Evaluating the Role and Efficacy Of Plerixafor in Rescue Mobilization of Autologous Peripheral Blood Stem Cells

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Abstract: In autologous hematopoietic stem cell transplantation patients for whom granulocyte-colony stimulating factor fails to mobilize a sufficient number of peripheral blood stem cells, plerixafor proposes an option for successful rescue mobilization. This paper evaluates the efficacy of plerixafor to mobilize peripheral blood stem cells (PBSCs) in patients who failed previous mobilization with G-CSF alone, by retrospectively analysing the PBSC results from lymphoma and myeloma (MM) patients between 2006 and 2011. Patients were classified according to the CD34+ cells/kg yield collected by apheresis: < 2 x 10^6 CD34+ cells/kg was considered collection failure, whereas ≥ 5 x 10^6 CD34+ cells/kg was considered good mobilization. 797 patients underwent one or more apheresis. The first mobilization success rate was 82%; 140 patients proved to be poor mobilizers. Suboptimal first mobilization was significantly associated with age >50 years (p=0.005) and the absence of chemotherapy in prior PBSCs stimulation (p=0.04). 149 rescue protocols were used in the 140 poor mobilizers, and 71 patients received plerixafor. In univariate analysis the remobilization rate without plerixafor was 42% and increased to 65% when plerixafor was added. In multivariate analysis, plerixafor administration reduced the PBSC remobilization failure risk by a half (OR=0.47). The median value of CD34+ cells/kg in transplants increased from 1.43 (range, 0.0–14.03) without plerixafor to 3.85 (range, 0–18.25; p=1 x 10^-4) with plerixafor. There were more good mobilizers after plerixafor use (35% with plerixafor versus 15% without plerixafor; p=0.005). Plerixafor efficacy was similar for lymphoma (60% remobilization) and MM (80%; p=0.12). These data show that plerixafor was effective in poor mobilizers and that it synergized with G-CSF to improve the quantity of collected PBSCs. Plerixafor also increased transplant feasibility by 23%. While the clinical results of this study are promising, economic data were not taken into account and there is a need for real work concerning the cost-effectiveness of this treatment. We propose a subsequent study in which the economic efficacy of plerixafor’s use is evaluated based on the financial aspects of the treatments received by the cohort evaluated in this paper.

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Introduction

Autologous stem cell transplantation (ASCT) remains an important part of front-line therapy in multiple myeloma (MM) and is mandatory in lymphoma relapse procedures. Mobilized peripheral blood stem cells (PBSCs) are currently used as the sole source of stem cells in these indications. PBSC collection is performed after granulocyte-colony stimulating factor (G-CSF) stimulation alone (steady-state) or following a chemotherapy cycle during the neutrophil recovery phase (chemo-primed). The CD34+ cell count in the autologous graft is one of the strongest contributing factors to successful fast engraftment; nevertheless, 10–15% of patients with haematological malignancies fail to mobilize an adequate quantity of PBSCs, and poor mobilization may affect patient outcome after transplantation. One way to improve PBSC collection is to repeat the mobilization procedure with an increased dose of G-CSF, but this often fails. Use of plerixafor is another way to enhance PBSC collection. Plerixafor is a pure antagonist of chemokine receptor-4 (CXCR4) that blocks the interaction of the receptor and its ligand, stromal cell-derived factor 1 (SDF-1). After administration of plerixafor, hematopoietic stem cells migrate outside of the bone marrow niche and circulate into the peripheral blood, allowing an efficient and effective apheresis harvest; concomitant G-CSF administration can amplify this process and increase the yield of these circulating cells.

In clinical studies of MM and lymphoma patients, plerixafor combined with G-CSF was well tolerated and significantly increased the number of PBSCs in patients who previously failed to mobilize PBSCs. To determine the efficacy of plerixafor, we report here on 3 years of experience using plerixafor as rescue stimulation in a haematological population of patients who failed a previous mobilization procedure plus G-CSF to successfully remobilize PBSCs in lymphoma and MM patients.

Patients and Methods:

Patients

We retrospectively analysed the results of consecutive PBSC collections performed in lymphoma and MM patients from 2006 to 2011 at two university hospitals working with the Bourgogne Franche-Comté EFS (French Blood Establishment). Specifically speaking, patients received medical care and ASCT respectively in the Besançon and Dijon university hospital haematology departments. In accordance with local policies, all patients provided informed written consent for the collection and analysis of data in their medical files. When patients were included in a clinical trial, specific written informed consent was obtained. The study was designed and conducted in accordance with the declaration of Helsinki and was approved by the institutional ethics committees.

Mobilization Procedure

For the first collection of cells, PBSC mobilization was performed either using G-CSF alone at a daily dosage of 5-10 µg/kg (steady state protocol) or after a chemotherapy course of high dose cyclophosphamide in MM patients or after one of two different regimens in lymphoma patients, namely R-CHOP or R-ACVBP (chemo-primed protocol). When ≥ 2 x 10^6 CD34+ cells/kg were available after the first collection process, the collection was considered a success and ASCT or even 2 ASCTs in some MM patients, could be planned without further PBSC harvest. When < 2 x 10^6 CD34+ cells/kg were available, the collection was considered a failure. If the first mobilization failed, a new mobilization procedure was performed, most often using the chemo-primed protocol. The decision to add plerixafor was made by the local investigator after the first collection failure in patients considered at high risk of secondary PBSC mobilization failure.

In the steady-state protocol, the daily dose of plerixafor was 0.24 mg/kg administered 8-11 hours before the first apheresis session on the evening of the fourth day of G-CSF injection. Alternatively using the chemo-primed protocol, if the CD34+ cell count was < 15/mm^3 and the leucocyte count > 1 G/l, plerixafor was administered on the evening 8-11 hours before the first apheresis session. If < 2 x 10^6 CD34+ cells/kg were collected after the first collection procedure, an additional dose of plerixafor could be delivered on day 2 or 3 following the collection.

Collection Procedure

PBSC harvesting started when the peripheral circulating CD34+ cell count increased to >15/mm^3, which was generally on the 5th day of G-CSF administration in the steady-state protocol or when leucocytes increased to > 1 G/l in the chemo-primed protocol. The CD34+ cell count was then checked daily to determine this time point. Blood stem cells were collected with one of two blood cell separators: the COBE Spectra (Terumo BCT®, Lakewood, CO, USA) or the COM.TEC (Fresenius Kabi®, Bad Homburg, Germany). At least two total blood volumes were processed at each apheresis session. Anticoagulant citrate dextrose solution was used. The quality of the harvested product was evaluated by counting the total nucleated and CD34+ cells, which was expressed as the number of cells/kg body weight of the patient. An apheresis session could be repeated on the following day until at least 2 x 10^6 CD34+ cells/kg were acquired. Alternatively, sessions were halted if the CD34+ count in the peripheral blood was < 15/mm^3. The colony-forming unit-granulocyte macrophage (CFU-GM) content of the PBSCs was quantified systematically only when plerixafor mobilization was used.

Post-Transplantation Engraftment

The post-ASCT haematological engraftment was analysed to determine neutrophil recovery. Neutrophils
were counted from the day of ASCT until a neutrophil count ≥ 0.5 G/L was achieved. The duration of the hospital stay was also recorded and was measured from the day of the ASCT infusion until discharge.

Statistical analyses

The study was divided into two time periods: 2006-2008 (period 1, without plerixafor use) and 2009-2011 (period 2, plerixafor mostly used for remobilization). Patients were classified according to the CD34+ cells/kg yield that was collected by apheresis (before freezing). Patients with a total collected cell count < 2 x 10^6 CD34+ cells/kg were considered poor mobilizers. Conversely, patients with cumulative yields ≥ 5 x 10^6 CD34+ cells/kg were considered good mobilizers. Descriptive analyses were used to summarize the patient characteristics, risk factors, CD34+ cell collection parameters and time to neutrophil engraftment. We analysed the features of the first mobilization to identify mobilization failure risk factors. Next the results of rescue protocols to evaluate the efficacy of plerixafor were evaluated. Data are presented as median (range). We performed univariate and multivariate analyses, and the differences between categorical variables were calculated with the χ² test. Significant factors with p values ≤ 0.05 in univariate analyses were included in a multivariate model that was analysed using logistic regression. All analyses were performed using SAS® software (version 9.2, 2008, Cary, NC, USA).

Results

Patients

During the two periods studied, 797 patients underwent one or more apheresis procedure for PBSC collection. There were no statistically significant differences between the populations recruited in Besançon and Dijon. The detailed baseline and demographic characteristics are summarized in Table 1. Patients were older (p = 0.05) and diagnoses of MM were more frequent (p = 0.045) during period 2; consequently, the use of bortezomib and lenalidomide was more frequent in the second period. The significant decrease in anthracycline use was mainly due to modifications in therapeutic strategies for MM and in the progressive withdrawal of the referent protocol, the combination of vincristine, Adriamycin, and dexamethasone (VAD).11

First Mobilization Attempt

All 797 patients were included in this analysis. Of these, 140 patients presented mobilization failures. The following parameters were tested in univariate analysis: median age, sex, inclusion period, diagnosis, number of previous cycles of chemotherapy, drugs (anthracyclines, vincristine, lenalidomide, and bortezomib) and type of mobilization procedure (i.e. use of G-CSF alone or in combination with chemotherapy). Patient age (>50 years old), MM diagnosis and the use of a steady state protocol were shown to be major risk factors for mobilization failure. Multivariate analysis of these factors showed that only age and the use of a steady-state protocol remained significant factors that affected mobilization (Table 2).

Remobilization Procedures and Plerixafor Use

A total of 149 rescue protocols were managed in 117 of the 140 patients who were poor mobilizers; 32 patients were mobilized a third and/or a fourth time. Of these 140 patients, 71 received plerixafor as part of the rescue mobilization protocol (22 after a steady-state protocol and 49 after a chemo-primed protocol). The use of plerixafor in the first rescue protocol was similar between the two sites. In Dijon, 39 (38%) of the 103 patients with a first mobilization failure received plerixafor, while 20 (54%) of the 37 patients with a first mobilization failure in Besançon received plerixafor; this difference was not significant (p = 0.09). Univariate analyses were performed using the same criteria previously applied for the whole cohort and the use of plerixafor was added in the model. The results showed that it was easier to succeed in remobilization when a patient suffered from MM (p = 3.10^-4), when the mobilization took place between 2009 and 2011 (p = 4 x 10^-5), and when the patient’s cells were mobilized with plerixafor (p = 0.003), no matter the age or remobilization protocol, steady-state vs. chemo-primed (p = NS). These three significant factors were then tested in multivariate analysis. Only a diagnosis of MM (p = 0.003) and the administration of plerixafor (p = 0.004) remained statistically significant factors for successful remobilization (Table 3). Plerixafor was prescribed significantly more often for remobilization in patients with MM (57% of MM rescue protocols) than for patients with lymphoma (33% of lymphoma rescue protocols) (p = 0.01) as shown in Figure 1. Regardless of diagnosis, the success rates for plerixafor remobilization were similar: 60% in cases of lymphoma versus 80% in cases of MM (p = 0.12).

Qualitative Studies of Blood Samples

The mean yield of CD34+ cells harvested after the first mobilization was 6 x 10^6 CD34+ cells/kg (range, 0–83.50), which was better than the yield after a mobilization procedure, 2.05 x 10^6 CD34+ cells/kg (range, 0–18.25) (p < 1.10^-5). The median level of CD34+ cells in PBSCs collected after remobilization increased from 1.43 x 10^6 CD34+ cells/kg (range, 0–14.03) without plerixafor to 3.85 x 10^6 CD34+ cells/kg (range, 0–18.25) with plerixafor (p = 1 x 10^-5). Thus, there was an increase of good mobilizers after plerixafor employment: 35% with plerixafor versus 15% without plerixafor (p = 0.05).

To determine predictive factors for plerixafor efficacy, we retrospectively studied the pre-apheresis blood counts of the 71 patients who received plerixafor. In the patients treated with plerixafor, blood tests performed on the morning of apheresis suggested that the presence of >200 myelocytes/mm³ in the peripheral blood could predict PBSCs collection success (Table 4).
Table 1. Patient demographics and baseline characteristics

|                        | Period 1 | Period 2 | Total  |
|------------------------|----------|----------|--------|
| Patients, n            |          |          |        |
| Besançon Hospital      | 144      | 155      | 299    |
| Dijon Hospital         | 218      | 280      | 398    |
| Total                  | **362**  | **435**  | **797**|
| Median age (range)     | 55 (3–76)| 58 (3–77)| 57 (3–77)|
| Sex ratio (male to female) | 1.74  | 1.65     | 1.70   |
| Disease diagnosis      |          |          |        |
| Multiple myeloma       | 145      | 206      | 351    |
| Lymphoma               | 169      | 186      | 355    |
| Other                  | 48       | 43       | 91     |
| Total                  | **362**  | **435**  | **797**|
| Previous chemotherapy lines, median | 1 (1–5) | 1 (1–5) | 1 (1–5) |
| Patients (n) previously exposed to: | | | |
| Lenalidomide           | 23       | 67       | 90     |
| Bortezomib             | 105      | 197      | 302    |
| Anthracycline          | 261      | 240      | 501    |
| Total                  | **389**  | **504**  | **893**|

Table 2. Risk factors that predict failure of the first mobilization

|                        | Univariate analysis | Multivariate analysis |
|------------------------|---------------------|-----------------------|
| Patients, n            | PBSCs failure n (%) | P     | OR | 95% CI | P    |
| All patients           | 797                 | 140 (18)                 |     |     |     |
| Year of PBSCs          |                     |                   |     |     |     |
| 2006–2008              | 362                 | 65 (18)                 |     |     |     |
| 2009–2011              | 435                 | 75 (17)                 | NS  |     |     |
| Patient age            |                     |                   |     |     |     |
| ≤50 years old          | 235                 | 26 (11)                 |     |     |     |
| >50 years old          | 562                 | 114 (20)                | **0.002** | **1.93** | **1.22–3.06** | **0.005** |
| Diagnosis of MM        |                     |                   |     |     |     |
| Yes                    | 351                 | 75 (21)                 |     |     |     |
| No                     | 446                 | 65 (15)                 | **0.02** | **0.65** | - | **NS** |
| Previous exposure to:  |                     |                   |     |     |     |
| Lenalidomide           | 90                  | 33 (37)                 | < **0.01** |     |     |
| Bortezomib             | 302                 | 69 (23)                 | < **0.01** |     |     |
| PBSCs stimulation      |                     |                   |     |     |     |
| Chemotherapy + G-CSF   | 618                 | 97 (16)                 |     |     |     |
| G-CSF alone            | 179                 | 43 (24)                 | **0.01** | **1.54** | (1.03–2.32) | **0.04** |

MM: multiple myeloma; PBSCs: peripheral blood stem cells; G-CSF: Granulocyte–colony stimulating factor
Table 3. Risk factors that predict failure after remobilization procedures

|                                    | Univariate analysis | Multivariate analysis |
|------------------------------------|---------------------|-----------------------|
|                                    | Rescue protocols, n | PBSC failure, n (% of rescue protocols) | P | OR | 95% CI | P |
| Total                              | 149                 | 70                    |    |    |        |    |
| Year of PBSCs mobilization         |                     |                       |    |    |        |    |
| 2006–2008                          | 67                  | 44 (66)               |    |    |        |    |
| 2009–2011                          | 82                  | 26 (32)               | 0.0001 | - | - | NS |
| Patient age                        |                     |                       |    |    |        |    |
| ≤50 years old                      | 29                  | 13 (45)               |    |    |        |    |
| >50 years old                      | 120                 | 57 (47.5)             | 0.8 |    |        |    |
| ≤55 years old                      | 50                  | 26 (52)               |    |    |        |    |
| >55 years old                      | 99                  | 44 (44)               | 0.39 |    |        |    |
| ≤60 years old                      | 82                  | 28 (34)               |    |    |        |    |
| >60 years old                      | 67                  | 42 (63)               | 0.32 |    |        |    |
| Hematological diagnosis            |                     |                       |    |    |        |    |
| Myeloma                            | 79                  | 26 (33)               |    |    |        |    |
| Other malignancies                 | 70                  | 44 (63)               | 0.0003 | 0.35 | (1.75–6.66) | 0.003 |
| Plerixafor administration          |                     |                       |    |    |        |    |
| Yes                                | 71                  | 25 (36)               |    |    |        |    |
| No                                 | 78                  | 45 (58)               | 0.008 | 0.47 | (0.23–0.94) | 0.04 |

PBSCs: peripheral blood stem cells

Figure 1. Administration of plerixafor according to diagnosis
Table 4. Characteristics of PBSCs collected from patients receiving plerixafor

| Patients, n | Successes (%) | Failures (%) | P     |
|------------|--------------|-------------|-------|
| Median level of CD34+ circulating cells before apheresis | 46 | 25 | 3 x 10^{-3} |
| Nb cells/mm³ (range) | 25 (3.2–222.2) | 4 (0–50.7) | 1 x 10^{-3} |
| Myelemia count before apheresis | | | |
| Patient with myelemia <200 myelocytes/mm³ | 6 (23) | 20 (77) | < 1 x 10^{-5} |
| Patient with myelemia ≥200 myelocytes/mm³ | 39 (88) | 5 (11) | |
| Median level of CD34+ cells in the PBSC collection | | | |
| 10⁶/kg (range) | 4.84 (2.06–18.25) | 0.32 (0–1.73) | < 1 x 10^{-5} |
| Median level of CFU-GM in the PBSC collection | | | |
| 10⁷/kg (range) | 84.69 (0–373.6) | 7.7 (0–58.3) | < 1 x 10^{-5} |

Engraftment and Haematological Recovery

Of the 797 patients in the study, 732 (92%) secondarily underwent ASCT. We evaluated haematological recovery by studying the median time to neutrophil recovery (neutrophils >0.5 G/l). For the 657 patients that required the first mobilization, the median time to neutrophil recovery was 9 days (range, 4–11). For the 117 patients that required a rescue protocol, the median time to neutrophil recovery increased to 13 days (range, 6–42; p<1 x 10^{-4}). For these 117 patients, the addition of plerixafor did not have a significant impact: the median time to neutrophil recovery was 13.9 days (range, 5–41) in the plerixafor group versus 11.79 days (range, 4–30) in the no plerixafor group (p=0.23). In the 657 patients with a successful first mobilization, the median length of hospital stay after ASCT was 19 days (range, 5–80), which increased to 22 days (range, 7–64 days) when ≥2 mobilization procedures were needed (p<0.001).

Discussion:

Mobilization of autologous PBSCs remains of primary interest for performing ASCTs, especially in patients with refractory lymphoma or in young patients with MM. This mobilization process remains one of the factors that limit the feasibility of ASCT. The objective of PBSC mobilization is to obtain as many CD34⁺ cells as possible, because PBSC counts are correlated with bone marrow aplasia duration. A first mobilization with G-CSF alone or in combination with chemotherapy succeeds in 70–95% of patients; this means that 5–30% of patients will be poor mobilizers. Plerixafor represents a new approach to optimizing PBSC mobilization in rescue protocols. It is approved for this use in the European Union in combination with G-CSF to enhance the mobilization of hematopoietic stem cells to the bloodstream for collection and later use in ASCT. It is accepted for use in patients with lymphoma or MM who do not succeed in providing a sufficient PBSC count with G-CSF alone or G-CSF following cytotoxic chemotherapy.

This study retrospectively evaluates the efficacy of plerixafor for remobilizing patients who failed previous mobilizations. We recruited a cohort of consecutive patients that needed ASCT; the study included a large number of patients who were treated at two centres with similar patient management practices and working with the same collection centre for PBSC harvesting. There were no significant differences in plerixafor prescription between the two hospitals (p=0.18), so this cohort offers a reliable and homogeneous representation of the population that needs to undergo ASCT for the treatment of lymphoma or MM. In our study, the first mobilization success rate was 82%, which is similar to rates reported in the literature. Plerixafor was administered to half of the 18% who were poor mobilizers.

Various factors have been reported to impact stem cell mobilization and identification of risk factors of PBSC mobilization failure is important for making the decision about whether to prescribe plerixafor or not for the subsequent mobilization attempt. In our multivariate analysis of the first mobilization course, age >50 years old and absence of chemotherapy in prior PBSC stimulation were significantly associated with suboptimal mobilization. These factors have already been identified in previous studies and the nature of pre-mobilization chemotherapy schemes have also been identified as significant risk factors. Studying the cohort of poor-mobilizing patients was a useful way to demonstrate plerixafor efficacy. Successful remobilization rates with plerixafor varied from 64% to 88% in different studies.

In our cohort, the successful remobilization rate without plerixafor was 42%, and increased to 65% when plerixafor was added. In multivariate analysis, plerixafor administration reduced the PBSCs remobilization failure risk by a half (OR=0.47, p=0.003); these results are in accordance with those already published. Plerixafor allowed 23% of supplemental poor-mobilizer patients to undergo a successful PBSC collection as compared to remobilization with G-CSF alone. Plerixafor efficacy was similar for both diagnoses, with a 60% remobilization success rate in lymphoma cases and an 80% success rate in MM cases (p<0.001). In 2012, Sancho et al. concluded that plerixafor was effective regardless of the type of haematological malignancy.
The significant difference between plerixafor prescription rates according to diagnosis ($p=0.01$) may have been due to differences in treatment strategies for MM versus lymphoma patients. Patients with MM are mobilized rapidly after diagnosis during their front-line treatment, while in the era of rituximab, ASCT is part of the rescue protocol in relapsing or refractory lymphoma patients only and PBSCs were collected mostly after a salvage regimen.

We also found that the use of chemo-primed protocols with plerixafor do not have a beneficial impact on PBSC remobilization as compared to steady-state protocols. These results are in opposition to those of many studies, which concluded that chemo-primed protocols are superior to steady-state protocols in terms of PBSC collection. The addition of G-CSF can increase by 2.5 times the circulating CD34+ cell level because G-CSF boosts hematopoietic restoration after aplasia induced by chemotherapy. However, none of these studies made a difference between the use of plerixafor after a first or subsequent mobilization procedure. Our data showed that during remobilization procedures, the most important risk factor of failure is no longer the use of a steady-state protocol but the amount of previous chemotherapy lines administered. For example, a previous treatment with lenalidomide could be an important factor leading to high risk of mobilization failure.

The third part of the study described the differences in blood test results during the ASCT procedure. Notably, high PBSC content correlates not only with transplant feasibility but also with lower incidences of complications, infections, and transfusion requirements. In order to perform apheresis at the optimal time as well as collect as many PBSCs as possible, we looked at pre-apheresis blood cell counts in plerixafor patients. Currently, the peripheral blood CD34+ cell count is still considered to be the best predictor of apheresis cell yield and is used to determine the adequate time of apheresis. In cases of PBSCs success, we effectively observed a significantly higher level of CD34+ cells in the peripheral blood but also the presence of a high myelemia count (> 200 myelocytes/mm3), which was highly significant.

We decided to evaluate only the qualitative blood samples of the 71 patients who received plerixafor. To our knowledge, this outbreak of myelemia has not been studied yet in this setting. Only a limited bone marrow reserve, characterized by a low platelet count, a low peripheral blood CD34+ number and a low bone marrow cellularity is a risk factor for poor PBSC mobilization. Other studies have identified impaired glucose tolerance and osteolytic lesions as significant predictors of mobilization failure in MM patients. Several studies in the beginning of the G-CSF PBSC mobilization procedures have already shown that the enumeration of immature circulating cells could be of interest to determine the optimal timing of PBSC collection and compare favourably with CD34+ counts. This parameter, myelemia, is of potential clinical interest and merits a more extensive study.

Conclusion

This study demonstrated that plerixafor was an effective drug for poor mobilizers: it synergized with G-CSF and improved the quantity and possibly the quality of collected PBSC. The successful remobilization rate was significantly increased (23%) when plerixafor was employed. We found that patients >50 years old who were previously mobilized using a steady-state protocol were at very high risk of PBSC mobilization failure and were good candidates for plerixafor use. More studies taking both clinical and economic data into account are needed to analyse the cost effectiveness of plerixafor's use in rescue mobilization. This is why we will conduct a cost-effectiveness analysis on this studies cohort with the objective of determining overall per-patient expenditures with or without plerixafor.

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