QUANTIFICATION OF THE TIME AND EFFORT ASSOCIATED WITH AUTOLOGOUS PERIPHERAL BLOOD STEM CELL MOBILIZATION : A EUROPEAN PERSPECTIVE

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INTRODUCTION:

Autologous stem cell transplantation (ASCT) in conjunction with high-dose chemotherapy is the standard treatment approach for the management of patients with non-Hodgkin's lymphoma (NHL). Autologous stem cell transplantation requires a multiple intervention approach involving mobilization, stem cell collection (apheresis), cell processing and cryopreservation, conditioning chemotherapy and reinfusion. ASCT success has been advanced through the introduction of plerixafor, which is indicated in combination with G-CSF to enhance mobilization of hematopoietic stem cells to the peripheral blood (PBSC) for collection and subsequent autologous transplantation in patients whose cells mobilize poorly. However, due to cost and healthcare resource considerations, many institutions across Europe have developed their own treatment strategies. Health economic and clinical outcomes data validating these strategies are limited. To assess the impact of mobilization on the management of NHL patients undergoing ASCT, a multi-country, multi-center retrospective, non-interventional study was conducted across three European countries to assess resource utilization associated with PBSC mobilization and apheresis in NHL patients in the era prior to and following approval of plerixafor (to the "Pre-P" era through June 1, 2009, and "P" era from July 1, 2010 onwards; "P", respectively).

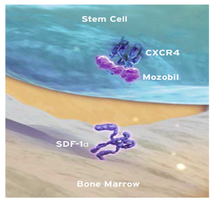
BACKGROUND:

- In Europe, plerixafor (P) is approved in combination with granulocyte colony stimulating factor (G-CSF) to enhance mobilization of hematopoietic stem cells to the peripheral blood for collection and subsequent autologous transplantation in patients with lymphoma and multiple myeloma (MM) whose cells mobilize poorly.

- Plerixafor (Mozobil®) in combination with G-CSF has been shown to increase mobilization of peripheral blood stem cells (PBSC) as compared to G-CSF alone in patients undergoing autologous stem cell transplantation (ASCT).

- The mechanism of action of plerixafor includes the blockage of the CXCR4-SDF-1α interaction, releasing stem cells from the bone marrow into the circulating blood (Figure 1).

Figure 1. Mechanism of Action of Plerixafor



- Failure to proceed to ASCT occurs due to poor mobilization in patients with non-Hodgkin's lymphoma (NHL) and multiple myeloma (MM) treated with G-CSF or G-CSF in combination with chemotherapy. Adding plerixafor to the treatment regimen to reduce risk of mobilization failure may also reduce the number of apheresis sessions needed to support transplantation. Therefore, the use of plerixafor may have positive impact on resource utilization by hospitals and cost-effectiveness of care.

OBJECTIVE:

The objectives of this retrospective, non-interventional study was to analyze the impact of plerixafor on the efficiency of the hematological department in hospitals in three European countries-Germany, France and Italy-conducting PBSC mobilization and collection, primarily in ASCT patients.

METHODS:

The study population included patients aged ≥ 18 years, with a primary diagnosis of Non-Hodgkin's Lymphoma (NHL) across ten centers in Germany, France and Italy undergoing peripheral blood stem cell (PBSC) mobilization. Subjects enrolled had to have a peripheral CD-34+count x 10^6/kg or ≤ 20/µL prior to first apheresis. Data from these centers are presented here. Figure 2 shows the study schema.

Hospital records from patients undergoing ASCT were collected for the period between 2005 and 2014. The records were divided into two groups: Group 1 included patients treated before the introduction of plerixafor for clinical use in Germany, France and Italy, i.e. prior to 2009, while group 2 included patients treated after the introduction of plerixafor.

Cost of apheresis included personnel labor time, equipment, stem cell collection, cell processing and cryopreservation and thawing. Cost estimates are derived from adjusted hospital tariffs, review of hospital data and physician interviews.

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Part I: Retrospective medical record

- Identification of NHL patients. For the pre-plerixafor (Pre-P) era patients, the peripheral CD-34+ count recorded immediately prior to the first apheresis; for plerixafor (P) era patients, it was that recorded immediately prior to plerixafor administration.

Part II: Prospective time and motion evaluation of apheresis in NHL patients performed at each center

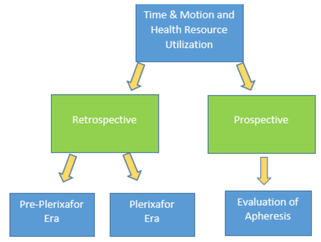
- 5 events recorded per center
- Apheresis events were measured in consecutive patients scheduled to be candidates for PBSC mobilization.
- The study end points are the difference in mean time/effort to perform apheresis (including apheresis related AEs, if any) and total costs associated with apheresis to the hospital between patients in the Pre-P versus P eras.

OUTCOME MEASURES:

Study outcome measures include the following:

- number of visits for administration of mobilizing agents
- duration (days) of administration of mobilizing agents
- agents used as mobilizing agents
- adverse events detected during mobilization
- number of apheresis sessions
- time (duration) of apheresis sessions
- attainment of CD34+ target (yes, no)
- days until CD 34+ target level was met

Figure 2. Study Schema



Ethics approval was obtained for all centers involved. Patients were analyzed in anonymized fashion and no informed consent was required for this study.

STATISTICAL ANALYSIS:

Patient data was recorded using an electronic case report form and aggregated for clinical comparisons. The analysis included all subjects with peripheral CD-34+count x 10^6/kg or ≤ 20/µL. For pre-plerixafor (Pre-P) era patients, the peripheral CD-34+ count x 10^6/kg was that recorded immediately prior to the first apheresis (≤ 20 mcg/ml), while for plerixafor (P) era patients, it was that recorded immediately prior to plerixafor administration and after administration.

Statistical analysis was performed using SAS version 9.3 (Cary, NC). For categorical variables, comparisons between pre-plerixafor era and plerixafor era patients were made using Chi Square or Fisher's Exact, as appropriate. For linear variables, Student's t-test was used when data was normally distributed, and Wilcoxon rank sum was used when distributions were not normal. Differences between groups were considered significant when $p < 0.05$.

RESULTS:

- A total of 235 patients were included in the analysis: 115 pre-plerixafor (Pre-P) era and 120 in the plerixafor (P) era.

- Baseline demographics and other clinical characteristics were statistically similar in both treatment arms. In addition, patients in the two groups were equally and comparably distributed among the NHL subtypes (**Table 1**). For both groups, the majority of the plerixafor era patients were Stage 4 NHL at the time of first diagnosis.

- The analysis of the number of apheresis sessions demonstrated a highly statistically significant reduction (p<0.001) for the P era group, including number of sessions, total blood volume collected and total apheresis time required to reach the targeted PBSC compared with Pre-P era group. Total cost differences between cohorts was calculated based on actual clinical and resource utilization differences. The number of CD-34+cells collected after first day in the P era group was also highly statistically significant compared with pre P group (p<0.001).

- Mean apheresis procedural costs were **€** 6836 in the pre-plerixafor era (Pre-P) and **€** 4779 in the plerixafor era (P), representing a mean reduction of **€** 2057 in apheresis costs. The reduction in total apheresis costs was highly statistically significant reduction (p<0.001) in favor of the plerixafor (P) era (**Table 2**).

Table 1. Patient characteristics, demographics and relevant cancer history at baseline by

	Pre-Plex Era (n=115)	Plex Era (n=120)	P<
Age in Years			
Mean (SD)	55 (11)	56 (11)	
Median (Q1-Q3)	58 (47-63)	59 (51-64)	
Range (min-max)	(22-73)	(20-78)	0.27 (a)
Height in cm			
Mean (SD)	171 (10)	171 (9)	
Median (Q1-Q3)	127 (165-178)	127 (165-178)	
Range (min-max)	(150-204)	(143-193)	0.90 (a)
Weight in kg			
Mean (SD)	73 (15)	73 (15)	
Median (Q1-Q3)	72 (60-85)	72 (30-82)	
Range (min-max)	(43-111)	(47-118)	0.74 (a)
Months since Diagnosis			
Mean (SD)	31 (45)	28 (48)	
Median (Q1-Q3)	10 (4-38)	11 (5-30)	
Range (min-max)	(0-216)	(2-270)	0.98 (b)
Gender			
Female – N (%)	44 (38%)	46 (38%)	
Male – N (%)	71 (62%)	74 (62%)	0.99 (c)
Nation			
France – N (%)	59 (51%)	63 (53%)	
Germany – N (%)	39 (34%)	61 (43%)	
Italy – N (%)	17 (15%)	6 (5%)	0.03 (c)
NHL Subtype			
Folic – N (%)	25 (22%)	26 (22%)	
Diffuse – N (%)	44(38%)	48((40%)	
Mantle – N (%)	17 (15%)	17 (14%)	
Other – N (%)	29 (25%)	29 (24%)	0.99 (c)
Disease Stage at Diagnosis			
1 – N (%)	6 (5%)	6 (4%)	
2 – N (%)	9 (8%)	9 (13%)	
3 – N (%)	16 (14%)	16 (13%)	
4 – N (%)	78 (68%)	78 (68%)	
Unknown – N (%)	6 (5%)	6 (3%)	0.74 (c)
(a) = Student's t-test (b) = Wilcoxon Rank Sum (c) = Chi Square			

Table 2. Apheresis activities by era

	Pre-Plex Era (n=115)	Plex Era (n=120)	P<
Initial Peripheral CD34			
Mean (SD)	12.6 (5.5)	8.3 (4.8)	
Median (Q1-Q3)	14.0 (9.0-17.5)	7.5 (4.2-12.0)	
Range (min-max)	(0.0-20.0)	(1.0-20.0)	0.001 (b)
Number of Apheresis Sessions			
Mean (SD)	2.2 (1.0)	1.6 (0.7)	
Median (Q1-Q3)	2.0 (2.0-3.0)	1.0 (1.0-2.0)	
Range (min-max)	(1.0-5.0)	(1.0-4.0)	0.001 (b)
Estimated Apheresis Cost €			
Mean (SD)	6336 (2967)	4779 (2032)	
Median (Q1-Q3)	6166 (6166-9249)	3083 (3083-6166)	
Range (min-max)	(3083-15415)	(3083-12332)	0.001 (b)
Total Apheresis Blood Volume			
Mean (SD)	25.6 (12.6)	18.3 (10.5)	
Median (Q1-Q3)	23.9 (15.0-32.3)	15.4 (11.4-23.3)	
Range (min-max)	(3.4-68.9)	(4.1-67.0)	0.001 (b
Total Minutes of Apheresis			
Mean (SD)	461 (219)	336 (144)	
Median (Q1-Q3)	420 (290-565)	285 (224-453)	
Range (min-max)	(135-1273)	(125-880)	0.001 (b)
CD34 Cells, Total			
Mean (SD)	4.5 (2.9)	4.2 (2.4)	
Median (Q1-Q3)	4.1 (2.4-5.3)	3.6 (2.8-4.9)	
Range (min-max)	(0.4-16.7)	(0.8-13.8)	0.55 (b)
CD34 Cells, First Apheresis			
Mean (SD)	2.3 (2.3)	3.0 (2.1)	
Median (Q1-Q3)	1.5 (1.0-2.4)	2.5 (1.6-3.7)	
Range (min-max)	(0.4-12.2)	(0.5-13.8)	0.001 (b)
**x 10^6/kg (b) = Wilcoxon Rank Sum			

DISCUSSION: The data from this retrospective health resources and cost analysis conducted in 9 centers across Germany, France and Italy demonstrates the positive impact of plerixafor on clinical outcomes, which results in both operational efficiencies and cost savings to the hospital for patients undergoing ASCT who are at risk of mobilization failure. When plerixafor was added to the regimen, there were highly statistically significant reductions (p<0.001) across apheresis activities, including the mean total number of apheresis sessions. Highly statistically significant reductions (p<0.001) were also shown in the calculated apheresis costs for the plerixafor group: **€** 4779 for P vs **€** 6836. The total apheresis yield of CD34+ cells was not significantly different between the two groups. However, after the first apheresis, statistically more CD+ 34 cells were collected in the P era group compared with Pre-P era group. Importantly, these positive data trends and statistically significant findings in reductions in apheresis and cost were consistent across each of the centers for the entire study.

CONCLUSION: Autologous stem cell transplantation (ASCT) in conjunction with high-dose chemotherapy is the standard treatment approach for the management of patients with non-Hodgkin's lymphoma (NHL). ASCT requires a multiple intervention approach involving mobilization, stem cell collection (apheresis), cell processing and cryopreservation, and conditioning chemotherapy and reinfusion. ASCT success has been advanced through the introduction of plerixafor, which is indicated in combination with G-CSF to enhance mobilization of hematopoietic stem cells to the peripheral blood (PBSC) for collection and subsequent autologous transplantation in these whose cells mobilize poorly. This study demonstrates that use of plerixafor is associated with statistically significant reductions in resource utilization, including number of apheresis sessions. These reductions allow for improved hospital efficiency and cost savings for patients with NHL undergoing autologous PBSC mobilization vs patients in the pre-P era. Further research demonstrating application of these resource utilization efficiencies and positive cost-savings as well as improved access for ASCT in routine clinical care is warranted to optimize treatment for NHL patients.

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