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Successful Stem Cell Remobilization Using Plerixafor (Mozobil) Plus Granulocyte Colony-Stimulating Factor in Patients with Non-Hodgkin Lymphoma: Results from the Plerixafor NHL Phase 3 Study Rescue Protocol

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In a phase 3 multicenter, randomized, double-blinded, placebo-controlled study of 298 patients with non-Hodgkin lymphoma (NHL), granulocyte colony-stimulating factor (G-CSF) plus plerixafor increased the proportion of patients who mobilized $\geq 5 \times 10^6$ $CD34^+$ hematopoietic stem cells (HSCs)/kg compared with placebo plus G-CSF ($P < .001$). Patients in either study arm who failed mobilization ($< 0.8 \times 10^6$ $CD34^+$ cells/kg in 2 collections or $< 2 \times 10^6$ $CD34^+$ cells/kg in 4 collections) were eligible to enter the opened-label rescue protocol. Following a 7-day minimum rest period, these patients received G-CSF (10 μg/kg/day) for 4 days, followed by daily plerixafor (0.24 mg/kg) plus G-CSF and apheresis for up to 4 days. Of the 68 patients failing initial mobilization (plerixafor, n = 11; placebo, n = 57), 62 patients (91%) entered the rescue procedure (plerixafor, n = 10; placebo, n = 52). Four of 10 patients (40%) from the plerixafor group and 33 of 52 (63%) from the placebo group mobilized sufficient $CD34^+$ cells ($\geq 2 \times 10^6$ cells/kg) for transplantation from the rescue mobilization alone ($P = .11$). Engraftment of neutrophils (11 days) and platelets (20 days) was similar to that in patients who did not fail initial mobilization, and all patients had durable grafts at the 12-month follow-up. Common plerixafor-related adverse events (AEs) included mild gastrointestinal (GI) effects and injection site reactions. There were no drug-related serious AEs. These data support that plerixafor plus G-CSF can safely and effectively remobilize patients with NHL who have failed previous mobilization.

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INTRODUCTION

Between 11% and 53% of patients with non-Hodgkin lymphoma (NHL) do not successfully mobilize sufficient hematopoietic stem cells (HSCs) for transplantation with either cytokines alone or in combination with chemotherapy [1-7]. Typically these patients undergo a repeat mobilization procedure, usually within 2 weeks of the initial procedure. Early remobilization has been associated with better mobilization outcome and lower risk of disease progression and infection [4].

Conventionally, patients who fail cytokine-only mobilization are treated with increasing doses of granulocyte colony-stimulating factor (G-CSF), G-CSF plus another cytokine (eg, granulocyte monocyte colony-stimulating factor [GM-CSF] or an investigational agent, such as hepatocyte growth factor or stem cell factor), G-CSF plus chemotherapy, or G-CSF plus an investigational agent. The success rate with these regimens is typically only 20%-50%, however [4,8-10]. Results of remobilization studies are typically confounded by such factors as the lack of a well-defined patient population with any strict inclusion/exclusion criteria and the lack of a consistent definition of poor mobilization.

Plerixafor is a small-molecule bicyclam derivative that blocks the interaction between the chemokine receptor, CXCR4, and stromal cell-derived factor 1 (SDF-1) [11]. Plerixafor plus G-CSF has been shown

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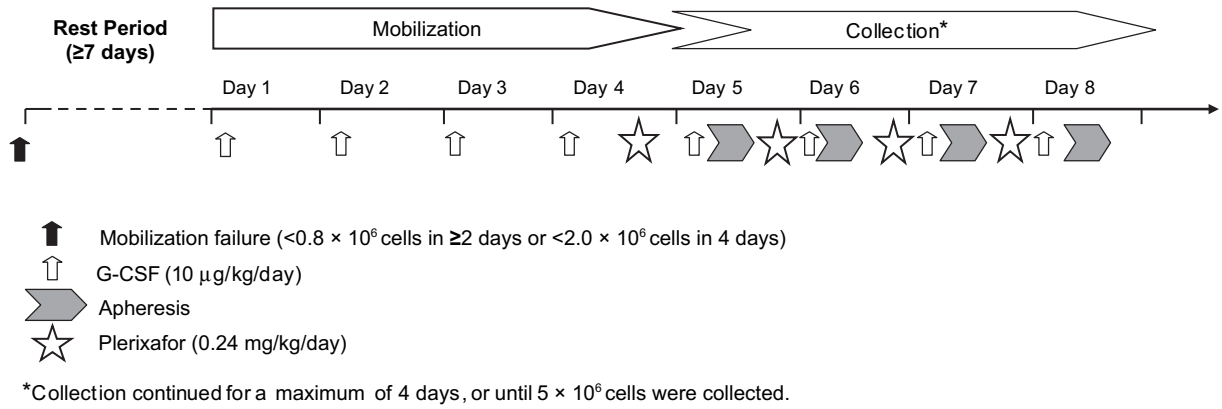


Figure 1. Study design and treatment plan.

to effectively and rapidly mobilize HSCs in all patients with NHL or multiple myeloma (MM) who were found to be poor mobilizers with a G-CSF regimen [2]. In a phase 2 study of 49 patients with NHL or MM, 28 patients were deemed to be heavily pretreated, as defined by having previously received 10 or more cycles of chemotherapy, platinum-based chemotherapy, or irradiation to bone marrow (BM)-bearing sites [12]. Administration of plerixafor plus G-CSF resulted in a median fold increase in $CD34^+$ cell count that was similar in the heavily pretreated and non-heavily pretreated patients. In addition, the median number of aphereses, median yield of $CD34^+$ cells, and engraftment of both neutrophils and platelets were similar in the 2 groups, indicating that plerixafor plus G-CSF resulted in successful mobilization even in the heavily pretreated patients.

In a phase 3 randomized study comparing placebo plus G-CSF with plerixafor plus G-CSF for $CD34^+$ HSC mobilization in patients with NHL, the minimum cell yield for transplantation was defined as $\geq 2 \times 10^6$ $CD34^+$ cells/kg within 4 aphereses [13]. Patients who achieved cumulative yields of $<0.8 \times 10^6$ $CD34^+$ cells/kg after 2 days of apheresis or $<2 \times 10^6$ $CD34^+$ cells/kg after 4 days of apheresis were considered to have failed mobilization and were given the option of entering an opened-label rescue protocol for remobilization with plerixafor plus G-CSF. The purpose of the present analysis was to assess whether plerixafor plus G-CSF is a generally safe and effective remobilization strategy for patients who have failed a prior mobilization attempt with placebo plus G-CSF or plerixafor plus G-CSF.

METHODS

Study Design and Patients

Patients in the placebo or plerixafor arm of the randomized phase 3 study [13] who were unable to collect either a total of $\geq 0.8 \times 10^6$ $CD34^+$ cells/kg in 2 days of apheresis or $\geq 2 \times 10^6$ $CD34^+$ cells/kg in 4 days of apheresis had the option of entering an opened-label rescue protocol, for which a separate informed consent was obtained. Study staff and patients remained blinded to the study treatment received before entering the rescue protocol.

Study Treatment

Following a rest period of at least 7 days after the initial mobilization attempt, patients were given G-CSF (10 μg/kg/day) s.c. for 4 days (days 1-4). On the evening of day 4, patients were given plerixafor 0.24 mg/kg s.c. On the morning of day 5, patients were given G-CSF (10 μg/kg/day) s.c., followed by apheresis. Apheresis was started approximately 10-11 hours after each dose of plerixafor. The patients continued to receive an evening dose of plerixafor followed by G-CSF the next morning, before apheresis, for up to a total of 4 aphereses or until $\geq 5 \times 10^6$ $CD34^+$ cells/kg were collected (Figure 1). The efficacy of mobilization was assessed by the peripheral blood (PB) $CD34^+$ cell count performed locally, as well as by the yield of $CD34^+$ cells/kg collected by apheresis.

Transplantation

After completion of HSC collection, patients underwent myeloablative (MA) chemotherapy using the same regimens as used in the parent phase 3 study, followed by transplantation. All transplantations were performed within 5 weeks of the last apheresis, according to the standard of care at the study center. A minimum of $\geq 2 \times 10^6$ $CD34^+$ cells/kg (actual body weight) were required for transplantation; transplantation with fewer than 2×10^6 cells/kg was permitted only at the investigator's discretion. In the event that a sufficient number of cells for transplantation could not be obtained from the collection, cells could be retained to be pooled and transplanted at a later date at the investigator's discretion.

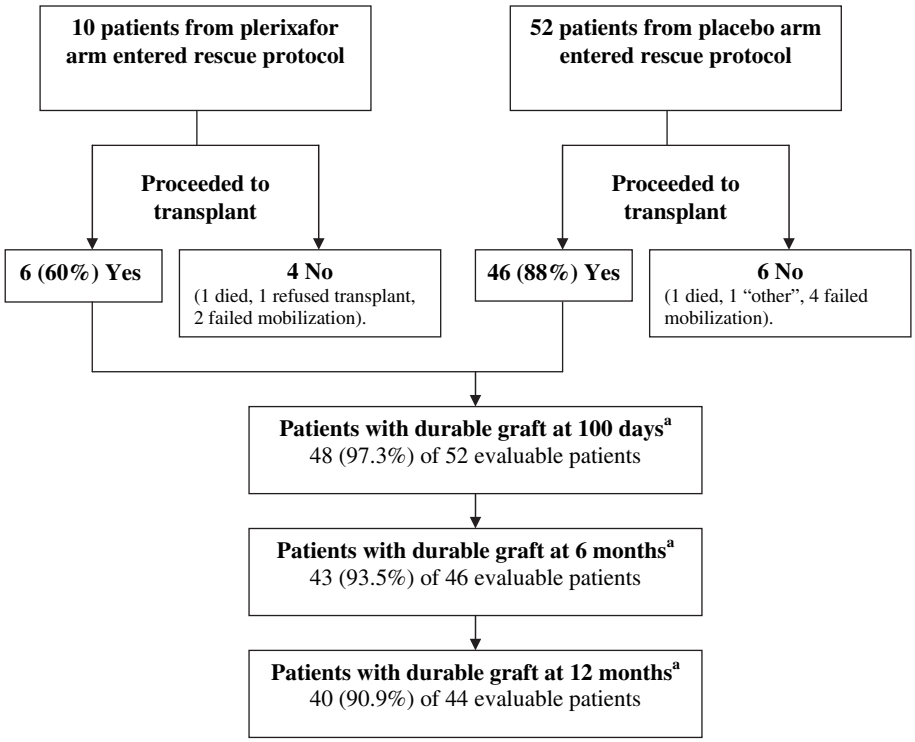


Figure 2. Patient disposition.

Engraftment

Neutrophil engraftment was defined as neutrophil count of $\geq 0.5 \times 10^9$/L for 3 consecutive days or $\geq 1.0 \times 10^9$/L for 1 day. Platelet engraftment was defined as platelet count of $\geq 20 \times 10^9$/L without a transfusion during the preceding 7 days. Graft durability was defined as maintenance of normal blood counts according to at least 2 of the 3 following criteria: platelet count $>50 \times 10^9$/L without transfusion for at least 2 weeks before the follow-up visit, hemoglobin level ≥ 10 g/dL with no erythropoietin support or transfusions for at least 1 month before the follow-up visit, and absolute neutrophil count (ANC) $>1 \times 10^9$/L with no G-CSF treatment for at least 1 week before the follow-up visit. Graft durability was assessed by the investigator at each study site. Patients who achieved, but did not maintain, these blood counts because of other causes (eg, recurrent or progressive disease, renal failure, chronic bleeding, severe infection, drug-induced cytopenia, development of new hematologic problems) were considered to have durable grafts.

Safety

Safety was monitored by the incidence of adverse events (AEs), serious adverse events (SAEs), and changes from baseline in medical history, clinical laboratory measurements (ie, chemistry, hematology including complete blood count with differential, urinalysis, and coagulation), vital sign parameters, and physical examination findings. Safety issues arising during the course of the study were evaluated throughout by an independent Data Safety Monitoring Board.

Statistical Analysis

Descriptive statistics were used to summarize $CD34^+$ cell collections, number of days of apheresis, PB $CD34^+$ cell counts, and days to neutrophil and platelet engraftment. Continuous data are presented as mean, standard deviation, median, minimum, and maximum for treatment assignment in the phase 3 study and overall. All analyses were performed using SAS software (SAS Institute, Cary, NC) and Excel software (Microsoft, Redmond, WA).

RESULTS

Patients

In the parent phase 3 study, 150 patients with NHL were randomized to the plerixafor group and 148 patients were randomized to the placebo group. Eleven of the 150 patients in the plerixafor group (7.3%) and 57 of the 148 patients in the placebo group (38.5%) failed mobilization. Of these 68

Table 1. Patient Demographics and Baseline Characteristics: Medical, Surgery, and Oncology History

	Plerixafor (n=10)	Placebo (n=52)	Total (n=62)
Age, years, mean (SD)	54.6 (13.1)	59.9 (8.8)	59.0 (9.7)
Male, n (%)	7 (70.0%)	36 (69.2%)	43 (69.4%)
Ethnic origin, n (%)			
Caucasian	9 (90.0%)	47 (90.4%)	56 (90.3%)
African-American	0 (0.0%)	1 (1.9%)	1 (1.6%)
Asian	1 (10.0%)	1 (1.9%)	2 (3.2%)
Hispanic/Latino	0 (0.0%)	3 (5.8%)	3 (4.8%)
Time from initial diagnosis to randomization, months, median (range)	18.5 (6 to 136)	15.5 (4 to 95)	15.5 (4 to 136)
Time from most recent progression/ relapse to randomization, months, median (range)	3.5 (3 to 5)	5.0 (2 to 16)	4.0 (2 to 16)
Disease diagnosis, n (%)			
Diffuse large B cell lymphoma	4 (40.0%)	23 (44.2%)	27 (43.5%)
T cell lymphoma	3 (30.0%)	4 (7.7%)	7 (11.3%)
Mantle cell lymphoma	2 (20.0%)	7 (13.5%)	9 (14.5%)
Follicular lymphoma	0 (0.0%)	7 (13.5%)	7 (11.3%)
Other	1 (10.0%)	11 (21.1%)	12 (19.4%)
Disease stage at initial diagnosis, n (%)			
I	1 (10.0%)	3 (5.8%)	4 (6.5%)
II	1 (10.0%)	12 (23.1%)	13 (21.0%)
III	1 (10.0%)	17 (32.7%)	18 (29.0%)
IV	7 (70.0%)	19 (36.5%)	26 (41.9%)
Missing	0 (0.0%)	1 (1.9%)	1 (1.6%)
Disease stage before mobilization, n (%)			
I	0 (0.0%)	6 (11.5%)	6 (9.7%)
II	1 (10.0%)	9 (17.3%)	10 (16.1%)
III	2 (20.0%)	12 (23.1%)	14 (22.6%)
IV	5 (50.0%)	17 (32.7%)	22 (35.5%)
Missing	2 (20.0%)	8 (15.4%)	10 (16.1%)
Remission status before mobilization, n (%)			
First complete remission	3 (30.0%)	9 (17.3%)	12 (19.4%)
First partial remission	3 (30.0%)	5 (9.6 %)	8 (12.9%)
Second complete remission	1 (10.0%)	17 (32.7%)	18 (29.0%)
Second partial remission	3 (30.0%)	21 (40.4%)	24 (38.7%)
Received previous radiotherapy, n (%)	5 (50.0%)	13 (25.0%)	18 (29.0%)

patients, 62 (10 in the plerixafor group and 52 in the placebo group) elected to receive treatment with plerixafor plus G-CSF in the rescue protocol. Patient disposition is shown in Figure 2. The remaining 6 patients achieved yields of 0.31, 0.41, 0.59, 1.42, 1.74, and 2.45 $\times$ 10^6 $CD34^+$ cells/kg in the first mobilization but chose not to enter the rescue protocol. The $CD34^+$ cell yields achieved in the first mobilization for these 6 patients were similar to those achieved by the 62 patients who entered the rescue procedure (median, 0.78 $\times$ 10^6 $CD34^+$ cells/kg; range, 0.03-2.33 $\times$ 10^6 $CD34^+$ cells/kg).

Of the 62 patients who failed the initial mobilization and entered the rescue protocol, 6 (1 from the plerixafor arm and 5 from the placebo arm) either missed a dose of G-CSF or suffered a G-CSF administration error during the first mobilization. The demographic and baseline characteristics of the patients who entered the rescue protocol were similar to those of the overall study population (Table 1). Fifty-two of the 62 patients proceeded to autologous stem cell transplantation (described below). All 52 patients completed 100 days posttransplantation follow-up, 46 of the 52 patients (88.5%) completed a 6-month follow-up, and 44 of the 52 patients (84.6%) completed a 12-month follow-up.

Efficacy

Mobilization

Thirty-seven of the 62 patients in the rescue protocol (59.7%) achieved cumulative yields of $\geq 2 \times 10^6$ $CD34^+$ cells/kg in 4 or fewer days of apheresis, including 4 of 10 (40.0%) previously treated in the plerixafor group and 33 of 52 (63.5%) previously treated in the placebo group (Table 2). The between-group difference with respect to the proportion of responders during rescue was not statistically significant ($P = .11$, Fisher's exact test). In addition, 7 of the 62 patients (11.3%), all of whom were previously treated in the placebo group, achieved $\geq 5 \times 10^6$ cells/kg in 4 or fewer days of apheresis. The overall median cell yield obtained during rescue mobilization with plerixafor was higher than that obtained in the same patients in the first mobilization (2.4×10^6 vs 0.78×10^6 $CD34^+$ cells/kg). The greatest increase was observed in those patients who were first mobilized in the placebo group (median, 2.9×10^6 $CD34^+$ cells/kg).

The $CD34^+$ cell yield by apheresis day for patients in the rescue protocol is depicted in Figure 3. The majority of $CD34^+$ cells were collected during the first and second days of apheresis during the rescue procedure.

Table 2. Mobilization and Transplantation Outcomes

	Plerixafor (n=10)	Placebo (n=52)	Total (n=62)
Number of $CD34^+$ cells collected in first mobilization $\times 10^6$ /kg, median (range)	1.1 (0.03 to 1.9)	0.78 (0.06 to 2.3)	0.78 (0.03 to 2.3)*
Number of $CD34^+$ cells collected in rescue mobilization $\times 10^6$ /kg, median (range)	1.3 (0.01 to 3.4)	2.9 (0.16 to 7.3)	2.4 (0.01 to 7.3)
Number of aphereses in rescue mobilization, median (range)	4 (1 to 4)	3 (1 to 4)	3 (1 to 4)
Number of patients achieving $\geq 2 \times 10^6$ $CD34^+$ cells/kg in 4 or fewer days of apheresis	4 (40.0%)	33 (63.5%)	37 (59.7%)
Number of patients achieving $\geq 5 \times 10^6$ $CD34^+$ cells/kg in 4 or fewer days of apheresis†	0 (0.0%)	7 (13.5%)*	7 (11.3%)
Number of $CD34^+$ cells transplanted $\times 10^6$ /kg, median (range)‡,¶	3.1 (1.1 to 4.3)	3.8 (1.2 to 10.5)	3.8 (1.1 to 10.5)
Number of patients proceeding to transplantation§	6 (60.0%)	46 (88.75%)	52 (83.9%)
Median days to neutrophil engraftment	10	11	11
Median days to platelet engraftment	22	20	20

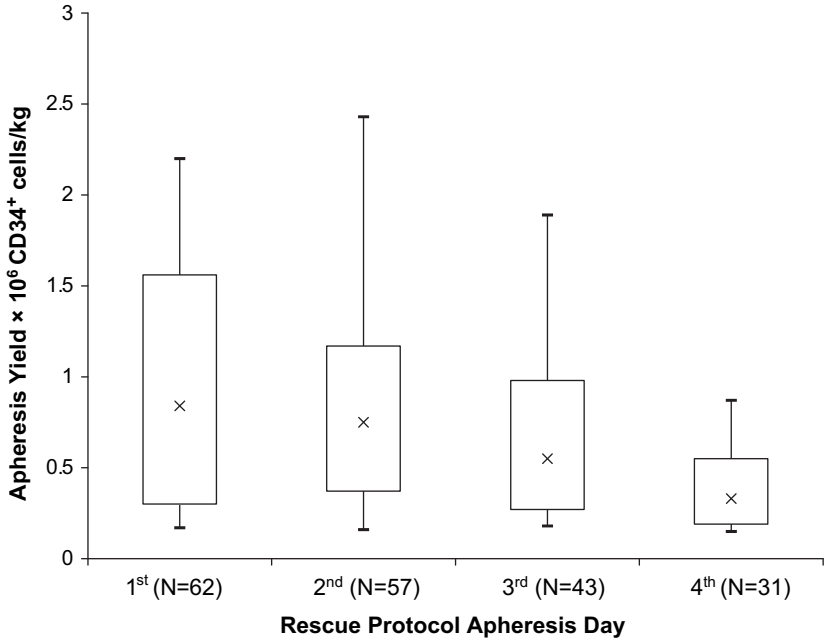
*Three patients entered the rescue procedure based on a $CD34^+$ count of $<2 \times 10^6$ cells/kg as determined by the local laboratory. Calculations performed later by the central laboratory determined the $CD34^+$ counts to be $\geq 2 \times 10^6$ cells/kg, and these results are presented here.
†The 7 patients who collected $\geq 5 \times 10^6$ $CD34^+$ cells/kg compose a subset of patients who collected $\geq 2 \times 10^6$ $CD34^+$ cells/kg.
‡Transplantation data were not available for 10 patients.
§Some patients in both groups received mixed cells for transplantation.
¶Six patients received $<2 \times 10^6$ $CD34^+$ cells/kg, 1 patient through bone marrow harvest.

PB $CD34^+$ cell counts

PB $CD34^+$ cell counts were available for a total of 48 patients, including 9 patients previously treated in the plerixafor group and 39 previously treated in the placebo group. The remaining 14 patients were missing a least one PB $CD34^+$ cell count and thus were excluded from the analysis. The median number of PB $CD34^+$ cells on day 4 (before the first dose of plerixafor in the rescue protocol) was 2.7 cells/μL (range, 0.0-15.6 cells/μL) in the patients previously treated in the plerixafor group and 1.5 cells/μL (range, 0.0-70.2 cells/μL) in those previously treated in the placebo group ($P = .176$). On day 5, 10-11 hours after the first plerixafor dose, the median number of PB $CD34^+$ cells was 4.9 cells/μL (range, 0.0-26.3 cells/μL) in the patients previously treated in the plerixafor group and 11.0 cells/μL (range, 0.0-93.0 cells/μL) in those previously treated in the placebo group ($P = .263$). The median fold increase over the 24-hour period from day 4 to day 5 associated with the first dose of plerixafor was 1.6 (range, 0.4 to 2.0) in patients previously treated in the plerixafor group and 6.7 (range, 0.3 to 23.0) in those previously treated in the placebo group ($P < .001$).

Transplantation and engraftment

Of the 62 rescue patients, 52 (84%) proceeded to transplantation. Generally, the transplanted cells



Note: Error bars represent the 10-90% range, boxes represent the 25%-75% range, "×" represents the median.

Figure 3. $CD34^+$ cell yields by apheresis day.

Table 3. Graft Durability Based on Laboratory Criteria

Time Point Posttransplantaton	Patients With a Durable Graft	Platelet Count $\geq 150 \times 10^9$/L	Platelet Count $\geq 100 \times 10^9$/L	Neutrophil Count $\geq 1.5 \times 10^9$/L	Neutrophil Count $\geq 1.0 \times 10^9$/L
100 days	48/52 (92.3%)	21/47 (44.7%)	32/47 (68.1%)	38/46 (82.6%)	39/46 (84.8%)
6 months	43/46 (93.5%)	21/37 (56.8%)	28/37 (75.7%)	34/37 (91.9%)	37/37 (100.0%)
12 months	40/44 (90.9%)	14/18 (77.8%)	16/18 (88.9%)	18/18 (100.0%)	18/18 (100.0%)

Percentages are based on the overall number of patients with available data at each time point.

consisted of cells combined from the first and rescue mobilizations. Nine patients received cells from the rescue procedure only. Five patients underwent further mobilization with G-CSF alone and/or BM harvest poststudy and received cells combined from the first and rescue mobilizations, plus cells from these subsequent collections. For these 5 patients, the cumulative on-study collections were 1.19, 1.28, 1.49, 1.92, and 1.94×10^6 $CD34^+$ cells/kg. Six patients received a transplant containing $<2 \times 10^6$ $CD34^+$ cells/kg (minimum, 1.14×10^6 $CD34^+$ cells /kg). Of the 10 patients who did not undergo transplantation, 6 (2 previously treated in the plerixafor group and 4 previously treated in the placebo group) failed to mobilize sufficient cells to proceed to transplantation, and the remaining 4 (2 previously treated in the plerixafor group and 2 previously treated in the placebo group) withdrew from the study before completing mobilization and HSC collection (1 elective withdrawal, 2 deaths because of progressive disease, and 1 "other;" details not provided).

The median time to neutrophil engraftment was 11 days in all patients (Table 2). Fifty of the 52 patients (96.2%) achieved successful platelet engraftment, with a median time to platelet engraftment of 20 days. Of the 2 patients who did not achieve platelet engraftment, 1 patient achieved a total yield of 1.25×10^6 $CD34^+$ cells/kg during the rescue procedure and 0.06×10^6 $CD34^+$ cells/kg during the initial phase 3 study and received a total of 2.81×10^6 $CD34^+$ cells/kg, combined from both collections plus cells from off-study collection. This patient died from multisystem organ failure 11 days after transplantation. The second patient experienced a delay in platelet recovery as a consequence of a severe infection. This patient received cells combined from rescue and first collections (5.78×10^6 $CD34^+$ and 0.73×10^6 $CD34^+$ cells/kg, respectively). After transplantation, the patient was admitted to the hospital for a small bowel obstruction and subsequently experienced a septic episode. The patient underwent surgery to resolve the bowel obstruction and received antibiotic treatment for *Clostridium difficile* colitis. This patient survived and met platelet engraftment criteria approximately 10 months after transplantation.

Graft durability

Graft durability was assessed at 100 days, 6 months, and 12 months posttransplantation. The proportion of patients who maintained a durable graft based on laboratory criteria and achieved threshold platelet and neutrophil counts is summarized in Table 3. Based on laboratory criteria alone, 9 patients did not meet the hematologic criteria for graft durability at 1 or more time points. At 100 days posttransplantation, 48 of the 52 patients had durable grafts, 3 patients did not meet the hematologic criteria for graft durability, and 1 patient died before the visit. At 6 months posttransplantation, 46 patients were evaluable, and 3 patients did not meet the criteria for graft durability. At 12 months posttransplantation, 44 patients were evaluable, and 4 patients did not meet the criteria for graft durability. Collectively, of the 9 patients who did not meet the criteria for graft durability, 3 died before laboratory analysis and 6 were considered to have durable grafts based on investigator assessment at last available follow-up or before death from disease progression. Based on a combination of laboratory and clinical criteria and investigator evaluation, no patient was considered to have graft failure.

Patient survival

At the last recorded follow-up (52 patients evaluated at 100 days, 46 patients evaluated at 6 months, and 44 patients evaluated at 12 months posttransplantation), 53 of the 62 rescue patients (85.5%) were alive. Nine rescue patients died (2 previously treated in the plerixafor group and 7 previously treated in the placebo group). Two deaths, 1 from each treatment group, occurred following mobilization and HSC collection, with the patients not proceeding to transplantation. Both of these deaths resulted from disease progression. The remaining 7 deaths occurred after transplantation (range, 2-45 weeks posttransplantation) and were due to disease progression in 1 patient, respiratory failure secondary to disease progression in 1 patient, relapse in 2 patients, multiple infections and septic shock in 1 patient (who was considered to have a durable graft before these events), and multisystem organ failure in 2 patients. The 1-year posttransplantation survival for the patients entered on rescue was similar to that in the entire phase 3 group.

Safety

Adverse events

Overall, the safety findings for the patients treated in the rescue protocol were consistent with those of the overall phase 3 study population. During the period of

Table 4. AEs Experienced by≥10% of Patients during Mobilization, Treatment, and Apheresis

AE, n (%)	Plerixafor (n = 10)	Placebo (n = 52)	Total (n = 62)
Any AE	10 (100.0)	49 (94.2)	59 (95.2)
Diarrhea	6 (60.0)	21 (40.4)	27 (43.5)
Injection site erythema	4 (40.0)	17 (32.7)	21 (33.9)
Bone pain	2 (20.0)	16 (30.8)	18 (29.0)
Nausea	2 (20.0)	16 (30.8)	18 (29.0)
Paresthesia	4 (40.0)	11 (21.2)	15 (24.2)
Headache	1 (10.0)	13 (25.0)	14 (22.6)
Hypokalemia	1 (10.0)	10 (19.2)	11 (17.7)
Vomiting	1 (10.0)	8 (15.4)	9 (14.5)
Arthralgia	1 (10.0)	7 (13.5)	8 (12.9)
Back pain	3 (30.0)	4 (7.7)	7 (11.3)
Fatigue	0 (0.0)	7 (13.5)	7 (11.3)
Injection site pruritus	2 (20.0)	5 (9.6)	7 (11.3)
Paresthesia oral	1 (10.0)	6 (11.5)	7 (11.3)
Hypomagnesemia	1 (10.0)	5 (9.6)	6 (9.7)*
Muscle spasms	1 (10.0)	5 (9.6)	6 (9.7)*
Pain	1 (10.0)	5 (9.6)	6 (9.7)*

AE indicates adverse events.
*Rounded to 10% for the purpose of this table.

treatment, mobilization, and apheresis, 59 of the 62 rescue patients (95.2%) experienced at least 1 AE considered to be related to the study treatment (Table 4). The most common drug-related AEs occurring during this period, in descending order, were diarrhea (43.5%), injection site erythema (33.9%), bone pain (29.0%), nausea (29.0%), headache (29.0%), and paresthesias (24.2%). Most of the AEs related to the study treatment were mild or moderate. There were no life-threatening AEs.

Ten patients received 2 treatment cycles of plerixafor (median, 7 doses; range, 3-8 doses), with the first treatment cycle as part of the blinded study period and the second treatment cycle as part of the rescue protocol. The AE profiles for these patients were similar for each treatment and included injection site reactions, gastrointestinal effects, paresthesias, and headache. Almost all of these AEs were mild, and none was severe. No increased incidence or severity of these AEs was apparent during the second plerixafor treatment cycle.

Serious adverse events

A total of 44 SAEs were experienced by 22 of the 62 patients (35.5%). The most common SAEs—atrial fibrillation (3 patients), mucositis (2 patients), and hypotension (2 patients)—occurred after mobilization, following the myeloablative chemotherapy. None of these SAEs was related to the study treatment.

Adverse events leading to discontinuation of study treatment or study withdrawal

Four patients did not complete the rescue procedure because of AEs or withdrawal from the study. One patient received 4 doses of plerixafor during the first mobilization and then entered the rescue protocol. This patient experienced bone pain, headache, nausea, and vomiting, considered to be related to the study treatment; he discontinued plerixafor treatment after 1 dose in the rescue protocol, but subsequently proceeded to transplantation and completed the study. One patient experienced progression of NHL and sepsis considered to be unrelated to the study treatment and died before completion of mobilization and apheresis. Two other patients withdrew from the study during the mobilization period, but not because of AEs (1 elective withdrawal and 1 "other").

DISCUSSION

Our data demonstrate that of the 62 patients who entered the rescue protocol, 52 (83.9%) could proceed to transplantation after remobilization with plerixafor plus G-CSF. Patients who were initially mobilized with G-CSF alone in the placebo group of the phase 3 study had the best response to remobilization with plerixafor plus G-CSF: 4 of 10 (40.0%) in the plerixafor group and 33 of 52 (63.5%) in the placebo group achieved $\geq 2 \times 10^6$ $CD34^+$ cells/kg in 4 or fewer days of apheresis. Patients previously treated in the placebo group (7/52 13.5%) achieved cumulative yields of $\geq 5 \times 10^6$ $CD34^+$ cells/kg. This was likely because of the fold increase in PB $CD34^+$ cell count, which was not significant in the patients previously treated in the plerixafor group but was a mean of 7.9-fold in those previously treated in the placebo group. Six of 10 patients (60.0%) previously treated in the plerixafor group and 46 of 52 patients (88.75%) previously treated in the placebo group proceeded to transplantation, indicating that mobilization with plerixafor plus G-CSF increased the number of patients who achieved sufficient cell collections to proceed to transplantation, both as an initial therapy and during remobilization.

Of note, the baseline characteristics were similar in the patients in the rescue protocol and the overall phase 3 study population, suggesting that demographics, time from disease diagnosis, time from disease progression, disease stage, remission status, prior surgery, prior chemotherapy, and prior radiotherapy may not accurately predict mobilization failure in this population. The majority of patients (45/52; 86.5%) mobilized with G-CSF alone in the placebo group achieved a greater median yield of $CD34^+$ cells/kg during rescue mobilization (2.9×10^6 cells/kg) than in the first mobilization (0.78×10^6 cells/kg). Thus, the contribution to the pool of cells available for transplantation was generally greater from mobilization with plerixafor plus G-CSF than from mobilization with G-CSF alone. Forty percent of the patients who failed their first mobilization in the plerixafor group achieved sufficient cell yields for transplantation following mobilization on the rescue protocol. These patients received

a median of 7 doses of plerixafor combined from the first mobilization and the rescue protocol. These results illustrate that remobilization with plerixafor plus G-CSF still had some benefit when the original mobilization regimen included plerixafor, and that a 1-week recovery period between first and second mobilizations seemed to be effective for subsequent collections.

The majority of patients underwent successful transplantation following the rescue procedure. Nine of the 52 patients (17.3%) received cells from the rescue procedure only; the remaining patients received cells combined from the first and rescue mobilizations, plus cells from subsequent off-study collections in 5 cases. Despite the various cell sources, time to engraftment and graft durability were not markedly different between the patients in the rescue protocol and the overall study population. Transplantation with cells collected during the rescue protocol resulted in comparable rates of engraftment and graft durability as transplantation using cells from a single mobilization. This indicates that the quality of cells collected in the rescue protocol was similar to that of cells collected in the parent phase 3 study. In addition, hematologic data (ie, neutrophil counts, platelet counts, and hemoglobin) were similar between the rescue patients and patients in the parent phase 3 study at 100 days, 6 months, and 12 months posttransplantation. Engraftment of cells collected during the rescue procedure was timely and durable. Neutrophil engraftment was observed for all patients, and platelet engraftment was observed for all but 2 patients, both of whom experienced complications after transplantation.

Previous studies of mobilization with G-CSF alone in patients with NHL have shown that 50%-90% achieve sufficient cell collections for transplantation in the first mobilization [4,14,15]. Remobilization strategies including high-dose G-CSF, G-CSF plus GM-CSF, and G-CSF plus chemotherapy produce success rates of 24%-65%, depending on the definition of failure and on whether or not the subsequent mobilizations were pooled [4,8,10,16]. In the pivotal phase II study, the washout period ranged from 13 to 17 days from the time the first set of mobilizing cytokines was completed until the second set of mobilizing cytokines was initiated [2]. This interval seemed to be safe and effective for stem cell mobilization. Lefrere et al. [16] reported successful remobilization with high-dose G-CSF after a 7-day rest period in patients who failed chemomobilization. Thus, in the present study, a 7-day period was chosen based on a combination of clinical experience in earlier plerixafor studies, published literature, and the desire to keep the overall treatment period as short as possible.

In this study, we found a remobilization success rate of 63.5% in a median of 3 aphereses using plerixafor plus G-CSF following failed mobilization with G-CSF alone. This finding indicates that remobilization with plerixafor plus G-CSF is an efficient and effective method of collecting HSCs in patients who previously failed mobilization. These results are similar to those from previous studies of compassionate use of plerixafor, in which a diverse patient population (including those with NHL) was remobilized after failed mobilization with conventional cytokine and/or chemotherapy [16,17]. Entry into the compassionate use protocol (CUP) was limited to patients who had previously failed to proceed from mobilization to apheresis because of a low peripheral blood $CD34^+$ cell count (usually $\leq$10 cells/μL) or because of an initial apheresis yield below the minimum amount for transplantation, usually 2×10^6 $CD34^+$ cells/kg. In almost all cases, this assessment was made based on the first apheresis after mobilization. The median time between mobilization failure and treatment in the CUP was approximately 1 month. Some 60% of patients with NHL achieved a cumulative yield of $\geq 2 \times 10^6$ $CD34^+$ cells/kg in the CUP from a median of 3 aphereses [16]. The results of remobilization studies, including the CUP study, are typically confounded by such factors as the lack of a well-defined patient population with any strict inclusion/exclusion criteria and the lack of a consistent definition of poor mobilization. But the rescue protocol data presented here permit evaluation of remobilization in a well-defined population of patients with NHL. The rate of successful remobilization with plerixafor plus G-CSF following failed mobilization with G-CSF alone was 63.5%; this is consistent with the rate from the CUP study and superior to most successful remobilization rates from G-CSF, other cytokines, chemotherapy, and other investigational agents. In addition, mobilization of HSCs with plerixafor plus G-CSF carries no unexpected safety concerns.

In conclusion, in the phase 3 study, plerixafor plus G-CSF was shown to be a more effective regimen than G-CSF alone for initial mobilization in NHL patients. The rescue protocol demonstrates that remobilization with plerixafor plus G-CSF also has a benefit for a large proportion of failed mobilizers.

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