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ORIGINAL ARTICLE

Safety and preliminary efficacy of plerixafor (Mozobil) in combination with chemotherapy and G-CSF: an open-label, multicenter, exploratory trial in patients with multiple myeloma and non-Hodgkin's lymphoma undergoing stem cell mobilization

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Plerixafor, a novel CXCR4 inhibitor, is effective in mobilizing PBSCs particularly when used in conjunction with G-CSF. In four cohorts, this pilot study explored the safety of plerixafor mobilization when incorporated into a conventional stem cell mobilization regimen of chemotherapy and G-CSF. Forty (26 multiple myeloma and 14 non-Hodgkin's lymphoma) patients were treated with plerixafor. Plerixafor was well tolerated and its addition to a chemo-mobilization regimen resulted in an increase in the peripheral blood CD34+ cells. The mean rate of increase in the peripheral blood CD34+ cells was 2.8 cells/μl/h pre- and 13.3 cells/μl/h post-plerixafor administration. Engraftment parameters were acceptable after myeloblative chemotherapy, with the median day for neutrophil and plt engraftment being day 11 (range 8–20 days) and day 13 (range 7–77 days), respectively. The data obtained from the analysis of the cohorts suggest that plerixafor can safely be added to chemotherapy-based mobilization regimens and may accelerate the rate of increase in CD34+ cells on the second day of apheresis. Further studies are warranted to evaluate the effect of plerixafor in combination with chemomobilization on stem cell mobilization and collection on the first and subsequent days of apheresis, and its impact on resource utilization.
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Introduction

Plerixafor is a reversible inhibitor of the binding of SDF-l-α to its cognate receptor CXCR4. Early studies with plerixafor showed enhancement of circulating WBCs and PBSCs in healthy volunteers.[1–4] Flomenberg *et al.*[5] showed the superiority of plerixafor plus G-CSF over G-CSF alone for PBSC mobilization in patients with multiple myeloma (MM) and non-Hodgkin's lymphoma (NHL). When apheresis yields for the same patient were compared between plerixafor plus G-CSF and G-CSF alone, more CD34+ cells were collected with plerixafor plus G-CSF and in fewer apheresis days than with G-CSF alone.[6] These data led to two phase 3 multicenter, randomized, placebo-controlled studies that showed the efficacy of plerixafor plus G-CSF compared with G-CSF alone in patients with NHL and MM undergoing stem cell mobilization for auto-SCT).[7–10]

Chemotherapy plus G-CSF is an alternative PBSC mobilization strategy for use in patients undergoing auto-SCT. The addition of plerixafor to a chemotherapy and G-CSF mobilization regimen could provide advantages by increasing the number of PBSCs per apheresis collection and thereby decreasing the number of apheresis procedures required to collect an adequate number of PBSCs for transplantation. The primary aim of this feasibility study was to determine whether plerixafor given after mobilization with chemotherapy and G-CSF is safe and well tolerated. The secondary objectives of this study were: (i) to determine whether, in patients with MM or NHL, adding plerixafor to a chemotherapy and G-CSF mobilization regimen could increase the circulating levels of PBSCs by ⩾twofold, resulting in higher apheresis yields, and (ii) to determine the time to neutrophil and plt engraftment after autologous transplantation of the chemotherapy, G-CSF and plerixafor-mobilized PBSCs.

Materials and methods

Study design

This was a prospective, multicenter, open-label, sequential design pilot study conducted to evaluate the safety and feasibility of combining plerixafor with chemotherapy.

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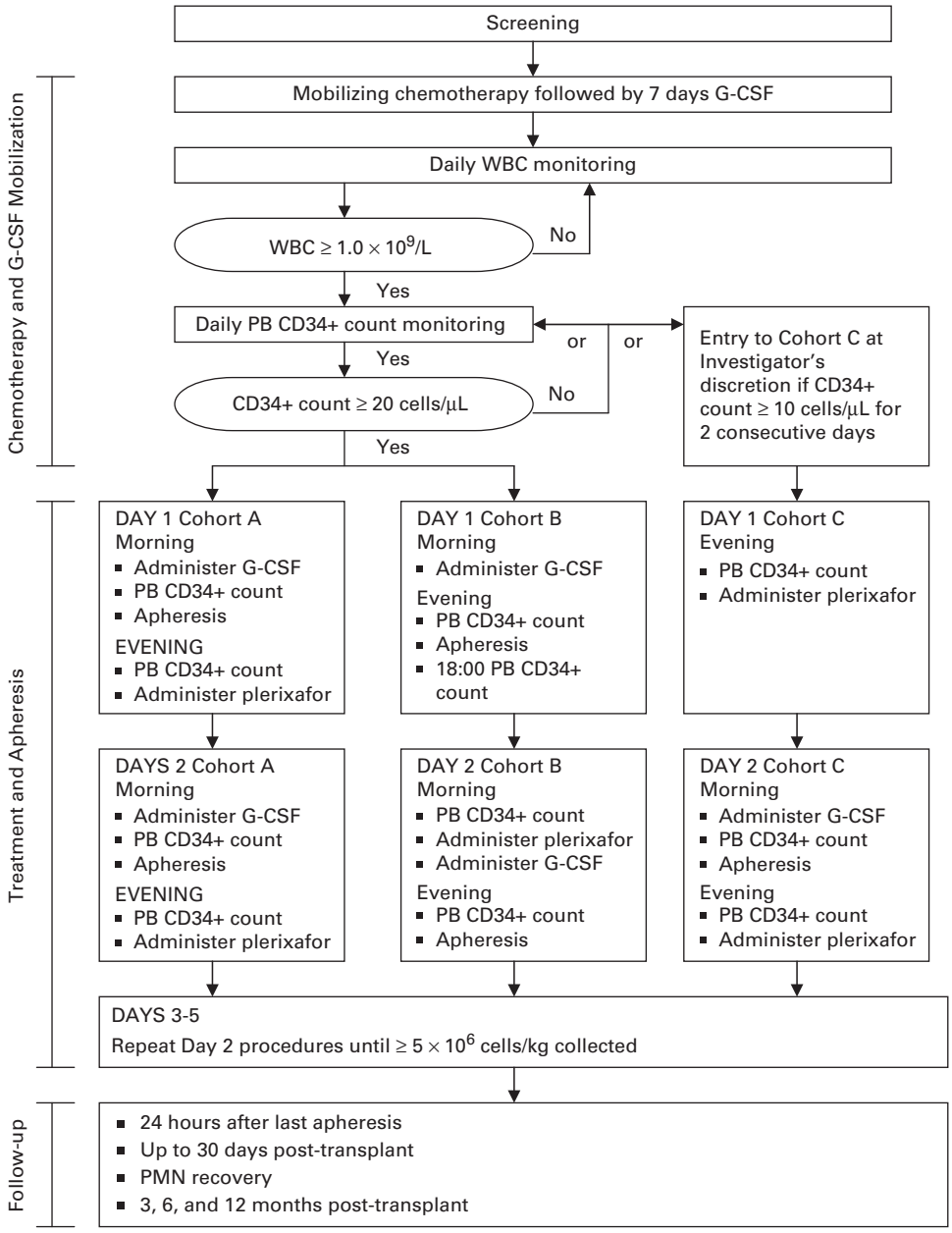

Figure 1 Cohorts A, B and C study schema.

Patients with MM or NHL who received a mobilizing regimen of chemotherapy and G-CSF to facilitate collection of PBSCs for autologous transplantation were eligible to participate in this protocol. To understand the effects of plerixafor after mobilization with chemotherapy and G-CSF, the study had to be conducted in four different cohorts (Figures 1 and 2). The principal goal of all four cohorts was to assess the safety of adding plerixafor to the combination of chemotherapy and G-CSF. Patients were not randomized to a specific cohort; rather, the study was conducted in a sequential manner. The aim of Cohort A was to show whether the addition of plerixafor to mobilization with chemotherapy and G-CSF resulted in enhanced CD34+ cell collection. To determine whether the enhanced collection was due to plerixafor or the delayed effects of chemotherapy, Cohort B was designed to assess the relative contribution of plerixafor administration to chemotherapy plus G-CSF treatment. Enrollment in Cohort A was completed first before enrollment in Cohort B began. Cohort C evaluated the safety and efficacy of plerixafor as a rescue regimen for patients who failed mobilization with chemotherapy and G-CSF. Cohort D was designed at one institution to explore the potential role of plerixafor to accelerate the time to PBSC collection after WBC recovery from chemotherapy and G-CSF mobilization.

Study patients

Patients were accepted on an IRB-approved study for stem cell mobilization and transplantation was an independent

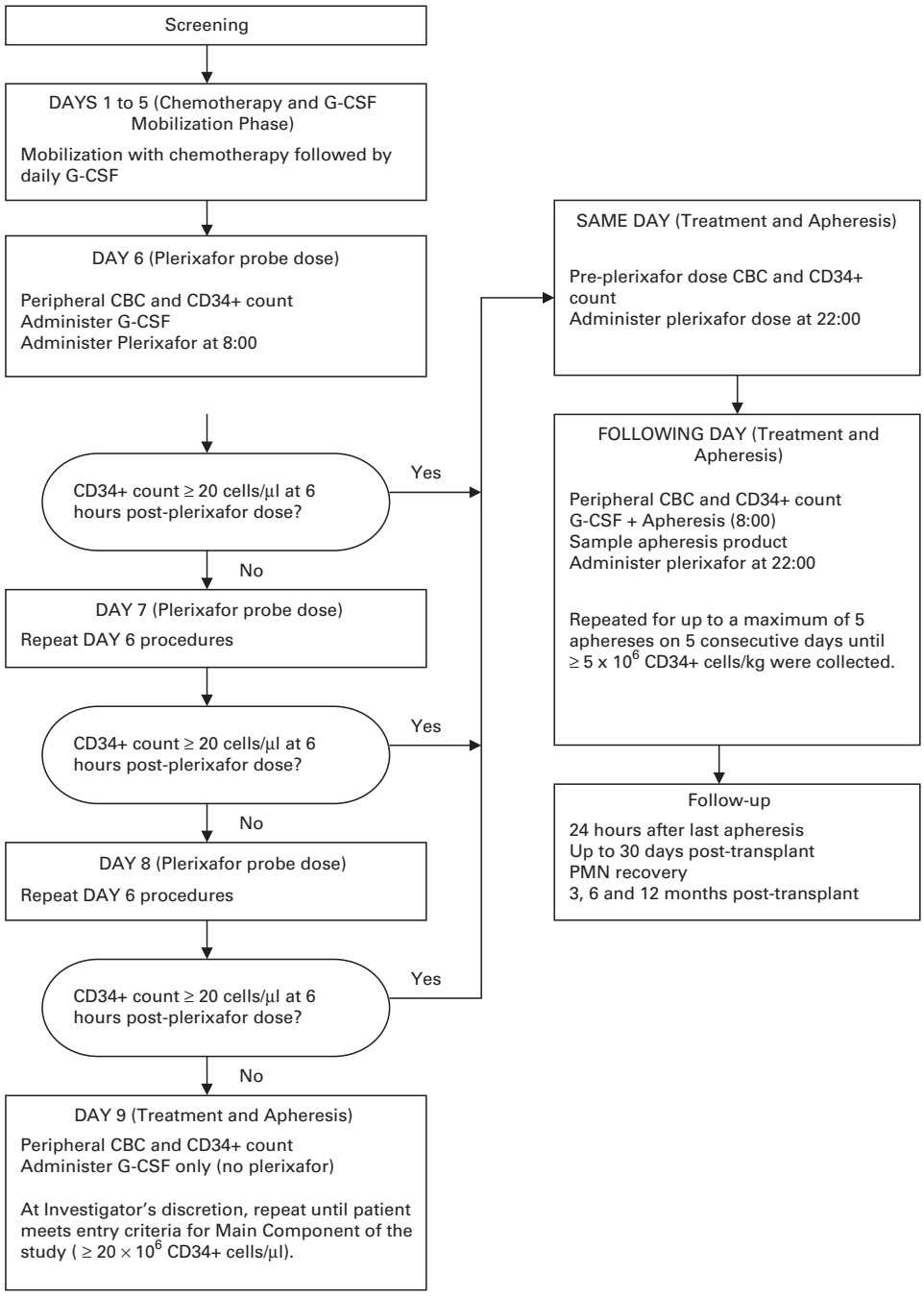

Figure 2 Investigational cohort (Cohort D) study schema.

consent visit. Patients with MM were included if they had stable disease, in first partial response/complete response, and in first relapse or second partial/complete response with $<40\%$ BM involvement. Patients with NHL were included if they were in first or second partial or CR without BM involvement, or $<10\%$ involvement for follicular lymphoma. Other inclusion criteria for all patients were age 18–70 years, no more than three previous regimens of chemotherapy, ECOG performance status of 0 or 1, WBC $>3.0\times10^9$/l, ANC $>1.5\times10^9$/l, plt $>100\times10^9$/l, creatinine clearance >60 ml/min for NHL patients or >40 ml/min for MM patients, normal liver enzymes, LVEF $>45\%$, FEV_1 $>60\%$ of predicted or DLCO $>45\%$ of predicted, negative for HIV, and women of child-bearing potential had agreed to use an approved form of contraception. Exclusion criteria were any comorbid conditions that rendered the patient at high risk from treatment complications, a residual acute medical condition resulting from earlier chemotherapy, brain metastases or carcinomatous meningitis, acute infection, fever, hypercalcemia, $\geqslant$grade 2 paresthesias, cardiovascular disease including proven or predisposition to ventricular arrhythmias, active

infection with hepatitis B or C, positive pregnancy test in female patients, lactating females, actual body weight >175% of their ideal body weight and experimental therapy within 4 weeks of enrollment.

Mobilization regimen

The selection of the chemotherapy mobilization regimen was per institutional preference based on disease. The institution's mobilization practice was not altered for this study except for the addition of plerixafor. G-CSF was administered s.c. at 10 μg/kg/day after chemotherapy until the day before the last day of apheresis. All patients received plerixafor 0.24 mg/kg/day s.c. for up to 5 days. In all cohorts, except for Cohort D, PBSC collection commenced the day after the peripheral blood CD34+ cell count reached ⩾20 cells/μl. The goal was to process 3 blood volumes per apheresis procedure.

In Cohort A, on the evening following the first apheresis collection, the patient returned to the transplant center at ~22:00 hours to receive plerixafor. The second apheresis procedure began 10–11 h after the plerixafor dose. The peripheral blood CD34+ cell counts were measured before the first apheresis, immediately before the plerixafor dose and before the second apheresis.

In Cohort B, patients received plerixafor on the morning of the second day of apheresis and apheresis began 6 h later. The rate of change in the peripheral blood CD34+ cells was calculated for two time periods; one was after the first apheresis but before the first plerixafor dose and the second was after the first plerixafor dose to the time of the second apheresis.

In Cohort C, patients were enrolled when the peripheral blood CD34+ cell count was ⩾10/μl but ⩽20/μl on two consecutive days. Plerixafor was administered on the evening before the first day of apheresis. Cohort C provided a rescue procedure for patients in Cohort A or Cohort B who did not proceed to apheresis due to low peripheral blood CD34+ cell counts.

In Cohort D, patients received mobilizing chemotherapy and G-CSF (10 μg/kg/day s.c.). After the completion of chemotherapy, patients received G-CSF (10 μg/kg/day s.c.) for five consecutive days. Starting on the 6th day after chemotherapy and before WBC recovery, patients received daily injections of G-CSF (10 μg/kg/day s.c.) and 'probe doses' of plerixafor (0.24 mg/kg/day s.c.) for up to three consecutive days. Patients who achieved a peripheral blood CD34+ cell count of ⩾20 cells/μl at ~6 h after the plerixafor dose would receive another dose of plerixafor in the evening of the same day and begin apheresis the next day. This was performed daily on days 6, 7 and 8 after chemotherapy. Patients who did not achieve a CD34+ cell count of ⩾20 cells/μl 6 h after any of the three plerixafor probe doses reverted to the procedure for Cohort A.

Transplantation

PBSCs collected on all aphereses days were infused after high-dose chemotherapy. Post-transplant G-CSF was given at 5 μg/kg/day per institutional standard until neutrophil engraftment using institutional standard definitions, but was generally defined as the first of two to three consecutive days of ANC ⩾500/mm^3. Tandem transplantation, two transplant procedures performed 3–6 months apart, was allowed for patients with MM.

Study endpoints

The primary end point in all cohorts was safety. All adverse events (AEs) were coded to a standard set of terms using the MedDRA version 10 AE dictionary. Safety data are reported for Period 1 defined as the time from the first day of G-CSF mobilization to the day before chemotherapy/ablative treatment in preparation of first transplant.

In Cohorts A and B, the secondary end point was the mean fold increase in CD34+ cells/kg between the first and second apheresis. For patients in Cohort B, as plerixafor was administered for the first time after the first apheresis, the rate of increase in the number of peripheral blood CD34+ cells was calculated both before and after the administration of plerixafor. The secondary end point in Cohort C was to determine the efficacy of plerixafor as a rescue mobilization agent for patients who failed chemotherapy and G-CSF. The secondary end point in Cohort D was to explore the potential role of plerixafor to accelerate the time to collection before WBC recovery. All cohorts were evaluated for post-transplant engraftment. Graft durability was defined as the maintenance of normal blood counts at 3, 6 and 12 months after transplant.

Statistical analysis

The results of this study are purely exploratory in nature and will be used to provide information on designing future studies. As such, there were no specific sample size requirements for this study. Efficacy analysis was carried out for patients who received plerixafor. For rate of change calculations, patients with missing peripheral blood CD34+ determinations were excluded. Patients with major protocol deviations, such as differing blood volumes processed during the first and second apheresis procedures, were excluded from the CD34+ yield analysis. Thus, the efficacy population is best described as per protocol population.

Results

Patient demographics and characteristics

The study was conducted from April 2004 to July 2006. A total of 44 patients were enrolled and 40 patients received plerixafor. Three patients in Cohort A collected sufficient cells for transplant from the first apheresis and did not receive plerixafor or proceed to the second day of apheresis. One patient in Cohort B elected to withdraw after the first apheresis and did not receive plerixafor. Of the 40 patients who received plerixafor, there were 26 patients with MM and 14 with NHL. There were 19 patients in Cohort A, 15 in Cohort B, one in Cohort C and five in Cohort D. Patient demographics and baseline characteristics of the 40 patients receiving plerixafor are summarized in Table 1.

Safety assessment

Of the 40 patients studied, 39 (97.5%) experienced at least one AE. Adverse events were graded as mild, moderate and

Table 1 Patient demographics and baseline characteristics

Demographics	*Multiple myeloma*				*Non-Hodgkin's lymphoma*			*All patients* (n = 40)
	Cohort A (n = 12)	*Cohort B* (n = 9)	*Cohort C* (n = 1)	*Cohort D* (n = 4)	*Cohort A* (n = 7)	*Cohort B* (n = 6)	*Cohort D* (n = 1)	
Female	6	4	1	0	4	4	0	19 (48%)
Male	6	5	0	4	3	2	1	21 (52%)
Age, median (range)	57 (44–70)	54 (48–70)	55	53 (50–68)	59 (30–66)	50 (43–63)	70.0	56 (30–70)
Characteristics	*Multiple myeloma* (n = 26)				*Non-Hodgkin's lymphoma* (n = 14)			*All patients* (n = 40)
Stage at study entry								
I	4 (15%)				0 (0%)			4 (10%)
II	5 (19%)				4 (29%)			9 (23%)
III	16 (62%)				2 (14%)			18 (45%)
IV	0 (0%)				8 (57%)			8 (20%)
Months since diagnosis	6.5 (3–40)				17.5 (2–134)			9 (2–134)
Months since progression/relapse	5.5 (5–6)				2.5 (2–33)			3 (2–33)
Earlier chemotherapy, median number of prior cycles (range)	26 (100%), 4 (2–6)				14 (100%), 8 (3–10)			40 (100%)
Earlier radiotherapy	11 (42%)				3 (21%)			14 (35%)
Chemotherapy use for mobilization	CY (*n* = 19); CY/etoposide with dexamethasone (*n* = 7)				Rituximab, etoposide, carboplatin, ifosfamide (RICE) (*n* = 8); etoposide, carboplatin, ifosfamide (ICE) (*n* = 2); rituximab, etoposide, cisplatin, methylprednisolone, cytarabine (RESHAP) (*n* = 3); etoposide, cisplatin, methylprednisolone, cytarabine (ESHAP) (*n* = 1).			

severe. In Period 1, 16 patients (41.0%) experienced AEs of mild intensity, 16 (41.0%) experienced AEs of moderate intensity and seven (18.0%) experienced AEs of severe intensity. In this period, only one patient (2.5%) experienced AEs that were considered life threatening. Twenty-four patients (60%) experienced AEs that were considered to be related to the study treatment, the majority of which were mild in severity (Table 2). Three patients experienced study treatment-related AEs that were moderate or severe in intensity, two of whom discontinued study treatment because of the AE: one patient experienced severe back pain, considered to be definitely related to the study drug, and the second patient experienced severe anxiety that was considered to be part of an acute systemic reaction possibly related to the study drug. This latter reaction occurred within 1 h of plerixafor injection and required medical follow-up with nasal oxygen for mild hypoxia. The patient continued with the apheresis the next morning.

Common adverse events that occurred within 30 days after the administration of plerixafor and before chemoablation and transplantation included nausea, diarrhea, injection site reactions, bone pain, paresthesias, headache and dizziness. A summary of adverse events considered possibly, probably or definitely related to the study treatment that occurred in Period 1 is shown in Table 2. Six patients experienced serious adverse events (SAEs) during the study treatment period. Five of these patients experienced SAEs of neutropenia starting before the first dose of plerixafor. Twenty-four days after the patient received plerixafor, the sixth patient experienced SAEs of neutropenia and staphylococcal sepsis immediately after salvage chemotherapy. The combination of plerixafor with chemotherapy did not result in massive leukocytosis resulting in adverse events related to the circulatory system. Complications such as infections during the mobilization phase were attributed to the residual effects of chemotherapy and not necessarily secondary to the administration of plerixafor.

No deaths occurred during the study period treatment period. One patient died approximately 9 months after transplant because of disease progression.

Peripheral blood CD34+ cell counts

In Cohort B, the rate of increase in the peripheral blood CD34+ cells was calculated on an hourly basis before and after the administration of plerixafor for 11 patients (six MM and five NHL) who received plerixafor and had peripheral blood CD34+ counts measured according to the protocol. The rate of change of peripheral blood CD34+ cells per hour is shown alongside the apheresis yield for the first (pre-plerixafor) and second (post-plerixafor) days of apheresis in Table 3. For all six out of six (100%) MM and two out of five (40%) NHL patients, the rate of increase of peripheral blood CD34+ cells after plerixafor administration was greater than before plerixafor administration. For the entire group of 11 patients, the mean rate of increase in the peripheral blood CD34+ cells was 2.8 cells/μl/h pre- and 13.3 cells/μl/h after plerixafor administration. Table 4 shows the peripheral blood CD34+ cell count pre- and post-plerixafor of Cohorts A and B. The overall median n-fold increase, calculated as

the ratio of peripheral blood CD34+ cell/μl following plerixafor and peripheral blood CD34+ cell/μl before plerixafor, was 1.7 in both Cohorts A and B.

Table 2 Adverse events experienced by ⩾two patients considered related to study treatment

Adverse events	*All patients* n *(%)*
Gastrointestinal disorders	13 (32.5%)
Nausea	8 (20.0%)
Diarrhea	6 (15.0%)
Flatulence	2 (5.0%)
Hypoesthesia oral	2 (5.0%)
General disorders and administration site conditions	11 (27.5%)
Injection site erythema	5 (12.5%)
Nervous system disorders	9 (22.5%)
Headache	4 (10.0%)
Paresthesia	4 (10.0%)
Dizziness	2 (5.0%)
Psychiatric disorders	3 (7.5%)
Anxiety	2 (5.0%)
Eye disorders	2 (5.0%)

Apheresis CD34+ cell yields

Apheresis yields are presented in Figure 3 for Cohorts A and B. In both cohorts, the first apheresis was performed pre-plerixafor and the second was performed post-plerixafor. A total of 34 patients received plerixafor in Cohorts A and B. The mean fold increase in CD34+ cells/kg between the first and second apheresis was 2.06. For Cohorts A and B, the mean fold increases were 1.85 ($n=19$) and 2.32 ($n=15$), respectively. The mean fold increase in CD34+ cells/kg collected was 2.00 for MM patients ($n=21$) and 2.15 for NHL patients ($n=13$).

Only one patient did not reach the threshold peripheral blood CD34+ cell count of 20 cells/μl after chemotherapy mobilization. The patient had a peak peripheral blood CD34+ cell count of 9 cells/μl, which declined to 1 cell/μl before plerixafor treatment in Cohort C. After the first dose of plerixafor, the peripheral blood CD34+ cells increased to 24 cells/μl and 2.75×10^6 CD34+ cells/kg were collected by apheresis; a second dose of plerixafor was administered and 2.48×10^6 CD34+ cells/kg were collected, resulting in a total collection of 5.23×10^6 CD34+ cells/kg.

Table 3 Apheresis yields and rate of change in the peripheral blood (PB) CD34+ cell count on day 1 and day 2 in cohort B

Disease group	*Patient*	*Day 1 (pre-plerixafor)*		*Day 2 (post-plerixafor)*	
		Apheresis yield/ 10^6 cells/kg	*Rate of change in PB CD34+ cells/μl/hour*	*Apheresis yield/ 10^6 cells/kg*	*Rate of change in PB CD34+ cells/μl/hour*
MM	1	13.8	3.0	25.4	Not available
MM	2	11.5	4.7	19.6	Not available
MM	3	6.9	3.6	23.5	21.1
MM	4	14.3	3.5	24.1	16.7
MM	5	64.23	6.9	69.57	10.4
MM	6	7.54	6.5	18.23	20.8
MM	7	3.92	Not available	15.48	25.5
MM	8	11.91	−2.1	11.98	15.8
MM	9	5.5	−0.1	10.29	10.3
NHL	10	1.61	0.5	1.35	−0.5
NHL	11	5.46	2.3	11.8	−0.5
NHL	12	32.09	2.2	20.98	1.4
NHL	13	4.99	Not available	9.02	ND
NHL	14	4.02	1.2	6.38	8.7
NHL	15	4.79	4.7	41.85	29.8

Abbreviations: MM = multiple myeloma; NHL = non-Hodgkin's lymphoma; ND = not determined.

Table 4 Cohorts A and B—peripheral blood CD34+ cell count pre- and post-plerixafor

Cohort A	*Median peripheral blood CD34+ pre-plerixafor on day 1 (cells/μl)*	*Median peripheral blood CD34+ following plerixafor on day 2 (cells/μl)*	*Median n-fold increase*
NHL ($n=7$)	33	64	2.3
MM ($n=12$)	150	235	1.7
Overall ($n=19$)	82.1	160	1.7
Cohort B	*Median peripheral blood CD34+ pre-plerixafor on day 2 (cells/μl)*	*Median peripheral blood CD34+ at 6 h after plerixafor administration on day 2 (cells/ μl)*	*Median n-fold increase*
NHL ($n=6$)	74.6	81	1
MM ($n=9$)	150	253	1.8
Overall ($n=14$)	129.2	200.3	1.7

Abbreviations: MM = multiple myeloma; NHL = non-Hodgkin's lymphoma.
n-fold increase = peripheral blood CD34+ cell/μl following plerixafor/peripheral blood CD34+ cell/μl before plerixafor.

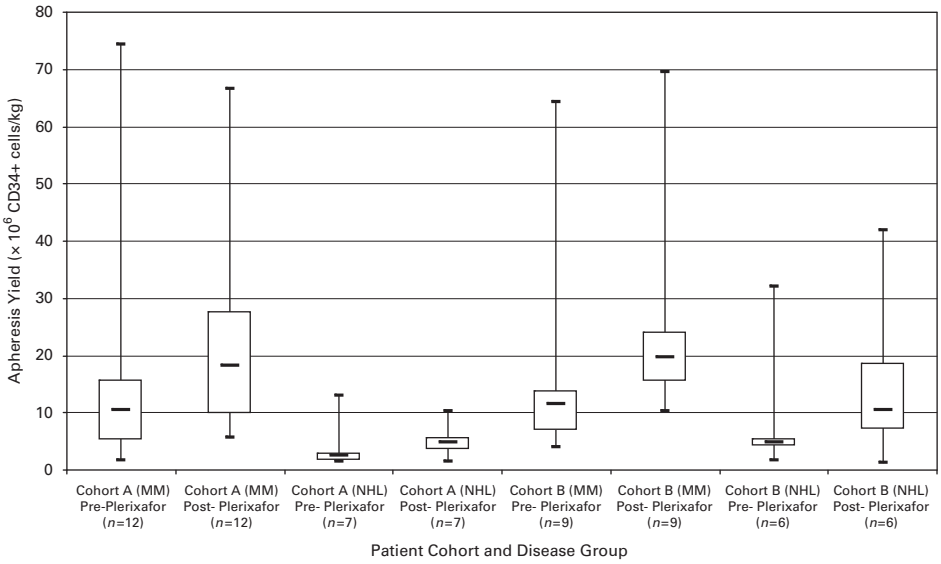

Figure 3 Apheresis yield for multiple myeloma (MM) and non-Hodgkin's lymphoma (NHL) patients in Cohorts A and B pre- and after plerixafor treatment.

Post chemotherapy mobilization administration of plerixafor (Cohort D)

In Cohort D, patients received plerixafor for 3 days starting on day 6 after chemotherapy. The patients had to reach a cell count of $\geqslant 20$ CD34+ cells/μl on the 6th, 7th or 8th day after chemotherapy before apheresis was initiated. No patients were able to proceed to apheresis before the WBC recovery and the majority underwent apheresis on the 9th day, when the peripheral blood CD34+ cells had exceeded 20 cells/μl. After the last dose of plerixafor administration on day 8, four of five patients in this cohort achieved $\geqslant 20$ CD34+ cells/μl on the 9th day. The fifth patient had a cell count of 17.7 CD34+ cells/μl on day 10 without administration of plerixafor.

Transplantation and engraftment

Forty patients underwent a total of 46 transplant procedures. PBSCs mobilized after chemotherapy, G-CSF and plerixafor resulted in timely engraftment after high-dose chemotherapy. The median day to neutrophil recovery was 11 (range 8–20). The median day to plt recovery without transfusion was 13 (range 7–77). The patient with plt engraftment at 77 days had slow plt engraftment (29 000 plts/μl at 100 days), followed by disease progression, and subsequently died at 9 months after transplant. For the rest of the patients, the longest time to plt engraftment was 35 days.

Graft durability was defined as maintenance of normal blood counts at 3, 6 and 12 months after transplant. Follow-up assessments were completed for all patients at 3 and 6 months after transplant. Thirty-five patients completed 12 months post-transplant visit. Thirty-five of 35 (100%) evaluable patients were determined to have a durable graft at 12 months after transplant. A total of five patients were not evaluable for graft durability: Two patients received allogeneic transplants off-study and were not assessed for graft durability; one patient died because of disease progression ~9 months after transplant; one patient returned for the 12-month visit and was determined to have a durable graft, but this information was not entered into the clinical database as the patient had not provided informed consent for the visit; lastly, one patient did not complete the 12-month follow-up assessment, but was assessed at 14 months after transplant and determined to have a durable graft.

The proportion of patients with NHL that reached plt counts $>100 \times 10^9$/l at 3, 6 and 12 months was 76.9, 76.9 and 75%, respectively. The proportion of patients with MM that reached plt counts $>100 \times 10^9$/l at 3, 6 and 12 months was 86.9, 94.4 and 95.4%, respectively.

Discussion

There are several clinically viable strategies to collect sufficient PBSCs for hematopoietic SCT.[11–13] Historically, chemotherapy plus G-CSF, or G-CSF alone, have been the preferred options.[14–16] Cytokine-only mobilization strategies are less toxic, take less time (typically 5–days) and therefore are potentially more cost-effective.[17] Chemotherapy-based mobilization strategies take longer (11–13 days), require additional monitoring and scheduling to ensure that initiation of apheresis coincides with the recovery of WBCs and peripheral CD34+ counts, and result in greater resource utilization. Despite these limitations, mobilization with chemotherapy remains an important option because of the greater yield of PBSCs for transplant. Chemotherapy-based strategies are also helpful when additional cytoreductive therapy is needed or desired before high-dose therapy.

This is the first study that evaluated the safety and preliminary efficacy of adding plerixafor to a mobilization regimen of chemotherapy plus G-CSF. Engraftment kinetics were also assessed for neutrophil and plt recovery. Safety was confirmed with the only SAEs reported being

unlikely to be associated with plerixafor. Furthermore, the four cohorts in the study allowed us to determine that (i) the addition of plerixafor to chemotherapy and G-CSF resulted in a twofold increase in CD34+ cells; (ii) this increase was a result of plerixafor administration and was observed with several chemotherapy regimens and disease states; (iii) administration of plerixafor on the same day of apheresis but 6 h before the procedure may allow for a more flexible application of the agent (Cohort B); (iv) the sole patient who failed mobilization with chemotherapy and G-CSF could be rescued with the timely addition of plerixafor (Cohort C); and (v) the early addition of plerixafor may allow for earlier initiation of apheresis after mobilization with chemotherapy and G-CSF (Cohort D). The PBSCs collected in this study produced prompt and durable engraftment.

This multicenter pilot study does have several inherent limitations. The number and complexity of the cohorts make generalizations regarding the data problematic. No single cohort contained a large number of patients. Different centers used alternative mobilizing and high-dose conditioning regimens. In addition, the plerixafor benefit observed might have been diminished by the study design, which called for a first day of collection after G-CSF and reserved the administration of plerixafor before the second apheresis. This allowed each patient to serve as their own control, but prevented the measurement of plerixafor effect early after the rise in circulating CD34+ cells after chemotherapy. Plerixafor may be more efficacious when administered early and less cost-effective when administered after an initial apheresis procedure. To definitively determine whether the addition of plerixafor to chemotherapy and G-CSF improves stem cell yield, a well-powered phase 2 or randomized controlled phase 3 study would need to be conducted.

The CD34+ cell mobilization in this trial was generally robust. Most patients had adequate CD34+ cell collection on the first day of apheresis. Three patients withdrew before plerixafor administration and did not undergo a second apheresis procedure because of sufficient cells being collected in the first apheresis. A moderately pre-treated group of patients was sought to explore the potential role of combining plerixafor with chemotherapy and G-CSF. Even in this group of patients, additive benefits with plerixafor were noted. As a general observation, MM patients had superior PBSC collections when compared with NHL patients (Figure 3). In addition, MM patients had fairly consistent and higher magnitude increases after the administration of plerixafor. In this series, MM patients had fewer previous chemotherapy regimens when compared with NHL patients. Induction MM chemotherapy regimens (used at diagnosis and before stem cell mobilization) are on average less intensive than second-line or salvage NHL regimens. In Cohort B, two patients with NHL had a decrease in CD34+ cell yield on day 2. We currently have no explanation for this as the study was designed as a feasibility trial.

The principal adverse events after plerixafor administration were bone pain, gastrointestinal disorders, headache, paresthesia and injection-site reactions. On the basis of other reports, the bone pain was likely related to G-CSF.[2–5] There were no drug-related serious adverse events. However, two patients discontinued plerixafor therapy, one for back pain and the other for a systemic reaction. Overall, these data imply that plerixafor can safely be added to chemotherapy-based mobilization regimens.

Although this pilot study was not specifically designed to show any benefit of using plerixafor after chemotherapy until after the onset of WBC recovery, the data from Cohort D suggest that the addition of plerixafor after chemo-ablation may provide benefit as in this cohort the majority of the patients achieved $\geqslant$20 CD34+ cells/μl by day 9, after the last dose of plerixafor administration on day 8. Unlike this study, future studies incorporating plerixafor in a chemotherapy-based mobilization regimen should initiate the drug during WBC recovery rather than before WBC recovery.

In this 44-patient study, a single patient mobilized poorly and was rescued on Cohort C. Certainly, the incidence of poor mobilization is much higher in routine stem cell transplant practice. Before the introduction of plerixafor, progress in this area was largely lacking. Published efficacy analyses of a subset of 115 patients with NHL ($n=63$), MM ($n=35$) or HD ($n=17$) who previously failed mobilization with chemotherapy and/or cytokine treatment showed successful hematopoietic stem cell collection in 60.3% of NHL, 71.4% of MM and 76.5% of HD patients after mobilization with plerixafor and G-CSF.[18] The time to engraftment was similar to that of other studies, and the engraftment was durable.

Our results should form the basis for future trials to explore the clinical utility of plerixafor in chemotherapy-based mobilization regimens. Important subsequent trials would standardize the mobilization chemotherapy regimen given to patients, stratify on the basis of age, disease and earlier therapy and randomize MM and NHL patients to pre-apheresis plerixafor or placebo. In addition, studies could be designed to explore alternative plerixafor administration schedules and chemotherapy regimens to optimize CD34+ cell recruitment/release during recovery from chemotherapy as well as improve the predictability of CD34+ cell collection.

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