Plerixafor for Autologous Peripheral Blood Stem Cell Mobilization in Patients Previously Treated with Fludarabine or Lenalidomide

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Fludarabine and lenalidomide are essential drugs in the front-line treatment of non-Hodgkin lymphoma (NHL) and multiple myeloma (MM), respectively. Data suggests that fludarabine and lenalidomide therapy may have a deleterious effect on stem cell mobilization. In the European compassionate use program, 48 patients (median age 57 years) previously treated with fludarabine (median 5 cycles; range: 1-7 cycles) were given plerixafor plus granulocyte colony-stimulating factor (G-CSF) for remobilization following a primary mobilization attempt. The overall median number of $CD34^+$ cells collected was 2.3 $\times$ 10^6/kg (range: 0.3-13.4). The minimum required number of $CD34^+$ cells ($\geq$2.0 $\times$ 10^6/kg) was collected from 58% of patients in a median of 2 days. Thirty-five patients (median age = 57 years) previously treated with lenalidomide (median 5 cycles; range: 1-10 cycles) were given plerixafor plus G-CSF for remobilization. The overall median number of $CD34^+$ cells collected was 3.4 $\times$ 10^6/kg (range: 1.1-14.8). The minimum required number of $CD34^+$ cells ($\geq$2.0 $\times$ 10^6 per kg) was collected from 69% of patients in a median of 2 days. In conclusion, salvage mobilization with plerixafor plus G-CSF is successful in the majority of patients with MM previously treated with lenalidomide. In fludarabine-exposed patients, only 58% of patients will achieve successful salvage mobilization with plerixafor plus G-CSF, suggesting the need for novel mobilization regimens algorithms in this subgroup of patients.

Biol Blood Marrow Transplant 18: 314-317 (2012) © 2012 American Society for Blood and Marrow Transplantation

KEY WORDS: Autologous stem cell mobilization, Plerixafor, Salvage mobilization, Fludarabine

INTRODUCTION

High-dose chemotherapy with or without radiotherapy followed by autologous hematopoietic stem cell transplantation (HSCT) is an effective treatment for patients with non-Hodgkin lymphoma (NHL) [1,2] and multiple myeloma (MM) [3]. At present, granulocyte colony-stimulating factor (G-CSF)-mobilized peripheral blood stem cells are the preferred stem cell source for autologous HSCT [4]. The success of HSC mobilization is usually assessed by the total number of $CD34^+$ stem cells collected, with a cutoff of 2.0 $\times$ 10^6 $CD34^+$ cells/kg recipient body weight being considered as a minimum requirement for transplant. Higher cell dose in the range of 4-5 $\times$ 10^6 $CD34^+$ cells/kg, however, are associated with faster neutrophils and platelets recovery [5]. Traditionally, HSC

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Financial disclosure: See Acknowledgments on page 316.

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Received August 2, 2011; accepted October 1, 2011

1083-8791/$36.00
doi:10.1016/j.bbmt.2011.10.003

mobilization has been achieved using G-CSF alone or in combination with chemotherapy, with a failure rate reported in 5% to 30% of cases [6]. The main risk factors for failure or suboptimal mobilization are advanced age (>60 years), progressive disease, bone marrow involvement, or previous chemotherapy including drugs such as fludarabine [7] or lenalidomide [8]. Indeed, given the increasing use of fludarabine as part of the treatment armamentarium of different lymphoma subtypes, and the wide use of lenalidomide in MM treatment regimens, collection of adequate numbers of autologous $CD34^+$ stem cells in patients who are candidates for autologous HSCT is becoming a matter of concern [9]. Plerixafor (previously AMD3100) reversibly and selectively antagonizes the CXCR4 chemokine receptor resulting in mobilization of $CD34^+$ cells to the peripheral blood [10]. Before the drug approval in Europe, a plerixafor compassionate use program (CUP) was available from July 2008 to August 2010 to provide access to the drug for patients with MM or lymphoma who had previously failed a mobilization attempt, and who were not eligible for another specific plerixafor trial. In this report, we present the efficacy data of plerixafor in a subgroup of patients in the CUP who were previously treated with fludarabine or lenalidomide.

PATIENTS AND METHODS

From June 2008 to August 2010, over 1400 patients were enrolled in the European CUP, and a European Consortium for Stem Cell Collection (ECOSM) collected data in one-half of patients treated. Eligibility criteria for the CUP were age >18 years, a diagnosis of NHL, Hodgkin's disease, or MM, and candidate for autologous HSCT but who had previously failed to collect a minimum of 2.0×10^6 $CD34^+$ cells/kg or did not even proceed to apheresis based on a low peripheral blood $CD34^+$ count (usually <10 cells/μL) after a conventional mobilization procedure. The current analysis focused on 83 patients included in this CUP who were previously treated with fludarabine or lenalidomide (for at least 1 treatment course including fludarabine or lenalidomide) before autologous stem cell collection, and for whom adequate data for analysis were available. All patients signed informed consents for inclusion in the CUP and for collection of their data.

The salvage mobilization protocol included nonpegylated G-CSF, administered at a dose of 10 μg/kg daily by subcutaneous injection on 4 consecutive days. In the evening of the fourth day, patients received subcutaneous plerixafor at a dose of 240 μg/kg. Apheresis was usually initiated on the fifth day, 10 to 12 h after plerixafor and 1 h after G-CSF administration. Apheresis and daily administration of G-CSF and plerixafor were continued until the patient collected enough $CD34^+$ cells for auto-HSCT (minimum of 2.0×10^6/kg), and a maximum of 7 plerixafor injections was allowed. The apheresis procedures were performed according to the standard protocols at each institution.

The primary endpoint for the current analysis was to assess the rate of successful mobilization defined as collection of a total number $\geq 2.0 \times 10^6$ $CD34^+$ cells/kg of body weight. Descriptive statistics were used to define characteristics of patients.

RESULTS AND DISCUSSION

This retrospective analysis included a total of 83 patients. Patients' characteristics and mobilization features are summarized in Table 1. A total of 48 patients were previously treated with fludarabine ("Flu group"), whereas 35 patients received lenalidomide ("Len group"). All 48 patients from the "Flu group" had a diagnosis of NHL, whereas all patients from the "Len group" had MM. In the Flu group, the overall median number of $CD34^+$ cells collected after salvage mobilization with plerixafor was 2.3×10^6/kg (range: 0.3-13.4). Of the 48 patients, 28 (58%) reached the minimum number of 2.0×10^6 $CD34^+$ cells/kg, whereas only 3 patients (6%) collected $\geq 5.0 \times 10^6$ $CD34^+$ cells. The collection target of 2.0×10^6/kg was reached in a median of 2 apheresis sessions (range: 1-3).

The overall median number of $CD34^+$ cells collected in the Len group was 3.4×10^6/kg (range: 1.1-14.8). Among these 35 patients, 24 patients (69%) collected the minimum number of $CD34^+$ cells ($\geq 2.0 \times 10^6$/kg), including 12 patients (34%) who were able to collect $\geq 5.0 \times 10^6$ cells/kg. In the Len group, 7 patients (20%) had received a prior autologous HSCT before salvage mobilization with plerixafor. Both targets were reached with a median of 2 apheresis sessions (range: 1-4).

In this salvage CUP program, 58% of patients previously exposed to fludarabine successfully mobilized $\geq 2.0 \times 10^6$ $CD34^+$ cells/kg using plerixafor plus G-CSF, among them only 3 patients (6%) were able to collect an optimal graft of $\geq 5.0 \times 10^6$ $CD34^+$/kg, allowing for at least 2 HSCT procedures. Interestingly, previously published data suggested that first-line mobilization success rates in patients pretreated with fludarabine can range from 46% to 63% [11-13] with G-CSF alone, G-CSF plus chemotherapy, or G-CSF plus stem cell factor. Furthermore, second-line mobilization regimens are considered to be of little effect in this subgroup of patients [14,15]. Therefore, results observed in the current analysis in

Table 1. Study Population Characteristics

Characteristic (%)	Fludarabine (n = 48)	Lenalidomide (n = 35)
Patient age, median (range)	57 (36-69)	57 (34-66)
Patient gender		
Male	26 (54)	18 (51)
Female	22 (46)	17 (42)
Fludarabine or lenalidomide cycles, median (range)	5 (1-7)	5 (1-10)
Diagnosis and disease status		
NHL	48 (100)	0
Multiple myeloma	0	35 (100)
Previous chemotherapy: number of lines, median (range)	3 (1-6)	4 (1-9)
Previous autograft		
Yes	0	7 (20)
No	43 (90)	20 (57)
Data missing	5 (10)	8 (23)
Radiotherapy		
Yes	5 (10)	3 (9)
No	36 (75)	24 (68)
Data missing	7 (15)	8 (23)
Mobilization strategy with plerixafor		
Steady-state G-CSF mobilization	38 (79)	27 (77)
Chemotherapy + G-CSF mobilization	10 (21)	8 (23)
No. of patients collected	44 (92)	34 (97)
$CD34^+$ cells collected/kg, median (range)	2.3 (0.3-13.4)	3.4 (1.1-14.8)
No. of patients who reached $\geq 2.10^6$ $CD34^+$	28 (58)	24 (69)
No. of apheresis days to reach $\geq 2.10^6$ $CD34^+$	2 (1-3)	2 (1-4)
No. of patients who reached $\geq 5.10^6$ $CD34^+$	3 (6)	12 (34)
No. of apheresis days to reach $\geq 5.10^6$ $CD34^+$	2 (1-3)	2 (1-3)

a salvage setting can be viewed as encouraging. However, one cannot ignore that nearly one-half of fludarabine-treated patients failed to be rescued after salvage remobilization with plerixafor, raising the issue of the use of this drug as front-line therapy in order to optimize the overall results in this subgroup predicted to be very poor mobilizers and thus improve treatment options [9].

In contrast, in patients previously treated with lenalidomide, salvage remobilization with plerixafor plus G-CSF was significantly more effective with 69% of the 38 patients successfully mobilizing $\geq 2.0 \times 10^6$ $CD34^+$ cells/kg, including 34% of cases achieving $\geq 5.0 \times 10^6$ $CD34^+$ cells/kg. In the literature, mobilization failure rates in patients pretreated with lenalidomide ranged from 7% to 45% [8,16,17], suggesting that second-line agents are likely to be needed for these patients. In patients with MM, chemotherapy-based mobilization has been shown to be effective for remobilization, especially in patients treated with lenalidomide but at the cost of increased toxicity [17]. Results from this current analysis after lenalidomide therapy are comparable to the results published by Micallef et al. [18] as part of the U.S. CUP, who reported, in 40 patients previously treated with lenalidomide undergoing a remobilization attempt after primary mobilization failure, achievement of the minimum required number of $CD34^+$ cells in 80%. With this background, the International Myeloma Working Group recently published comprehensive recommendations for stem cell mobilization in patients with MM in the era of novel therapeutic agents. In patients treated with lenalidomide-based regimens, collection of autologous stem cells is recommended within the first 4 cycles. In case of failure of the front-line collection procedure using G-CSF, second-line collection with G-CSF plus plerixafor is 1 of the recommended options [19].

In terms of postautologous HSCT outcome, the design of this CUP-based analysis did not allow assess to such data, especially engraftment kinetics. However, based on previously published data [20], it has already been well established that engraftment features when using autologous $CD34^+$ stem cells mobilized with G-CSF and plerixafor are at least as good as those of patients transplanted with stem cells mobilized without plerixafor.

In conclusion, the majority of patients treated with lenalidomide can undergo successful salvage second-line mobilization with plerixafor plus G-CSF. However, in patients treated with fludarabine, results are less appealing in the salvage setting, warranting larger prospective studies evaluating the efficacy of plerixafor for front-line mobilization in this subgroup of patients.

ACKNOWLEDGMENTS

Financial disclosure: The authors acknowledge the financial support of Genzyme Corp. for their help in data collection. However, Genzyme Corp. did not participate in either the definition or data analysis. M.M. thanks C. Chabannon (Institut Paoli-Calmettes, Marseille, France) for helpful discussions. All authors have received honoraria or educational grants support from GENZYME whose product was discussed in this manuscript.

AUTHORSHIP STATEMENT

F. Malard analyzed data and wrote the manuscript; M. Mohty recruited patients, supervised research, analyzed data, and wrote the manuscript; N. Kröger, I. Gabriel, K. Hübel, J. Apperley, G. Basak, K. Douglas, C. Geraldes, O. Jaksic, Z. Koristek, F. Lanza, R. Lemoli, G. Mikala, D. Selleslag, and N. Worel recruited patients and commented on the manuscript; R.F. Duarte recruited patients, supervised research, analyzed data, and helped write the manuscript. All authors approved submission of the manuscript for publication purposes.

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