing analysis applied to retrospective data to compare time & effort for matched patients
- Patients matched based on number of chemotherapy courses received

Secondary endpoints included

- # visits for mobilization
- # days receiving mobilizing agents
- # & duration apheresis sessions
- time from apheresis to transplant
- transplant outcome
- attainment of CD34+ cell target & days until target met
- Adverse Events during mobilization

Exploratory and descriptive analysis

Time to perform apheresis per patient at a given hospital
Cost of apheresis per patient in terms of costing per site



Categorical variables:

- comparisons between Pre-P era & P era patients made using Chi Square or Fisher's Exact, as appropriate

Linear variables:

- Student's t-test when data normally distributed;
Wilcoxon rank sum used when distributions not normal

Differences between groups considered significant when $p < 0.05$



Pre-P era: 118 NHL pts identified as poor mobilizers & underwent at least one apheresis session

P era: 134 patients with CD34+ cell count < 20 cells/ μ l and who underwent at least one apheresis session identified

Demographic characteristics of two patient groups comparable

- Diffuse large B-cell lymphoma most common subtype (38-40%), followed by follicular lymphoma (22-24% and mantle cell lymphoma (13-14%)

	Pre-plerixafor era (n=118)	Plerixafor era (n=134)	P<
Mean Age in years (SD)	54 (12)	56 (11)	0.26 (a)
Gender N (%)			0.83 (c)
Male	46 (39%)	54 (40%)	
Female	72 (61%)	80 (60%)	
Nation			0.70 (c)
France – N (%)	59 (50%)	63 (47%)	
Germany – N (%)	39 (33%)	51 (38%)	
Italy – N (%)	20 (17%)	20 (15%)	
NHL subtype			0.93 (c)
Follicular – N (%)	26 (22%)	32 (24%)	
Diffuse – N (%)	45 (38%)	54 (40%)	
Mantle – N (%)	17 (14%)	18 (13%)	
Other – N (%)	30 (25%)	30 (22%)	
Disease Stage at Diagnosis			0.51 (c)
I – n (%)	6 (5%)	6 (4%)	
II – n (%)	9 (8%)	19 (14%)	
III – n (%)	16 (14%)	18 (13%)	
IV – n (%)	81 (69%)	87 (65%)	
Unknown – n (%)	6 (5%)	4 (3%)	
Mean Chemotherapy courses (SD)	1.2 (0.6)	1.2 (0.6)	0.14 (b)
Mean Chemotherapy Days (SD)	4.2 (5.7)	4.6 (5.6)	0.04 (b)



Initial CD34+ cell count significantly higher in patients from Pre-P era compared with P era ($p < 0.001$)

However, CD34+ cell yield significantly higher after first apheresis session for P era patients ($p < 0.001$)

Total CD34+ cell yield similar between groups ($p=0.73$)

More patients reached 2×10^6 cells/kg in P era as compared to Pre-P era (91% vs 83%; $p=0.06$)

	Pre-plerixafor era (n=118)	Plerixafor era (n=134)	P<
Mean Initial peripheral CD34+ count (cells/ μ l) (SD)	12.6 (5.5)	8.7 (4.9)	0.001 (b)
Mean Number of apheresis sessions (SD)	2.2 (1.0)	1.6 (0.7)	0.001 (b)
Mean Total Apheresis Blood Volume (SD)	25.5 (12.5)	18.6 (10.3)	0.001 (b)
Mean Total minutes of apheresis (SD)	461 (216)	350 (150)	0.001 (b)
Mean Estimated apheresis cost in €(SD)	6212 (2674)	4457 (1860)	0.001 (b)
Mean CD34+ cells, total ($\times 10^6$ cells/kg) (SD)	4.4 (2.9)	4.4 (2.6)	0.73 (b)
Mean CD34+ cells, first apheresis ($\times 10^6$ cells/kg) (SD)	2.3 (2.3)	3.2 (2.2)	0.001 (b)



Time-motion analysis for prospectively enrolled patients yielded similar results for time spent on apheresis from the retrospective data.

- | An additional 30 minutes was spent on apheresis equipment set-up and cleaning

Despite lower CD34+ cell count in P era, apheresis outcome measures favored P era patients:

- | Underwent fewer apheresis sessions ($p < 0.001$)
- | Spent less time on apheresis ($p < 0.001$)
- | Which led to a reduction in costs associated with apheresis from €6,212 to €4457 ($p < 0.001$)



Forty patients in Pre-P era and 88 patients P era identified with initial CD34+ count ≤ 10 cells/ μ l

Among these patients, apheresis outcomes favored P era, including total CD34+ yield ($p < 0.02$)

Matched pair analysis carried out in which each P era patient matched with a patient from Pre-P era from same center and with same CD34+ cell levels

- Analysis results in agreement with analysis on full population

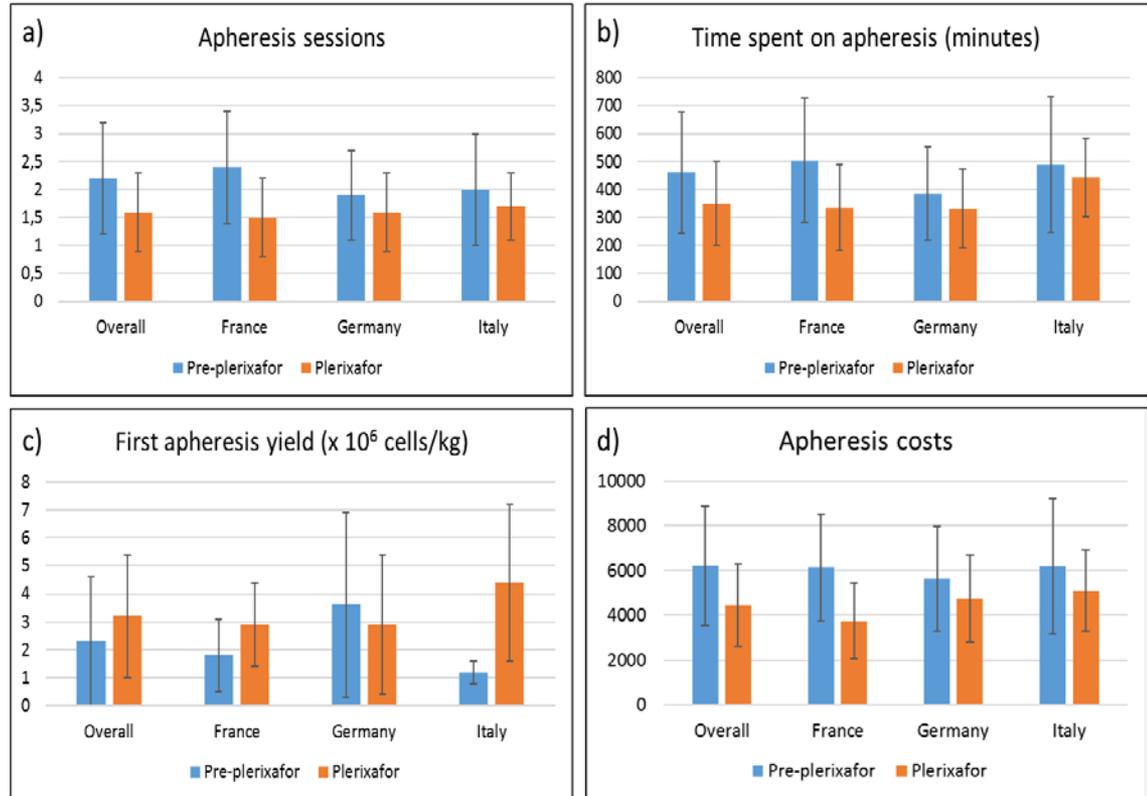
	Pre-plerixafor era (n=40)	Plerixafor era (n=88)	P<
Mean Initial peripheral CD34+ (cells/ μ l) (SD)	6.4 (3.3)	5.7(2.7)	0.10 (b)
Mean Number of apheresis sessions (SD)	2.2(0.9)	1.6(0.6)	0.001 (b)
Mean Total apheresis blood volume (l) (SD)	27.2(13.9)	19.6(10.7)	0.001 (b)
Mean Total minutes of apheresis (SD)	456(207)	361(151)	0.001 (b)
Mean Estimated apheresis cost in €(SD)	6174(2455)	4622(1845)	0.001 (b)
Mean CD34+ cells, total ($\times 10^6$ cells/kg) (SD)	3.2(2.0)	4.2(2.2)	0.001 (b)
Mean CD34+ cells, first apheresis ($\times 10^6$ cells/kg) (SD)	1.5(1.4)	2.7(1.4)	0.001 (b)



At a country level, some differences were observed

French data mimics overall results, while reductions in time and effort were more modest for German sites

At single Italian site, introduction of plerixafor reduced number of apheresis sessions and time spent on apheresis and tCD34+ cell yield significantly higher in the P era



Mean numbers shown for Pre-P and P era (SD); a) Mean number of apheresis sessions b) Mean number of minutes spent on apheresis c) mean number of first apheresis yield. d) mean apheresis costs



Only analyzed cost and effort associated with apheresis

- Costs associated with hospitalization, mobilization or remobilization, transplantation, platelet and RBC infusions and other post-transplantation care were not taken into account

Only impact of plerixafor on apheresis analyzed, which was thought to be more comparable between institutions

- Some country and/or institution specific differences persisted: not all sites use plerixafor preemptively in all patients with CD34+ levels < 20 cells/ μ l.
- Some patients may proceed to the first apheresis session and receive plerixafor only if the initial yield is insufficient and this might impact first apheresis yield
- Different sites also used different chemo-mobilization strategies



Current study conducted in 10 centers across Germany, France and Italy demonstrated positive impact of plerixafor on clinical outcomes

- With plerixafor, highly statistically significant reductions ($p < 0.001$) across apheresis activities achieved, including mean total # apheresis sessions
- Total apheresis CD34+ cells yield not significantly different between groups. However, after first apheresis, statistically more CD+ 34 cells collected in P era group compared with Pre-P era group ($p < 0.001$)
 - | Patients in P era had significantly (30%) lower cell count before apheresis, indicating comparable cell yield a success
- Highly statistically significant reductions ($p < 0.001$) in calculated apheresis costs for plerixafor groups in all countries, with mean cost reductions between €866 and €2385
- Costing analyses at different study sites resulted in average cost per apheresis session €2,515 for France, €2,928 for Germany, €3,089 for Italy
- Average apheresis cost across the three nations was €2,844 corresponding to \$3,100, similar to the cost per apheresis session of \$3,200



ASCT requires multiple intervention approach

- Success advanced through introduction of plerixafor, which is indicated in combination with G-CSF to enhance PBSC mobilization

Current study demonstrated positive impact of plerixafor on clinical outcomes

- Results in both operational efficiencies & cost savings to hospital for patients
- Reductions allow for improved hospital efficiency & cost savings for patients with NHL undergoing autologous PBSC mobilization for P era vs pre-P era

Importantly, these positive data trends and statistically significant findings in reductions in apheresis & cost consistent across each center for entire study

Further research demonstrating application of these resource utilization efficiencies and positive cost-savings as well as improved access for ASCT in routine clinical care warranted to optimize treatment for NHL patients