Quantification of The Time and Effort Associated with Autologous Peripheral Blood Stem Cell Mobilisation: A European Perspective

Kai Hübel[1], Nabih Azar[2], John Reitan[3], Richard Kadota[4], Sarah Naoshy[4], Zhimin Xiao[5], Mohamad Mohty[6]

[1]University Hospital of Cologne, Cologne, Germany, [2]Pitié-Sâlpétrière Hospital, Paris, France
[3]RJM Group, USA, [4]Formerly Sanofi, Cambridge, USA, [5]Sanofi, Cambridge, USA,
[6]Saint-Antoine Hospital, Paris, France

Abstract

Introduction: The European Medicines Agency has approved Plerixafor in combination with G-CSF to enhance mobilisation of hematopoietic stem cells to the peripheral blood (PBSC) for collection and subsequent autologous transplantation in patients with lymphoma and multiple myeloma whose cells mobilise poorly. The aim of this non-interventional study was to assess resource utilization, including time, effort and costs to the hospital, associated with PBSC mobilisation and apheresis in the pre-plerixafor (Pre-P) and plerixafor (P) eras.

Patients and Methods: The study population includes patients aged ≥18 years, with a primary diagnosis of Non-Hodgkin's Lymphoma (NHL), who underwent PBSC mobilisation at European centres. Part I of the study, currently ongoing, is a retrospective medical record review of 200 NHL patients from 7 centers across France and Germany. Selected patients are evenly divided between two eras: 1) prior to approval of plerixafor (until 1 June, 2009), pre-P era, and 2) after approval of plerixafor (1 July, 2010 and onwards), P era. Outcome measures include number of visits for administration of mobilising agents; duration (days) of administration of mobilising agents; agents used as mobilising agents; adverse events (AEs) detected during mobilisation; number of apheresis sessions; hours of apheresis sessions; attainment of CD34+ target (yes, no) and days until CD 34+ target level was met.

Part II of the analysis is an ongoing prospective time and motion evaluation of apheresis performed at each center (20 events recorded per center). Apheresis events are measured in consecutive patients scheduled for PBSC mobilisation. Patient consent was obtained. Time-motion assessments will be obtained retrospectively (Part I) and prospectively (Part II) and will include the total time to prepare the patient, perform apheresis and manage AEs. Costs will be evaluated and quantified through micro-costing group interviews with local hospital administration.

The primary study end point is difference in mean time&effort to perform apheresis (including apheresis related AEs, if any) and total costs associated with mobilisation to the hospital between patients in the "Pre-P" versus "P eras."

Results: At time of abstract submission, data collection is ongoing at all centers. Interim results will be presented. It is hypothesized that the key findings of this study will demonstrate the favorable impact of novel interventions on the number of apheresis procedures required to reach a target PBSC as well as failure rate of mobilisation, thus translating into reduced total transplant costs without increased toxicity.

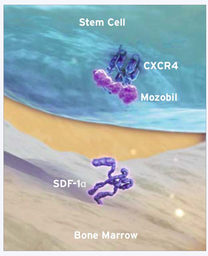
Discussion: The financial implications for transplant centers could be significant and may lead to further studies aiming to optimize staff time and resource utilization related to apheresis in real-world practice.

Funding provided by Sanofi.

Background

- In Europe, plerixafor (P) is approved in combination with Granulocyte colony stimulating factor (G-CSF) to enhance mobilisation of hematopoietic stem cells to the peripheral blood (PB) for collection and subsequent autologous transplantation in patients with lymphoma and Multiple Myeloma (MM) whose cells mobilise poorly[1].
- 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[2] (Figure 1).
- As demonstrated by two Phase III trials for NHL (study 3101) and MM (study 3102) in patients undergoing stem cell mobilization, the addition of plerixafor to G-CSF resulted in significantly higher proportion of NHL and MM patients collecting a target number of stem cells (≥ $5x10^6$ and ≥ $6x10^6$ CD34+ cells/kg, respectively), and in fewer apheresis days, compared to G-CSF alone[3,4]. Plerixafor + G-CSF has also been shown to be effective in patients who failed prior mobilization regimens[5]. Plerixafor may reduce the number of apheresis procedures required without increasing the toxicity and/or the failure rate, and this may reduce total transplant costs.

Figure 1
Mechanism of Action of Plerixafor



Objective

There are increasing budget concerns and intense competition for hospital resources required to evaluate and manage patients preparing for stem cell mobilization and transplantation, especially when newer therapies, i.e. plerixafor, are available and may be more suitable for some patients. In light of this, we aimed to assess mean time and effort to perform apheresis (including apheresis related AEs, if any) and total costs associated with mobilization to hospitals between patients in the "Pre-P" versus "P eras."

Methods

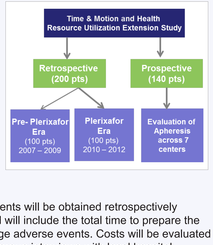
The study population includes patients aged ≥ 18 years, with a primary diagnosis of Non-Hodgkin's Lymphoma across 7 centers in France and Germany undergoing peripheral blood stem cell mobilization. The study will consist of two parts (Figure 2):

- **Part I:**
  - Ongoing retrospective medical record review study of 200 NHL patients from the sites. Selected patients will be evenly divided between two eras:
    1. **Pre-Plerixafor era (until 1 June 1 2009):** prior to approval of plerixafor
    2. **Plerixafor era (1 July 2010 and onwards):** after approval of plerixafor
- **Part II:**
  - Ongoing prospective study of time and motion evaluation of apheresis performed at each center in the pre-plerixafor and plerixafor eras (20 events measured per center).

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
- hours of apheresis sessions
- attainment of CD34+ target (yes, no)
- days until CD 34+ target level was met

Figure 2
Study Schema



In addition, time and motion assessments will be obtained retrospectively (Part I) and prospectively (Part II) and will include the total time to prepare the patient, perform apheresis and manage adverse events. Costs will be evaluated and quantified through micro-costing group interviews with local hospital administration.

The primary study end points are difference in the mean time to perform apheresis (including apheresis related adverse events, if any) and costs to the hospital in terms of micro-costing per patient.

Ethics approval was obtained in France and Germany for all centers involved.

Statistical Analysis:
Patient data was recorded using an electronic case report form and aggregated for clinical comparisons. An interim analysis is presented based on the retrospective patient population (Part I) collected to date. Subjects (N=96) had peripheral CD-34+count lower than 20/μL. For pre-plerixafor era patients, the peripheral CD-34+ count was that recorded immediately prior to the first apheresis, while for plerixafor era patients, it was that recorded immediately prior to plerixafor 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

Patient Characteristics

- At time of this interim data analysis, there were 96 total patients available, with 44 in the pre-plerixafor era and 52 in the plerixafor era. The majority of patients were from French centers (73/96 or 79.2%).
- Baseline characteristics were similar in both treatment arms (Table 1).
- The majority of patients were stage IV NHL at time of first diagnosis in both groups.

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

Characteristics	Pre-Plerixafor Era (*n = 44*)	Plerixafor Era (*n = 52*)	P value
Gender, *n* (%)			
Male	28 (64%)	29 (56%)	0.43
Mean age, y (SD)	54 (12)	55 (12)	0.49
Mean weight, kg (SD)	72 (13)	71 (12)	0.47
Mean Height, cm (SD)	172 (9)	170 (8)	0.19
Non-Hodgkin's Lymphoma subtype, *n* (%)			
Follicular Lymphoma	10 (23%)	12 (23%)	0.31
Diffuse Large B Cell Lymphoma	22 (50%)	17 (33%)	
Mantle Cell Lymphoma	3 (7%)	6 (12%)	
Other*	9 (20%)	17 (33%)	
Country *n* (%)			
France	38 (86%)	35 (67%)	0.03
Germany	6 (14%)	17 (33%)	
Disease stage at time of first diagnosis *n* (%)			
Stage I	3 (7%)	2 (4%)	0.44
Stage II	3 (7%)	6 (12%)	
Stage III	5 (11%)	10 (19%)	
Stage IV	28 (64%)	32 (62%)	
Missing	5 (11%)	2 (4%)	
Time since diagnosis (months)			
Mean (SD)	22 (30)	31 (52)	0.41

*"Other" Lymphoma sub-types include: Angioimmunoblastic T Cell Lymphoma, Extranodal NK TCell Lymphoma, NK Cell Leukaemia, Burkitts Lymphoma, Lymphoma Large Cell, Low Grade Lymphoma(Indolent), Lymphoma(Indolent) 2, T Cell Lymphoma 2, Anaplastic T Lymphoma, Large B Cell NHL, T Cell NHL 2, Peripheral T Cell Lymphoma, B-NHL

Efficacy

- CD34+ cell yields
  - There was approximately 74% higher yield of CD34+ cells at the first apheresis session with the use of plerixafor when compared to the pre-plerixafor patients.
  - The total apheresis yield of CD34+ cells was not significantly different between the two groups.

Apheresis sessions

- There was a statistically significant decrease in the mean number of apheresis sessions and total minutes of apheresis associated with the use of plerixafor. Additionally, there was a statistically significant difference in the total apheresis blood volume exchanged between groups.

Table 2
CD34+ Yield and Volume of Aphereses between the Pre-Plerixafor and Plerixafor Eras

Parameter	Pre-Plerixafor Era (*n = 44*)	Plerixafor Era (*n = 52*)	P value
Peripheral CD34+ cell count ($1X10^6$ CD34+/L)			
Mean (SD)	12.5 (4.8)	7.9 (4.3)	p<0.001
Median (range)	12.5(2.0 - 20.0)	7.0 (1.0 - 18.0)	
Number of Apheresis Sessions (n)			
Mean (SD)	2.4 (1.0)	1.4 (0.5)	p<0.001
Median (range)	2.0 (1.0 - 5.0)	1.0 (1.0 - 3.0)	
Total apheresis blood volume (L)			
Mean (SD)	26.2 (13.0)	15.6 (6.0)	p<0.001
Median (range)	24.4 (3.4 - 68.9)	13.0 (4.1 - 30.3)	
Total minutes of apheresis			
Mean (SD)	489 (247)	295 (118)	p<0.001
Median (range)	423 (135 - 1,225)	265 (145 - 665)	
Total Apheresis Yield CD34+ Cells ($1x10^6$/kg)			
Mean (SD)	4.6 (2.7)	4.1 (2.4)	0.21
Median (range)	4.4 (0.6 - 16.7)	3.7 (1.4 - 13.8)	
First Apheresis Yield CD34+ Cells ($1x10^6$/kg)			
Mean (SD)	1.9 (1.7)	3.3 (2.3)	p<0.001
Median (range)	1.3 (0.5 - 10.8)	2.6 (0.8 - 13.8)	

Discussion

- The retrospective component (Part 1) of this study, assessing patients mobilized with or without plerixafor, has shown that when plerixafor was added to the regimen, there were statistically significant reductions in the mean number of apheresis sessions, minutes of apheresis and total blood volume exchanged.
- The total aphereses yield of CD34+ cells was not significantly different between the two groups, even though plerixafor era patients had significantly lower levels of PB CD34+ cells prior to administration of plerixafor.
- This is an interim analysis, and data collection is ongoing at all centers. Final results of the retrospective assessment of 200 patients will be reported following study completion. The results of costs and health resource utilization comparison are concurrently being collected.

Conclusion

The initial trends observed from this interim analysis suggest the favorable impact of plerixafor on the number of apheresis procedures, total blood volume exchanged and total apheresis time required to reach the targeted PBSC. These outcomes may result in cost differences to transplant centers when addressing stem-cell mobilization for patients with and without plerixafor.

Funding provided by Sanofi.

Writing assistance provided by Meghan Gallagher, Sanofi.

References

1. European Medical Agency: Summary of product characteristics for plerixafor http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/001030/WC500030686.pdf
2. Genzyme: Plerixafor injection Product Monograph
3. DiPersio JF, Micallef IN et al. Phase III prospective randomized double-blind placebo-controlled trial of plerixafor plus granulocyte colony-stimulating factor compared with placebo plus granulocyte colony-stimulating factor for autologous stem-cell mobilization and transplantation for patients with non-Hodgkin's lymphoma. *J Clin Oncol*. 2009;27(28):4767-73
4. DiPersio JF, Stadtmauer EA et al. Plerixafor and G-CSF versus placebo and G-CSF to mobilize hematopoietic stem cells for autologous stem cell transplantation in patients with multiple myeloma. *Blood*. 2009; 113(23):5720-6.
5. Calandra G, McCarty J et al. AMD3100 plus G-CSF can successfully mobilize CD34+ cells from non-Hodgkin's lymphoma, Hodgkin's disease and multiple myeloma patients previously failing mobilization with chemotherapy and/or cytokine treatment: compassionate use data. *Bone Marrow Transplant*. 2008; 41(4):331-8.