A phase 2 pilot study of pegfilgrastim and filgrastim for mobilizing peripheral blood progenitor cells in patients with non-Hodgkin's lymphoma receiving chemotherapy

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ABSTRACT

Background
Growth factors are frequently used to aid peripheral blood progenitor cell mobilization from bone marrow. This phase 2 study examined the efficacy and safety of pegfilgrastim for mobilizing peripheral blood progenitors cells for autologous transplantation.

Design and Methods
Patients with non-Hodgkin's lymphoma received one cycle of mobilizing chemotherapy (ifosfamide, carboplatin and etoposide, ICE). Twenty-four hours later they were randomized, double-blind, to receive a single dose of pegfilgrastim 6 mg or 12 mg, or filgrastim 5 μg/kg/day (until the end of leukapheresis). Following leukapheresis (collection phase), patients rested or received one or two 'salvage' cycles of ICE. High-dose BEAM chemotherapy was then given before peripheral blood progenitor cell transplantation. The primary end-point was the patients' mean yield of $CD34^+$ cells/kg during the collection phase.

Results
Ninety patients were randomized and received a study drug; 63% completed the collection phase. The patients' mean (95% CI) $CD34^+$ cell harvest per leukapheresis was 0.8 (0.5-1.4), 0.8 (0.5-1.6) and 1.2 (0.7-2.0)$\times 10^6$ cells/kg for the pegfilgrastim 6 mg, pegfilgrastim 12 mg and filgrastim groups, respectively. Twenty (69%), 17 (59%) and 23 (72%) patients in these three groups achieved the targeted minimum harvest ($\geq 2\times 10^6$ cells/kg). The mean total harvests were 1.7, 1.4 and 2.2$\times 10^6$ cells/kg, respectively. Post-transplantation, the median days to absolute neutrophil count recovery ($\geq 0.5\times 10^9$/L) were 12, 11, and 11, respectively. Pegfilgrastim and filgrastim were generally well tolerated.

Conclusions
Pegfilgrastim (6 or 12 mg) was effective for mobilizing peripheral blood progenitors cells in patients with non-Hodgkin's lymphoma. These data may aid the design of studies to clarify optimal dosing and leukapheresis with pegfilgrastim.

Key words: filgrastim, pegfilgrastim, non-Hodgkin's lymphoma, mobilization, peripheral blood progenitor cell transplantation.

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Introduction

High-dose chemotherapy can confer significant survival and/or quality of life benefits for patients with hematologic malignancies including non-Hodgkin's lymphoma. Such treatment is, however, extremely myelosuppressive and its tolerability is dependent on effective hematopoietic support to facilitate recovery of bone marrow function. This support is provided by hematopoietic progenitor cells collected from either the blood (peripheral blood progenitor cells) or the bone marrow, with peripheral blood progenitor cell transplantation being preferred as it results in more rapid neutrophil and platelet recovery.[1]

Growth factors such as recombinant human granulocyte colony-stimulating factor (G-CSF, e.g. filgrastim) are used, possibly together with chemotherapy, to mobilize progenitor cells from the bone marrow into the peripheral circulation. Filgrastim must be administered daily, because it is cleared rapidly, with a plasma half-life of only 3–4 hours. Pegfilgrastim[2-5] is a pegylated form of filgrastim which is cleared primarily by neutrophils rather than the kidneys. It, therefore, has an extended serum half-life. In patients receiving myelosuppressive chemotherapy, a convenient, single, fixed dose of pegfilgrastim provides neutrophil support comparable to that provided by multiple daily injections of filgrastim.[6,7] Furthermore, limited data from previous studies suggest that a single dose of pegfilgrastim 6 or 12 mg can mobilize a sufficient number of peripheral blood progenitor cells to support early engraftment and sustained hematologic reconstitution when transplanted following high-dose chemotherapy.[8,9] There is also some evidence that a single dose of pegfilgrastim 12 mg can effectively mobilize peripheral blood progenitor cells in related and unrelated donors for allogeneic transplantation.[10]

The aim of the present randomized, double-blind, multicenter, phase 2 pilot study was to test the efficacy of two fixed doses of pegfilgrastim (6 mg and 12 mg) and a weight-determined dose of filgrastim (5 μg/kg/day) for mobilizing peripheral blood progenitor cells following chemotherapy in patients with non-Hodgkin's lymphoma.

Design and Methods

Patients

Eligible patients were aged ≥18 years with a diagnosis of non-Hodgkin's lymphoma and were suitable candidates for autologous peripheral blood progenitor cell transplantation according to institutional guidelines. They were required to have an Eastern Cooperative Oncology Group (ECOG) score ≤2, an absolute neutrophil count ≥1.5×10^9/L, and a platelet count ≥100×10^9/L.

Patients were excluded from the trial if they had >20% bone marrow involvement at screening, or had received more than one line of previous chemotherapy, or more than two cycles of any premobilization salvage chemotherapy before enrollment. In addition, prior treatment with any of the following chemotherapeutic agents was cause for exclusion: procarbazine, nitrogen mustard, nitrosoureas (including BCNU), melphalan or fludarabine. Patients were ineligible for the study if they had undergone previous bone marrow or peripheral blood progenitor cell transplantation, or had received total nodal irradiation or radiotherapy in the past 4 weeks. Receipt of any other investigational agent(s), interferon within 3 months or hematopoietic growth factors within 1 week of study entry also led to exclusion (if growth factor support had been given during previous chemotherapy cycles a white blood cell count <15.0×10^9/L was required at entry). Standard exclusion criteria with regard to renal or liver insufficiency, previous malignancy, significant cardiac disease and pregnancy were applied.

All patients provided written informed consent prior to any study-specific procedures being initiated.

Study design

This was a phase 2, double-blind, randomized, multicenter, pilot study conducted in 23 centers in Europe and Australia (clinicaltrials.gov: NCT00117455). The study protocol and amendments were reviewed by the local ethics committee in each institution and the study was conducted in accordance with local regulatory guidelines and/or International Conference on Harmonization (ICH) Good Clinical Practice (GCP).

The study consisted of three phases – a collection phase during which peripheral blood progenitor cells were mobilized and collected, a rest/optional chemotherapy phase in which patients were allowed to rest before transplantation (or receive salvage chemotherapy), and a transplant phase in which high-dose chemotherapy was administered before transplantation of the mobilized peripheral blood progenitor cells (Figure 1). In the collection phase, patients received one cycle of mobilizing chemotherapy (ICE: etoposide 100 mg/m^2 days 1, 2 and 3; carboplatin AUC of 5 on day 2; ifosfamide 5 g/m^2 day 2; the maximum dose of carboplatin was limited to 800 mg when creatinine clearance was ≤135 mL/min). Approximately 24 hours after completion of chemotherapy (i.e. day 4), patients were randomized in a 1:1:1 ratio to receive a single dose of 6 or 12 mg pegfilgrastim (Neulasta®, Amgen, CA, USA), or to commence treatment with daily filgrastim 5 μg/kg (Neupogen®, Amgen, CA, USA) (until the last day of leukapheresis). All study treatments were administered subcutaneously. A central interactive voice response system was used to obtain the computer-generated randomization number and blinded investigational products. In addition to active treatment, patients received either pegfilgrastim-matched placebo injections or fil-

grastim placebo injections from 24 hours after completion of chemotherapy until the end of leukapheresis. Low volume leukapheresis (≈10 L) was started when the peripheral $CD34^+$ cell count was ≥10/μL and the white blood cell count was ≤2.5×10^9/L (post-nadir), and continued until the $CD34^+$ cell yield was ≥5×10^6/kg, or for a maximum of five aphereses. Patients from whom < 2.0×10^6 $CD34^+$ cells/kg were harvested were withdrawn from the study and treated according to local clinical practice. Following the collection phase, patients could receive one or two additional cycles of ICE chemotherapy, with filgrastim 5 μg/kg/day as neutrophil support, or had a rest period of up to 6 weeks. Patients were withdrawn from the study if chemotherapy other than ICE was given during this period.

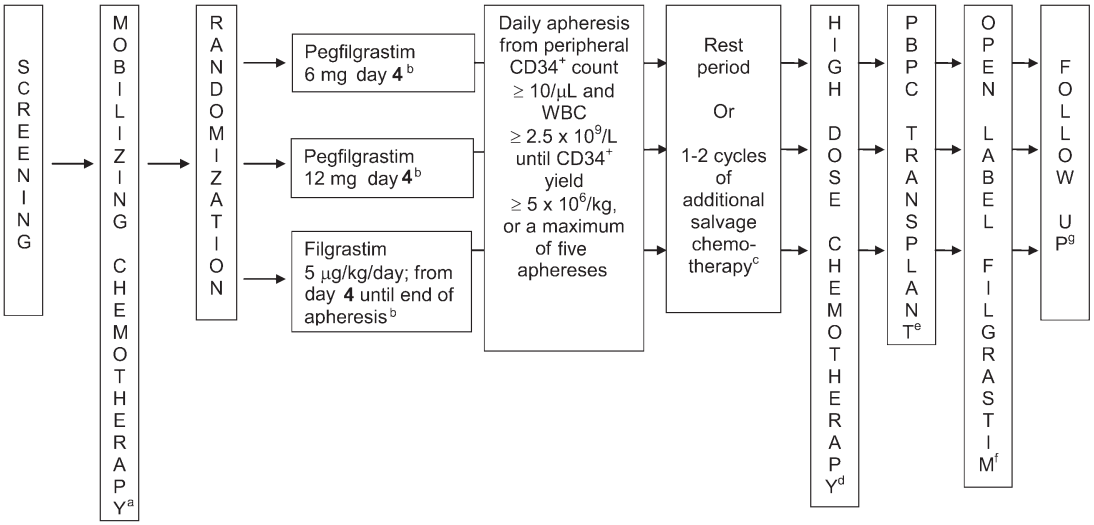
Patients then entered the transplant phase; they received high-dose BEAM chemotherapy (BCNU 300 mg/m^2 day –6, etoposide 800 mg/m^2 IV days –5 to –2, cytarabine 1600 mg/m^2 IV days –5 to –2, melphalan 140 mg/m^2 IV day –1) followed by peripheral blood progenitor cell transplantation (day 0) using the cells obtained during the collection phase. One day after the transplantation, patients received open-label filgrastim 5 μg/kg/day until the absolute neutrophil count reached ≥10×10^9/L. A follow-up blood assessment was conducted approximately 12 weeks post-transplant.

End-points

The primary end-point of this study was the patients' mean $CD34^+$ cells/kg yield (the total yield for a patient divided by the number of leukaphereses needed to collect the total yield). Secondary end-points were: the number and proportion of patients from whom ≥2×10^6 and ≥5×10^6 $CD34^+$ cells/kg were harvested; the number of leukaphereses needed to collect ≥2×10^6 $CD34^+$ cells/kg or ≥5×10^6 $CD34^+$ cells/kg; times to recovery of an absolute neutrophil count ≥0.5×10^9/L and ≥1.0×10^9/L post-transplant; times to platelet engraftment of ≥20×10^9/L and ≥50×10^9/L (independent of platelet transfusions), and cumulative patients' mean $CD34^+$ cells/kg yield through each leukapheresis (the cumulative yield for a patient through that number of leukaphereses divided by the number of leukaphereses that the patient needed for the cumulative yield to be collected).

Statistical power and analysis

The planned sample size was 30 patients in each treatment group. Efficacy end-points were analyzed for the population randomized into the study and receiving at least one dose of the study drug. Statistical analyses were descriptive with corresponding 95% confidence intervals (CI) provided where appropriate. Continuous end-points were summarized by geometric means or medians, while for categorical end-points the number and percentage of patients within each category are listed. Times to engraftment are summarized using the Kaplan-Meier method.



[a] Mobilizing chemotherapy = ICE = etoposide 100 mg/m^2 days1,2 and 3; carboplatin AUC 5 day 2; ifosfamide 5 g/m^2 day 2.
[b] Double-blind test article administration with pegfilgrastim (6 or 12 mg) on day 4 or daily filgrastim (5 μg/kg) from day 4 until end of apheresis.
[c] Rest period of up to a maximum of 6 weeks or 1-2 cycles of additional salvage (ICE) chemotherapy within an 8-10 week period. Patients who received additional salvage chemotherapy also received filgrastim 5 μg/kg/day from approximately 24 hours after the end of chemotherapy until an absolute neutrophil count (ANC) ≥ 10×10^9/L or for a maximum of 14 days, whichever is was sooner.
[d] High dose chemotherapy = BEAM = BCNU 300 mg/m^2 day -6; etoposide 800 mg/m^2 IV days -5 to -2; cytarabine 1600 mg/m^2 IV days -5 to -2; melphalan 140 mg/ m^2 IV day -1.
[e] Peripheral blood progenitor cell (PBPC) transplant given on day 0 (or day 0 and day 1 if transplant was to be given over 2 days).
[f] Filgrastim 5 μg/kg/day starting within 24 hours of start of transplant until ANC ≥ 10×10^9/L.
[g] Follow up assessments 12 weeks (day 84-100) post-transplant.

Figure 1. Study design and treatment schema.

Results

Patients

Between 19 February 2003 and 30 September 2004, 92 patients were randomized into the study, 90 of whom received a study medication: 29 received pegfilgrastim 6 mg, 29 pegfilgrastim 12 mg, and 32 received filgrastim. Two patients, both assigned to pegfilgrastim 6 mg, were withdrawn prior to receiving the study medication, one because of progressive disease and the other because of bone marrow involvement > 20%. The flow of patients through all study phases is shown in Table 1. With respect to individual phases, 58 (64%) patients who were randomized and received a study drug completed the collection phase. Twenty-two (24%) patients required no additional chemotherapy in the rest/optional salvage phase, while 36 (40%) patients were administered one or two extra cycles of ICE; 47 patients (52%) completed the phase. These patients had an on-study peripheral blood stem cell transplant and 42 (46%) completed the transplantation/follow-up phase. The main reason for withdrawal during the collection phase was failure to mobilize in 25 patients, 24 of whom did not attain a peripheral $CD34^+$ cell count ≥10/μL and/or white blood cell count ≥2.5×10^9/L. Eleven patients were withdrawn during the rest/optional salvage phase, seven of whom required salvage chemotherapy additional to that specified in the protocol.

Demographics and baseline characteristics were broadly comparable across the treatment groups (Table 2). There was a higher proportion of women in the pegfilgrastim 6 mg group, which may account for a lower mean baseline weight observed for this treatment group. Ninety-eight percent of patients had no bone marrow involvement. All patients had received prior first-line chemotherapy. There were more patients who had received prior salvage chemotherapy in the filgrastim group and fewer who had undergone prior radiotherapy in the pegfilgrastim 12 mg group. Numeric differences in hematologic parameters at baseline were not considered to be clinically relevant. One patient (filgras-

Table 1. Patients' disposition.

	Filgrastim	Pegfilgrastim	
		6 mg	12 mg
Number (%)			
Patients randomized	32 (100%)	31 (100%)	29 (100%)
Patients receiving study drug	32 (100%)	29 (94%)	29 (100%)
Patients who discontinued study	14 (44%)	20 (65%)	16 (55%)
Ineligibility determined	0	1 (3%)	0
Protocol deviation	0	0	1 (3%)
Adverse event	0	2 (6%)	0
Requirement for alternative therapy*	8 (25%)	10 (32%)	9 (31%)
Death	1 (3%)	2 (6%)	1 (3%)
Protocol specified criteria†	5 (16%)	5 (16%)	2 (7%)
Other	0	0	3 (10%)
Completed study	18 (56%)	11 (35%)	13 (45%)
Completed study per protocol‡	13 (41%)	10 (32%)	8 (28%)

*Principally a requirement for alternative treatment due to failure to mobilize peripheral blood progenitor cells; †The main protocol-specified reason for withdrawal was requirement for salvage chemotherapy other than ICE (etoposide, carboplatin, ifosfamide) (n = 8); ‡Disease response, hematology, and blood chemistry assessments were performed within 80–120 days of transplant.

Table 2. Baseline characteristics of the study population.

	Filgrastim (n = 32)	*Pegfilgrastim 6 mg (n = 29)*	*Pegfilgrastim 12 mg (n = 29)*
Demographics			
Median (range) age, years	59.0 (20–70)	54.0 (20–68)	55.0 (22–71)
Male, n (%)	20 (63%)	15 (48%)	18 (62%)
Median (range) weight, Kg	72.4 (51–140)	67.5 (50–100)	78.5 (46–101)
REAL classification, n (%)			
Diffuse large B-cell lymphoma	18 (56%)	22 (71%)	19 (66%)
Follicular lymphoma	5 (16%)	3 (10%)	4 (14%)
Disease stage			
I	2 (6%)	4 (13%)	3 (10%)
II	8 (25%)	7 (23%)	8 (28%)
III	11 (34%)	11 (35%)	8 (28%)
IV	11 (34%)	8 (26%)	10 (34%)
Hematologic parameters, median (range)			
White blood cell count $\times10^9$/L	5.24 (2.4–16.0)	6.70 (2.3–17.8)	5.40 (2.7–20.4)
Absolute neutrophil count $\times10^9$/L	3.39 (1.2–11.5)	4.82 (1.3–14.1)	3.20 (1.2–12.1)
$CD34^+$ $\times10^6$/L*	1.73 (0.0–53.0)	1.07 (0.0–103.0)	2.00 (0.0–30.0)
Platelets $\times10^9$/L	305.0 (78–604)	289.0 (107–899)	258.0 (103–831)
Prior treatment, n (%)			
Salvage chemotherapy	21 (66%)	15 (48%)	14 (48%)
Radiotherapy	9 (28%)	9 (29%)	5 (17%)

*Data available for 27, 24 and 25 patients in the filgrastim, pegfilgrastim 6 mg and pegfilgrastim 12 mg groups, respectively

tim group) had a low platelet count of 78×10^9/L at baseline; at screening the platelet count was 95×10^9/L, which was documented as an exception of eligibility post-randomization.

Cell harvest

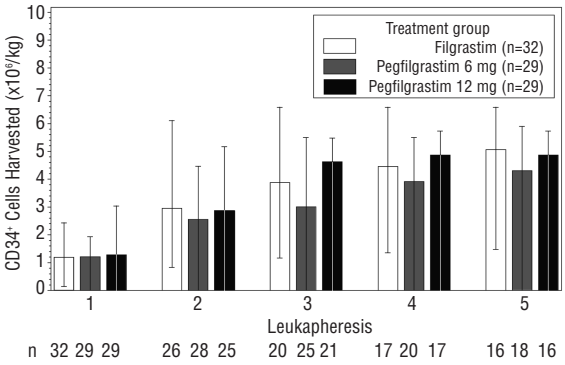
The geometric patients' mean CD34$^+$ cell harvest per leukapheresis (the primary end-point) is shown in Table 3. In the analysis of all patients, those who did not have a leukapheresis were assigned an imputed harvest of 0.1 $\times10^6$ cells/kg. Twenty-four patients had no leukapheresis: eight patients (28%) in the pegfilgrastim 6 mg group, nine patients (31%) in the pegfilgrastim 12 mg group, and seven patients (22%) in the filgrastim group. To assess the impact of these patients, the primary end-point was also analyzed excluding patients with no harvest (Table 3).

Data regarding secondary end-points are also listed in Table 3. The analysis of patients achieving $\geq5\times10^6$ cells/kg harvest is, however, confounded by protocol deviations in the pegfilgrastim groups in which leukapheresis was stopped before patients reached this goal. The median (range) total CD34$^+$ harvests were 4.3×10^6 (0.0–11.7), 4.9×10^6 (0.0–11.4), and 5.1×10^6 (0.0–14.3) cells/kg for the pegfilgrastim 6 mg, pegfilgrastim 12 mg and filgrastim groups, respectively (non-mobilizers were assigned a harvest of 0). When patients with no leukaphereses were excluded, the median total cell harvests were 4.9×10^6 (3.9–6.0), 4.4×10^6 (3.0–6.4) and 5.1×10^6 (4.0–6.4) cells/kg, respectively. The cumulative median harvest per leukapheresis was comparable across all treatment groups (Figure 2). In contrast, CD34$^+$ mobilization may have had an earlier onset with pegfilgrastim 12 mg than with pegfilgrastim 6 mg or filgras-

Table 3. CD34$^+$ cell mobilization and post-transplant hematologic recovery.

	Filgrastim (n = 32)	*Pegfilgrastim 6 mg (n = 29)*	*Pegfilgrastim 12 mg (n =29)*
CD34$^+$ mobilization			
Cell harvest per leukapheresis, geometric mean $\times$ 10^6 cell/kg (95% CI)*	1.2 (0.7, 2.0)	0.8 (0.5, 1.4)	0.8 (0.5, 1.6)
Ratio of geometric mean vs filgrastim (95% CI)		0.70 (0.32, 1.50)	0.73 (0.33, 1.65)
Cell harvest per leukapheresis, geometric mean $\times$ 10^6 cell/kg (95% CI) in patients with ≥1 leukapheresis	2.3 (1.6, 3.4)	1.8 (1.3, 2.5)	2.2 (1.5, 3.3)
Ratio of geometric mean vs filgrastim (95% CI)		0.77 (0.5, 1.3)	0.97 (0.6, 1.7)
Achieved minimal target harvest $\geq2\times10^6$ cell/kg, n (%)	23 (72%)	20 (69%)	17 (59%)
Odds ratio for difference between pegfilgrastim/filgrastim (95% CI)		0.87 (0.25, 3.03)	0.55 (0.17, 1.83)
Number of leukaphereses required to achieve target, n (%)			
1	11 (34%)	7 (24%)	11 (38%)
2	7 (22%)	10 (34%)	5 (17%)
3	3 (9%)	2 (7%)	1 (3%)
4	2 (6%)	1 (3%)	0 (0%)
5	0 (0%)	0 (0%)	0 (0%)
Achieved optimal harvest $\geq5\times10^6$ cell/kg, n (%)	18 (56%)	12 (41%)	13 (45%)
Odds ratio for difference between pegfilgrastim/filgrastim (95% CI)		0.55 (0.18, 1.70)	0.63 (0.20, 1.95)
Number of leukaphereses required to achieve target, n (%)			
1	6 (19%)	1 (3%)	4 (14%)
2	6 (19%)	3 (10%)	4 (14%)
3	3 (9%)	5 (17%)	4 (14%)
4	1 (3%)	2 (7%)	1 (3%)
5	2 (6%)	1 (3%)	0 (0%)
Total harvest, geometric mean $\times$ 10^6 cells/kg (95% CI)	2.2 (1.2, 4.0)	1.7 (0.8, 3.3)	1.4 (0.7, 2.8)
Ratio of geometric mean vs filgrastim (95% CI)		0.77 (0.31, 1.91)	0.63 (0.25, 1.59)
Transplantation and engraftment			
Days to ANC recovery, median (95% CI)			
$\geq0.5\times10^9$/L	11 (10, 12)	12 (10, 13)	11 (10, 13)
$\geq1.0\times10^9$/L	11 (11, 12)	12 (11, 13)	11.5 (11, 13)
Days to platelet recovery, median (95% CI)			
$\geq20\times10^9$/L	10.5 (10, 12)	11 (8, 14)	11 (10, 12)
$\geq50\times10^9$/L	17 (14, 20)	19 (13, NE)	17 (15, 23)

ANC, absolute neutrophil count; CI, confidence interval; NE, not estimable
**patients with no leukapheresis were assigned an imputed harvest of 0.1x10^6 cells/kg*



NB. These data include those from patients who did not receive an apheresis who were assigned an imputed harvest of 0.1x10⁶ cells/kg.

Figure 2. Cumulative median (interquartile range) harvest by leukapheresis.

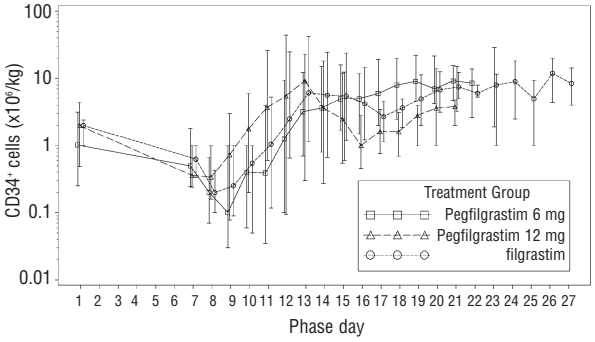


Figure 3. Median (interquartile range) peripheral CD34+ cell profile during the collection phase.

tim (Figure 3). The median (range) peak peripheral CD34+ cell concentrations were 20.2 (0.5-128.0), 30.0 (0.3-113.0), and 28.0 (2.1-199.00) cells/μL, in the pegfilgrastim 6 mg, pegfilgrastim 12 mg and filgrastim groups, while the median first day of apheresis was day 14.0 (13.0-17.0), 12.5 (11.9-14.3) and 14.0 (13.0-16.0), respectively. The peripheral CD34+ cell counts in the pegfilgrastim 6 mg and filgrastim groups were broadly similar throughout the collection phase. Among patients who mobilized, the median (range) number of filgrastim injections to achieve the target harvest of ≥2×10⁶ cells/kg was 11.0 (8.0-23.0). For the optimal harvest of ≥5×10⁶ cells/kg, 11.0 (9.0-21.0) filgrastim doses were used.

Transplantation and engraftment

Thirteen (45%), 16 (55%) and 18 (56%) patients in the pegfilgrastim 6 mg, pegfilgrastim 12 mg, and filgrastim groups, respectively, underwent peripheral blood progenitor cell transplantation. All recovered absolute neutrophil counts of ≥0.5 and ≥1.0×10⁹/L and platelet counts of ≥20×10⁹/L in the transplant phase, with the exception of one patient who died from organ failure. The median times to these end-points were similar across the three treatment groups at approximately 11 to 12 days (Table 3). The median time to achieve platelet recovery of ≥50×10⁹/L ranged from 17 days (pegfilgrastim 12 mg and filgrastim) to 19 days (pegfilgrastim 6 mg).

Safety and tolerability

During the collection phase, there was a relatively low incidence of treatment-related adverse events (Table 4). Serious adverse events were also infrequent during the collection phase with blood and lymphatic disorders being most common (Table 4). Only one serious adverse event, an electrolyte imbalance in the pegfilgrastim 6 mg group, was considered treatment-related.

Table 4. Adverse events during the collection phase.

Events, n (%)	*Filgrastim (n = 32)*	*Pegfilgrastim 6 mg (n = 29)*	*Pegfilgrastim 12 mg (n = 29)*
Patients with ≥1 AE	26 (81%)	21 (72%)	24 (83%)
Patients with ≥1 treatment-related AE	7 (22%)	4 (14%)	10 (34%)
Treatment-related AE in ≥5% of any group			
Arthralgia	2 (6%)	0 (0)	1 (3%)
Back pain	1 (3%)	2 (7%)	2 (7%)
Bone pain	4 (13%)	1 (3%)	3 (10%)
Headache	2 (6%)	1 (3%)	0 (0)
Patients with ≥1 serious AE	1 (3%)	7 (24%)	5 (17%)
Serious AE in > 1 person			
Anemia	0 (0)	2 (7%)	0 (0)
Thrombocytopenia	0 (0)	2 (7%)	2 (7%)
Treatment-related serious AE			
Electrolyte imbalance	0 (0)	1 (3%)	0 (0)
Withdrawals due to AE	0 (0)	1 (3%)	0 (0)

AE: adverse events.

In the rest/optional salvage chemotherapy phase, two (7%) patients in the pegfilgrastim 6 mg group reported treatment-related adverse events, as did one (3%) patient in the pegfilgrastim 12 mg group and one (3%) patient in the filgrastim group. Bone pain was the only treatment-related adverse event to occur in more than one patient. During the transplant/follow-up phase, one patient in the pegfilgrastim 6 mg group experienced pain in the extremity and jaw pain – events categorized by the investigator as possibly related to the study treatment.

There were two withdrawals due to adverse events – one in the collection phase due to neutropenic sepsis, and the other in the rest/optional salvage chemotherapy phase due to an electrolyte imbalance that began during the collection phase.

One patient (in the filgrastim group) died of sepsis during the rest/optional salvage phase, and three (pegfilgrastim 6 mg [n = 2] and pegfilgrastim 12 mg [n = 1])

died of multiorgan failure or cardiac failure during the transplant/follow-up phase. An additional patient (in the pegfilgrastim 12 mg group) died of disease progression after being withdrawn from the study. No deaths were considered to be related to pegfilgrastim or filgrastim.

Discussion

This phase 2, pilot study showed that pegfilgrastim 6 mg or 12 mg in conjunction with chemotherapy can be used for mobilization of CD34+ cells prior to peripheral blood progenitor cell transplantation in patients with non-Hodgkin's lymphoma. These data must be interpreted with caution due to the small sample size and high inter-patient variability, as illustrated by the broad confidence intervals around point estimates. This study was, however, planned only to provide proof of concept, and to provide information about the use of pegfilgrastim in this setting. A two-fold difference in yield between groups was required before statistical differences could be identified. Furthermore, the power of the study was reduced by the large number of patients in all three treatment groups who failed to mobilize sufficient CD34+ cells for harvest, and by patients withdrawing because they required salvage therapy other than ICE.

The failure of such large proportions of patients in all groups to mobilize peripheral blood progenitor cells is surprising and does not replicate the findings of previous authors.[9,10] For example, in a phase 2 study, when given on day 5, pegfilgrastim 6 mg was able to mobilize a target harvest of 2×10^6 CD34+ cells/kg in almost all (96%) of 25 lymphoma patients following ifosfamide, epirubicin and etoposide (IEV) chemotherapy.[8] Additionally, in a recent study in which patients with relapsed or primary refractory diffuse large B-cell lymphoma received rituximab plus ICE, 28 (82%) of 34 patients receiving filgrastim 5–10 μg/kg/day mobilized sufficient CD34+ cells for transplantation.[11] The failure of some patients in this study to mobilize peripheral blood progenitor cells may be a function of disease severity – a high proportion of patients in each arm had been pretreated with salvage chemotherapy (66% for filgrastim vs 48% for both pegfilgrastim groups). It is noteworthy, however, that a numerically higher proportion of patients given filgrastim achieved optimal harvest despite more of them having received salvage treatment. Previous authors have noted insufficient CD34+ cell yields in heavily-pretreated patients who received a single dose of pegfilgrastim 6 mg, and have described the use of additional injections of filgrastim to aid mobilization in this setting.[12] Given the neutrophil-mediated clearance of pegfilgrastim, mobilization induced by this agent could potentially be compromised by early recovery of neutrophils. However, just eight patients receiving pegfilgrastim had neutrophil recovery in advance of CD34+ levels, three of whom mobilized progenitor cells. The propensity to mobilize did not differ between patients whose absolute neutrophil count recovered before, in parallel with, or after, CD34+levels (*data not shown*). Furthermore, no substantial differences were noted in the first-line or salvage chemotherapeutic agents received by mobilizing and non-mobilizing patients (*data not shown*). There was some indication that the proportion of patients with cardiovascular or respiratory disease was greater among non-mobilizers than mobilizers, possibly indicating a lower overall level of health; however, more non-mobilizers had immunologic disease at baseline.

The timing of G-CSF administration may also be an important factor in determining mobilization. Here, G-CSF was given 1 day after chemotherapy (as indicated), but previous authors reported successful mobilization when the agent was given 2–4 days post-chemotherapy.[8,11,13] The circulation of numerous cytokines immediately post-chemotherapy may have an impact on the efficacy of growth factor-stimulated peripheral blood progenitor cell production.

Previous authors have demonstrated that pegfilgrastim 6 mg and 12 mg are equally potent with regard to peripheral blood progenitor cell mobilization and cell yield.[13] In the present study, however, there was some indication that pegfilgrastim 12 mg may be associated with more rapid mobilization of CD34+ cells than either pegfilgrastim 6 mg or filgrastim. Some other authors have also noted possible differences in the kinetics of cell mobilization following administration of filgrastim and pegfilgrastim. Limited animal[14] and human[13] data suggest that pegfilgrastim may mobilize progenitor cells more rapidly than does filgrastim, possibly reflecting the continuous high levels of G-CSF. For example, pegfilgrastim 6 or 12 mg was associated with earlier performance of the first apheresis (12 or 13 vs 15 days) in comparison with retrospective data for filgrastim.[13] Moreover, Willis *et al*. observed dose-dependent effects of pegfilgrastim on peripheral blood progenitor cell mobilization in chemotherapy-naïve patients.[15] Nevertheless, despite possible differences in mobilization kinetics, similar yields of CD34+ cells were obtained for pegfilgrastim and filgrastim in this and other studies.[13] Our data are consistent with those previously reported for filgrastim[16] and following transplantation there was no difference in absolute neutrophil counts and platelet recovery between the three groups.

The median number of filgrastim injections required to achieve both target and optimal cell harvests was 11, although some patients needed up to 21–23 injections. In practice, physicians are unlikely to use such prolonged courses of treatment. The cost-effectiveness of filgrastim compared with pegfilgrastim varies by country and was not specifically studied.

Both agents were well tolerated, with no discernable difference in the adverse events experienced by

patients receiving pegfilgrastim or filgrastim. As observed in previous studies,[5,17,18] adverse events associated with bone pain were most common, occurring in approximately 20% of patients in all three treatment groups.

In conclusion, these data support the concept that pegfilgrastim ≥6mg may provide a convenient alternative to filgrastim for use in conjunction with chemotherapy to mobilize peripheral blood progenitor cells for subsequent autologous transplantation in patients with non-Hodgkin's lymphoma. This phase 2 study provides no evidence to suggest differences in the efficacy or safety of 6 mg pegfilgrastim, 12 mg pegfilgrastim, and 5 μg/kg/day filgrastim in this setting. These results are encouraging and may potentially aid the design of studies to clarify optimal dosing and leukapheresis with pegfilgrastim ≥6 mg, as well as its cost-effectiveness compared to filgrastim.

Authorship and Disclosures

NR, JS, MB, HEJ, CdC and NS: study investigators, acquisition of data, critical review of manuscript for scientific content, sign-off of final document; RM: study investigator, critical review of manuscript for scientific content, sign-off of final document; NB: study design, statistical analysis, critical review of manuscript for scientific content, sign-off of final document; PB: study management, statistical analysis, interpretation of data, critical review of manuscript for scientific content, sign-off of final document; TS: interpretation of data, critical review of manuscript for scientific content, sign-off of final document. Three authors (NB, PB and TS) are employees of Amgen, the study sponsor. No other authors have any conflicts of interest to declare.

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