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ORIGINAL ARTICLE

European data on stem cell mobilization with plerixafor in non-Hodgkin's lymphoma, Hodgkin's lymphoma and multiple myeloma patients. A subgroup analysis of the European Consortium of stem cell mobilization

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The effectiveness of the novel hematopoietic stem cell mobilizing agent plerixafor was evaluated in nationwide compassionate use programs in 13 European countries. A total of 580 poor mobilizers with non-Hodgkin's lymphoma (NHL), Hodgkin's lymphoma (HL) and multiple myeloma (MM) were enrolled. All patients received plerixafor plus granulocyte CSF with or without chemotherapy. Overall, the collection yield was significantly higher in MM patients ($>2.0\times10^6$ CD34+ cells/kg: 81.6%; $>5.0\times10^6$ CD34+ cells/kg: 32.0%) than in NHL patients ($>2.0\times10^6$ CD34+ cells/kg: 64.8%; $>5.0\times10^6$ CD34+ cells/kg: 12.6%; $P<0.0001$) and also significantly higher in HL patients ($>2.0\times10^6$ CD34+ cells/kg: 81.5%; $>5.0\times10^6$ CD34+ cells/kg: 22.2%) than in NHL patients ($P=0.013$). In a subgroup analysis, there were no significant differences in mobilization success comparing patients with diffuse large B-cell lymphoma, follicular lymphoma and mantle cell lymphoma. Our data emphasize the role of plerixafor in poor mobilizers, but further strategies to improve the apheresis yield especially in patients with NHL are required.

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Keywords: plerixafor; mobilization; lymphoma subtypes; European centers

INTRODUCTION

The use of intensive chemotherapy followed by autologous hematopoietic stem cell (HSC) transplantation is well established in relapsed Hodgkin's lymphoma (HL) and non-Hodgkin's lymphoma (NHL). In multiple myeloma (MM), high-dose melphalan with autologous stem cell support remains the standard of care in first remission, despite the introduction of novel therapies. For successful autografting, a sufficient number of HSC must be mobilized from the BM to the peripheral blood and collected by apheresis. The required number of HSC for timely engraftment remains controversial, but most investigators accept a minimum CD34+ cell yield of 2.0×10^6 CD34+ cells/kg body weight (BW) for transplantation, although cell doses of 5.0×10^6 CD34+ cells/kg BW or higher are associated with faster engraftment of neutrophils and platelets.[1,2] Recovery from neutropenia is associated with a decrease in the incidence of febrile neutropenic episodes, resulting in reduced hospitalization times.[3] In European transplant centers, the HSC mobilization agent most widely used is G-CSF (available as filgrastim or lenograstim) alone ('steady state') or in conjunction with chemotherapy. Particularly in MM patients, the preferred mobilization regimen differs between European countries. France, Austria and Spain use predominately steady state mobilization, whereas the United Kingdom, Italy, Norway, The Netherlands, Czech Republic and Germany prefer G-CSF plus chemotherapy.

In August 2009, the European Medicines Agency approved plerixafor in combination with G-CSF to 'enhance mobilization of HSC to the peripheral blood for collection and subsequent autologous transplantation in patients with lymphoma and multiple myeloma whose CD34+ cells mobilize poorly'. Plerixafor is a bicyclam molecule, which blocks the CXCR4 chemokine receptor and inhibits binding of its cognate ligand stroma cell-derived factor 1, thereby inducing leukocytosis and mobilization of CD34+ cells.[4,5] Before approval, two major randomized trials and several non-randomized trials documented the effectiveness of plerixafor.[6–8] Subsequently, plerixafor was made available in Europe through compassionate use programs (CUPs) or named patient programs for patients who had prior failed mobilization attempts. A total of 13 European countries enrolled patients in CUPs. The results of studies from Spain and the United Kingdom, Austria, Poland and Germany have been published recently.[9–12] In Spain and the United Kingdom, 56 patients (32 MM, 24 lymphoma) with a median age of 60 years (range 33–69 years) from 15 centers were given G-CSF and plerixafor without

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additional chemotherapy. The German CUPs included a total of 60 patients (17 MM, 30 lymphoma, 13 with other diseases) with a median age of 56 years (range 2–75 years) from 23 centers. A total of 47 patients received a mobilization regimen using chemotherapy, G-CSF and plerixafor. Interestingly, in both studies, 75% of the patients reached the primary end point and collected $\geqslant 2.0 \times 10^6$ CD34+ cells/kg BW, irrespective of the mobilization regimen. In a subgroup analysis, patients with lymphoma experienced a lower rate of successful collection (Spain/UK: 63%, Germany: 64%) than patients with MM (Spain/UK: 84%, Germany: 88%). Observed adverse events were mild and manageable but were recorded more often in the Spanish/British CUPs compared with the German CUPs (34 vs 13.3%) despite the use of chemotherapy in the latter study.

This report describes an analysis of the data set of 580 patients enrolled in all of the European CUPs.

PATIENTS AND METHODS

The European CUPs granted access to plerixafor for patients diagnosed with lymphoma and MM who failed to mobilize sufficient numbers of HSC with conventional mobilization attempts. The following European countries enrolled patients in the CUPs between May 2008 and August 2009 and reported results to the European Consortium of Stem Cell Mobilization (ECOSM): Austria, Belgium, Croatia, Czech Republic, France, Germany, Hungary, Italy, Poland, Portugal, Slovakia, Spain and the United Kingdom. Plerixafor (*Mozobil*) was supplied by Genzyme Inc., Naarden, The Netherlands after patients registration. Mobilization data were recorded nationwide and transferred to the database of the ECOSM for further evaluation. All patients gave informed consent for participating in the CUPs and for data collection.

Inclusion and exclusion criteria

Eligible patients were those aged from 18 to 78 years and suffering from NHL, HL or MM who had previously failed mobilization or collection, or who, according to the treating physician, would not be able to provide enough HSCs based on the measurements of CD34+ cells in peripheral blood during mobilization.

A failed mobilization attempt was defined either as a CD34+ cell value below 10/μL measured in peripheral blood before apheresis or as a pooled cell harvest of below 2.0×10^6 CD34+ cells/kg BW in a maximum of seven apheresis sessions after mobilization with G-CSF alone or combined with chemotherapy. Other major inclusion criteria were: a signed informed consent form, an adequate cardiac, renal and pulmonary function sufficient to undergo apheresis procedure and transplantation, an Eastern Cooperative Oncology Group performance status of 0 or 1, WBC count $>2.5 \times 10^9$/L, ANC $>1.5 \times 10^9$/L, platelet count $>85 \times 10^9$/L, serum creatinine <1.5g/dL, liver function tests within twice the upper limit of normal and no active Hepatitis B or C infection. Major exclusion criteria included: the diagnosis of any acute leukemia including plasma cell leukemia, the diagnosis of myelodysplastic syndrome, vasculitis or autoimmune disease, brain metastases or carcinomatous meningitis, clinically significant heart disease or indications of previously undiagnosed cardiac ischemia or rhythm disturbance, acute infection and/or fever (>38 °C), hypercalcemia (>1 mg/dL above the upper level of normal), pregnancy or breast feeding, patients known to be HIV positive and obesity exceeding 175% of ideal BW. Patients receiving experimental treatment during mobilization were also excluded. There was no minimum time required between initial mobilization attempts and enrollment in the CUPs.

If an individual patient did not fulfill the inclusion/exclusion criteria but might benefit from plerixafor, enrollment in the CUPs was possible by agreement of Genzyme Inc.

European Union plerixafor CUP treatment protocol

Mobilization without chemotherapy started with a 4-day treatment with non-pegylated G-CSF. In general, a s.c. dosage of 10 μg/kg daily was administered in the morning. In the evening of the fourth day, plerixafor (240 μg/kg) was administered s.c. 10–11 h prior to apheresis. G-CSF was given on day 5 one hour before apheresis. If multiple days of collection were required, the schedule of plerixafor and G-CSF was repeated until a maximum of 7 days of plerixafor injections. Centers were also able to combine chemotherapy with G-CSF and plerixafor for mobilization. The exact procedure of plerixafor application following chemotherapy (for example, time point, required number of WBC) was determined by the local investigator. G-CSF was usually started at the neutrophil nadir after chemotherapy.

Apheresis

Harvesting was performed with devices at the local sites, mostly a COBE Spectra Apheresis System (CaridianBCT, Lakewood, CO, USA). Apheresis was started following local guidelines in most cases if CD34+ cell counts exceeded 10 cells/μL in the peripheral blood. Volume, processing and storage of apheresis product were done according to the standardized procedures (approximately three times the total blood volume) at each study center. Apheresis was performed on consecutive days. A maximum of seven collections were allowed; the required number of aphereses was determined by the local investigator. Pooling of multiple apheresis yields was also allowed. All laboratory tests were conducted at local site laboratories.

Outcome

A successful mobilization was defined as a total collection of $\geqslant 2.0. \times 10^6$ CD34+ cells/kg BW. Patients who collected a sufficient number of cells were able to proceed to high-dose chemotherapy followed by autologous transplantation, according to local standards. Measurement of WBC $>1.0 \times 10^9$/L and platelets $>20 \times 10^9$/L without platelet infusions were considered as engraftment.

Statistics

Descriptive statistics were used to summarize CD34+ cell collections, number of apheresis days, and days to WBC and platelet engraftment. Data are presented as median, minimum and maximum. A two-tailed unpaired *t*-test was used to determine statistical significance. All analyses were performed using Excel software (Microsoft, Redmond, WA, USA).

RESULTS

A total of 580 patients–304 male patients and 276 female patients–were included. A total of 270 patients were diagnosed with NHL, 54 with HL and 256 with MM. The median age was 57 years (range 12–76 years; two patients with NHL aged 12 and 15 were included). Regimens used for mobilization were G-CSF and plerixafor with or without chemotherapy. A median of two previous chemotherapy regimens before mobilization was applied (range 0–10). Patients' characteristics are included in Table 1.

Non-Hodgkin's lymphoma

In total, 270 patients (138 male, 132 female) diagnosed with NHL were enrolled in the European CUPs and were reported to ECOSM. The median age was 56 years (range 12–75 years). The median weight was 72 kg (range 43–132 kg) and patients had received a median of two prior chemotherapy regimens (range 0–10). The median number of previous mobilization regimen was one (range 0–7).

A median of two apheresis sessions (range 1–4) yielded a median of 2.56×10^6 CD34+ cells/kg BW (range 0–17.37). The defined minimum of 2.0×10^6 CD34+ cells/kg BW were collected in 175 patients (64.8%). A total of 34 patients (12.6%) yielded more than 5.0×10^6 CD34+ cells/kg BW. There were no differences in stem cell harvests regarding number of prior mobilization attempts or number of prior chemotherapeutic regimens.

In a subgroup analysis (as far as data were available), the mobilization success in patients with diffuse large B-cell lymphoma (DLBCL; $n = 28$) were compared with patients with follicular

Table 1. Patient characteristics and mobilization results of the European CUP

	NHL	*HL*	*MM*	*Total*
N	270	54	256	580
Age (years)				
Median	56	36	60	57
Min, max	(12, 75)	(19, 76)	(28, 76)	(12, 76)
Sex				
Female	138	30	108	276
Male	132	24	148	304
Weight (kg)				
Median	72	78	74	74
Min, max	(43, 132)	(48, 114)	(47, 120)	(43, 132)
Prior lines of treatment				
Median (min, max)	2 (0, 10)	3 (2, 5)	2 (0, 9)	2 (0, 10)
Radiation pretreatment (%)	34 (12.6%)	16 (29.6%)	45 (17.6%)	95 (16.4%)
Previous-failed mobilizations				
Median	1	1	1	1
Min, max	(0, 7)	(1, 1)	(0, 2)	(0, 7)
Apheresis sessions				
Median	2	2	2	2
Min, max	(0, 4)	(0, 4)	(0, 5)	(0, 5)
Yield ($\times 10^6$)				
Median	2.56	3.14	3.60	3.06
Min, max	(0, 17.37)	(0, 32.6)	(0, 15.27)	(0, 32.6)

Abbreviations: HL = Hodgkin's lymphoma; MM = multiple myeloma; NHL = non-Hodgkin's lymphoma.

lymphoma (FL; $n = 15$) and to patients with mantle cell lymphoma (MCL; $n = 24$). The groups were well balanced for age, weight and prior lines of therapy. Interestingly, the majority of patients were mobilized without the use of chemotherapy (DLBCL: 82.1%; FL: 66.7%; MCL: 83.3%). The collection yield was highest in DLBCL (median: 2.76×10^6 CD34+ cells/kg BW, range 0.64–7.87) and lowest in MCL (median: 2.27×10^6 CD34+ cells/kg BW, range 0–5.54). Patients with FL collected a median of 2.61×10^6 CD34+ cells/kg BW, range 0.52–8.77. However, these differences did not reach clinical significance. The minimum number of CD34+ cells ($> 2.0 \times 10^6$ CD34+ cells/kg BW) were collected from 67.9% of patients with DLBCL, from 62.5% of patients with MCL and from 53.3% of patients with FL. For detailed information, refer Table 2.

Hodgkin's lymphoma

A total of 44 patients (24 male and 30 female) diagnosed with HL were enrolled and recorded by ECOSM. As expected, patients with HL were younger than patients diagnosed with NHL or MM. The median age was 36 years (range 19–76 years). Although patients diagnosed with HL had a higher median number of prior treatment lines than NHL and MM patients, the maximum of previous chemotherapy regimens was lower than in the other groups (median 3, maximum 5 lines of therapy). Similar to NHL and MM patients, HL patients had failed a median of one previous conventional mobilization attempt (no range). HL patients yielded a median of 3.14×10^6 CD34+ cells/kg BW (range 0–32.6) in a median of two apheresis sessions (range 1–4).

Table 2. Patients characteristics and mobilization results in non-Hodgkin's lymphoma subtypes

	Diffuse large B-cell lymphoma	*Follicular lymphoma*	*Mantle cell lymphoma*
Patients (*n*)	28	15	24
Sex			
Male (*n*)	12	4	17
Female (*n*)	16	11	7
Age (years)			
Median	67	55	57
Min, max	(15, 67)	(39, 68)	(36, 68)
Weight (kg)			
Median	70	73	80
Min, max	(53, 107)	(55, 111)	(60, 132)
Prior chemotherapy regimens			
Median	3	3	2
Min, max	(1, 5)	(1, 6)	(1, 8)
Prior radiation therapy (*n*)	3 (10.7%)	3 (20%)	0
Prior mobilization attempts			
Median	1	1	1
Min, max	(1, 1)	(0, 3)	(0, 7)
Mobilisation regimen (n)			
Steady state (%)	23 (82.1%)	10 (66.7%)[a]	20 (83.3%)[a]
Chemotherapy-based (%)	5 (17.9%)	4 (26.7%)[a]	3 (12.5%)[a]
Yield ($\times 10^6$CD34+/kg BW)			
Median	2.76	2.61	2.27
Min, max	(0.64, 7.87)	(0.52, 8.77)	(0.00, 5.64)
$> 2.0 \times 10^6$ CD34+/kg BW	19 (67.9%)	8 (53.3%)	15 (62.5%)
$> 5.0 \times 10^6$ CD34+/kg BW	6 (21.4%)	1 (6.7%)	1 (4.2%)

[a]1 × no data.

In 44 patients (81.5%) the defined minimum of 2.0×10^6 CD34+ cells/kg BW was reached. In all, 12 patients (22.2%) collected more than 5.0×10^6 CD34+ cells/kg BW.

Multiple myeloma

A total of 256 patients diagnosed with MM were enrolled. A total of 148 male patients and 108 female patients with a median age of 60 years (range 28–76) received plerixafor. All MM patients had a median weight of 74 kg (range 47–120 kg), had received a median of two prior lines of treatment and had failed a median of one prior conventional mobilization attempt (range 0–2).

MM patients yielded a median of 3.60×10^6 CD34+ cells/kg BW (range 0–15.27) in a median of two apheresis sessions (range 1–5). The defined minimum of 2.0×10^6 CD34+ cells/kg BW were collected in 209 patients (81.6%). A total of 82 patients (32.0%) yielded more than 5.0×10^6 CD34+ cells/kg BW allowing tandem transplantation.

Overall, the CD34+ cell yield was significantly higher in MM patients than in NHL patients ($P < 0.0001$), and also significantly higher in HL patients than in NHL patients ($P = 0.013$). CD34+ cell yield was not statistically significant between MM patients and HL patients. Furthermore, the number of patients providing the defined minimum of 2.0×10^6 CD34+ cells/kg BW was significantly higher in MM patients compared with NHL patients ($P < 0.0001$) and also significantly higher in HL compared with NHL patients ($P = 0.017$).

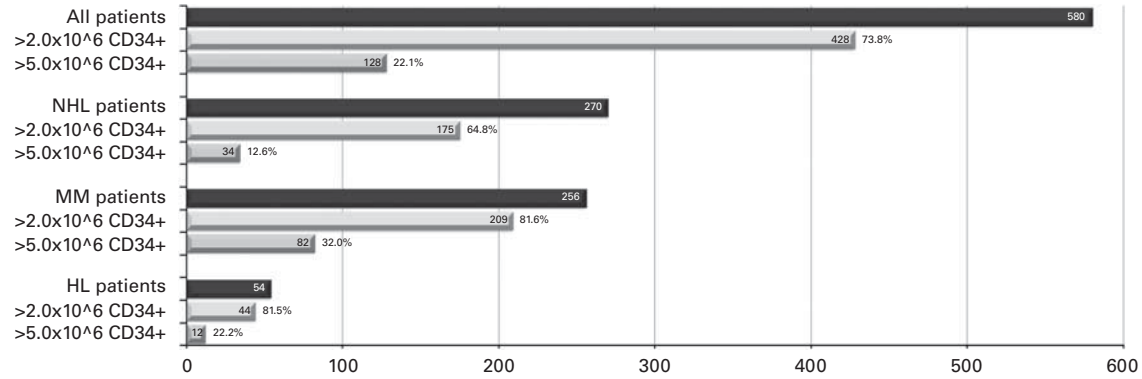

Figure 1. Mobilization success in all patients, and in patients with non-Hodgkin's lymphoma (NHL), multiple myeloma (MM) and Hodgkin's lymphoma (HL): results of patients from 13 European countries.

The results of the European study cohort are summarized in Table 1 and Figure 1.

Analyzing the mobilization strategies and collection success of individual countries demonstrates only minor variations compared with the global results. Most countries use both chemomobilization and steady state mobilization; however, there is a clear preference for using chemotherapy plus G-CSF/plerixafor in the Czech Republic, Germany, Hungary, Italy and Poland (data not shown). In these countries, chemomobilization is not limited to NHL and HL but also preferred in MM.

DISCUSSION

About 10 years ago, plerixafor (formerly known as AMD3100) was used for the first time for stem cell mobilization in humans.[5,13] These initial trials showed the potential of plerixafor to increase the number of circulating CD34+ HSC in the peripheral blood, fostering clinical research with plerixafor all over the world. It was rapidly realized that plerixafor alone is capable of mobilizing CD34+ cells, but significantly improves the mobilization efficacy of G-CSF when it is used in combination.[14] Failure of mobilization reduces the clinical options for these patients, for example, BM collection, allogeneic transplantation and so on. The fact that nearly 600 patients in a period of 15 months have been treated with plerixafor under compassionate use regulations in Europe (and reported to ECOSM) indicates a high failure rate as well as the medical need for an effective alternative mobilization regimen. The approval of plerixafor has broadened the choice of mobilization regimens for stem cell harvest, thereby increasing the pool of patients for whom transplantation is an option.

There are a number of acknowledged risk factors for poor or suboptimal mobilization, for example, age >60 years, progressive disease, severe BM involvement, previous chemotherapy and/or radiotherapy, type of chemotherapy, previously failed mobilization attempts, platelet counts $<100 \times 10^9$/L before apheresis and the occurrence of neutropenic fever during mobilization.[1,15–19] However, a reproducible model is still lacking.

Two major randomized studies documenting the benefit of plerixafor in a randomized setting have been published so far.[6,7] These trials included patients with NHL and MM who had their first mobilization attempt. Overall, both trials showed significant advantages in the plerixafor group compared with the placebo group concerning the primary end point of yielding $>5.0 \times 10^6$ CD34+ cells/kg BW in patients with NHL and $>6.0 \times 10^6$ CD34+ cells/kg BW in patients with MM. The percentage of patients who successfully met the primary endpoint was significantly higher in the plerixafor group than in the placebo group: 59 vs 20% in patients with NHL and 71.6 vs 34.4% in patients with MM. It must be emphasised that both trials excluded patients who failed prior conventional mobilization. However, in particular these transplant candidates are in need of novel mobilization regimens, and strategies allowing them to proceed to the life-saving therapeutic approach of auto-SCT. Calandra *et al*.[20] published the data of the US CUPs for plerixafor. A cohort of 115 poor mobilizers was assessed, the objective being to collect $>2.0 \times 10^6$ CD34+ cells/kg BW following mobilization with G-CSF and plerixafor. The rates of successful HSC collection was 60.3% for NHL patients but substantially higher in HL and MM patients (HL: 76.5%, MM: 71.4%).

Overall, the collection success for patients with NHL seems to be lower compared with patients suffering from HL or MM. As mentioned above, this was shown in first-line mobilization as well as in poor mobilizers with failed apheresis in the past. In our analysis, we demonstrated in a large cohort of 580 European patients significantly less efficacy of plerixafor and G-CSF (plus/minus chemotherapy) in NHL patients compared with HL patients or MM patients. The reason for low mobilization in NHL patients is not clear, but might be due to the fact that NHL patients are heavily pretreated and have a higher rate of BM involvement. It was also shown that remobilization was successful in 81.5% of HL patients. These results are quite similar to those reported by Cashen *et al*.[21] with 95% mobilization success in HL patients. In this investigation, plerixafor and G-CSF were used in first mobilization attempt. However, the patients had a delayed median time to platelet engraftment of 19 days.

In a subgroup analysis, we evaluated the collection data in aggressive NHLs (DLBCL, MCL) and indolent NHL (FL). Although the total number is relatively small, the collection yield did not differ significantly between DLBCL, MCL, and FL. However, it was somewhat surprising that more than 80% of patients with aggressive lymphomas were mobilized without the use of chemotherapy, as most investigators justify chemomobilization with the need of further tumor reduction. This might be especially applicable for aggressive lymphomas. It is not yet clear what is the reason for the high number of 'steady-state' mobilizations; maybe there are concerns about the use of plerixafor in combination with chemotherapy. Very recently it was shown that the addition of plerixafor is safe in the recovery phase after chemotherapy.[22]

In conclusion, our analysis documents the effectiveness of plerixafor in patients who have previously mobilized poorly. However, it is obvious that second mobilization was less effective in NHL patients and especially promising in HL patients and MM patients. At this time, it seems premature to define NHL as an independent risk factor for poor mobilization, but further studies should carefully explore this point, which may have implications for the development of further mobilization strategies.

CONFLICT OF INTEREST

The authors have also acted as consultants to Genzyme, but the opinions or views expressed in this paper are those of the authors and do not necessarily reflect the opinions or recommendations of Genzyme Corporation.

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Disclaimer

The material is original research, has not been previously published and has not been submitted for publication elsewhere while under consideration.

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