

Effective CD34+ Stem Cell Mobilization with Low-Dose Pegfilgrastim

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ABSTRACT

Introduction: Pegfilgrastim is administered in multiple clinical settings. A low-dose pegfilgrastim mobilization strategy was evaluated for stem cell collection.

Methods: Thirteen consecutive patients undergoing peripheral blood progenitor cell transplantation for hematologic malignancy received a single 6-mg injection of pegfilgrastim after chemotherapy. The CD34+ cell yield, number of apheresis procedures performed, cytokine cost, and time to engraftment were recorded. Thirteen previous patients who received filgrastim and chemotherapy for mobilization were used for comparison as the control group.

Results: Ten of thirteen patients were mobilized successfully. An average of 1.5

apheresis procedures was required. All engrafted successfully in a mean of 10.2 days. The cytokine cost per patient was \$3,250.

Discussion: Pegfilgrastim as compared with filgrastim resulted in decreased cytokine cost and fewer injections with a comparable number of CD34+ cells mobilized and no significant difference in the number of apheresis collection procedures performed or time to engraftment.

Conclusion: Single low-dose pegfilgrastim as part of a mobilization strategy for autologous peripheral blood stem cell transplant is a viable alternative to filgrastim.

INTRODUCTION

As a stem cell source for autologous bone marrow transplantation, filgrastim-based mobilized peripheral blood collections have surpassed bone marrow harvest collections.¹ Filgrastim's short

half-life of 3 to 4 hours, mediated by neutrophil endocytosis and renal clearance, requires daily to twice daily subcutaneous injections for peripheral blood stem cell (PBSC) mobilization.¹ Filgrastim can be modified by the addition of a polyethylene glycol (PEG) molecule. The resulting compound, pegfilgrastim, has a decreased renal clearance with a resultant increased serum half-life allowing for single injection dosing.²

As pegfilgrastim's main mechanism of clearance is via neutrophil-mediated endocytosis, one might conclude it would perform poorly as a stem cell mobilizer because its serum concentrations would fall quickly during periods of rapid leukocyte growth. However, murine data demonstrate PBSCs are mobilized in a more timely fashion by pegfilgrastim than filgrastim with the advantage of a single administration. Surprisingly, more PBSCs were harvested by this compound than with the standard of unmodified filgrastim.²

Data regarding the ability of pegfilgrastim to mobilize PBSCs in patients with hematologic malignancies are scarce; results in patients with myeloma suggest a 12-mg dose of pegfilgrastim is efficacious in mobilizing PBSCs.^{2,4}

Here the mobilization experiences of Stony Brook University Medical Center are reported with 13 consecutive patients undergoing peripheral blood progenitor cell transplantation using chemotherapy and a single 6-mg dose of pegfilgrastim. As a measure of efficacy, these results were compared with 13 previous patients mobilized with chemotherapy and daily filgrastim.

METHODS

After mobilization chemotherapy, 13 consecutive patients received a single 6-mg dose of pegfilgrastim. All patients had a confirmed hematologic malignancy requiring autologous bone marrow transplantation.

The mobilization chemotherapy regimen used was standard per the patients' diagnoses. A fixed 6-mg dose of pegfilgrastim supplied in single-use, preservative-free, pre-filled syringe was administered as single subcutaneous injection 24 to 48 hours after chemotherapy. Apheresis started when the absolute number of circulating white blood cells was $>4 \times 10^9/L$. PBSCs were collected by large volume leukoapheresis using an automated COBE Spectra v6.5 Apheresis Device (COBE Inc, Lakewood, CO) until a target collection of 5×10^6 CD34+ cells/kg was achieved or a maximum of 4 apheresis procedures were performed. Two patients in the pegfilgrastim group who did not achieve this goal were subsequently treated with filgrastim only, and the apheresis was repeated. Only the pegfilgrastim mobilization and apheresis data from these patients were included in the analysis.

The primary endpoint of the project was the successful mobilization of a target cell dose of 5×10^6 CD34+ cells/kg of the patient's ideal body weight. Secondary endpoints were the number of apheresis procedures required to obtain the target CD34+ cell dose, the days to engraftment, and cost-effectiveness.

Thirteen control patients for discussion were selected from our last 16 consecutive patients that underwent peripheral blood progenitor cell transplantation at the Stony Brook University Medical Center prior to the initiation of the pegfilgrastim program. Of our last 16 consecutive transplant patients, 13 were selected for comparison based on patient age, pretreatment, and diagnosis. No controls were selected who did not successfully mobilize or engraft. Filgrastim was dosed at a range of 5 to 16 mcg/kg and administered as either daily or twice daily injections 24 to 48 hours after chemotherapy and continued until mobilization completion. Statistical analysis was performed using

Table 1. Patient Characteristics

	Pegfilgrastim	Filgrastim
Number	13	13
Age (median)	53	52
Sex		
Male	10	
Female	3	4
Diagnosis		
NHL	4	3
HD	2	2
MM	6	7
AML	1	1
Chemotherapy		
Cy 4.5 or 2.5	8	10
ICE	2	1
R-ICE	2	2
HIDAC	1	4

NHL = non-Hodgkin's lymphoma; HD = Hodgkin's disease; MM = multiple myeloma; AML = acute myeloid leukemia; Cy = cyclophosphamide; ICE = ifosfamide/carboplatin/etoposide; R-ICE = rituximab plus ICE; HIDAC = high-dose cytarabine arabinoside.

a 2-tailed Student's *t*-test to compare mean outcomes between groups. A *P* value of <0.05 was used to reject the null hypothesis.

RESULTS

Patient Characteristics

Table 1 summarizes the demographics of the patients discussed in this report. The 13 consecutive patients in the pegfilgrastim group had a median age of 53 years (range 39 to 67). Six patients (46%) had a diagnosis of multiple myeloma, 4 (31%) had non-Hodgkin's lymphoma (NHL), 2 (15%) had stage IV Hodgkin's disease, and 1 (8%) had acute myeloid leukemia (AML). For comparison, the median age in the daily filgrastim group was 52 years (range 24 to 67). Seven patients (54%) had multiple myeloma, 3 had NHL (23%), 2 patients had

Hodgkin's disease (15%), and 1 had AML (8%).

Priming

Chemotherapy priming before mobilization did not vary between groups. Patients with multiple myeloma were treated with 4.5 g/m² of cyclophosphamide (1 patient with myeloma with a serum creatinine of 3.1 mg/dL received 2.5 g/m²); patients with relapsed stage IV Hodgkin's disease received ifosfamide/carboplatin/etoposide (ICE); the patients with AML received a high-dose cytarabine arabinoside backbone regimen, and patients with NHL received either 4.5 g/m² of cyclophosphamide or rituximab plus ICE.

Mobilization

Ten of thirteen (77%) patients were mobilized successfully in the pegfilgrastim group. Two of the three patients in the pegfilgrastim group who failed to mobilize received filgrastim and again failed to mobilize. There was no significant difference in the mean number of CD34+ cells/kg of ideal weight mobilized between the 2 groups (8.9 versus 7.8 × 10⁶/kg, *P*=0.67), see Figure 1.

Engraftment

All patients successfully engrafted following conditioning chemotherapy. The pegfilgrastim group had a mean time to engraftment (absolute neutrophil count >0.5 × 10⁹/L) of 10.2 days (range 9 to 12 days) while the filgrastim group engrafted in a mean of 10.4 days (range 9 to 11 days). There were no significant differences in time to engraftment between the study and control groups (*P*=0.66).

Apheresis

The mean number of days from cytokine administration to apheresis did not significantly differ between the pegfilgrastim and the filgrastim groups, 9.2 versus 9.6 days, respectively (*P*=0.60). Similarly,

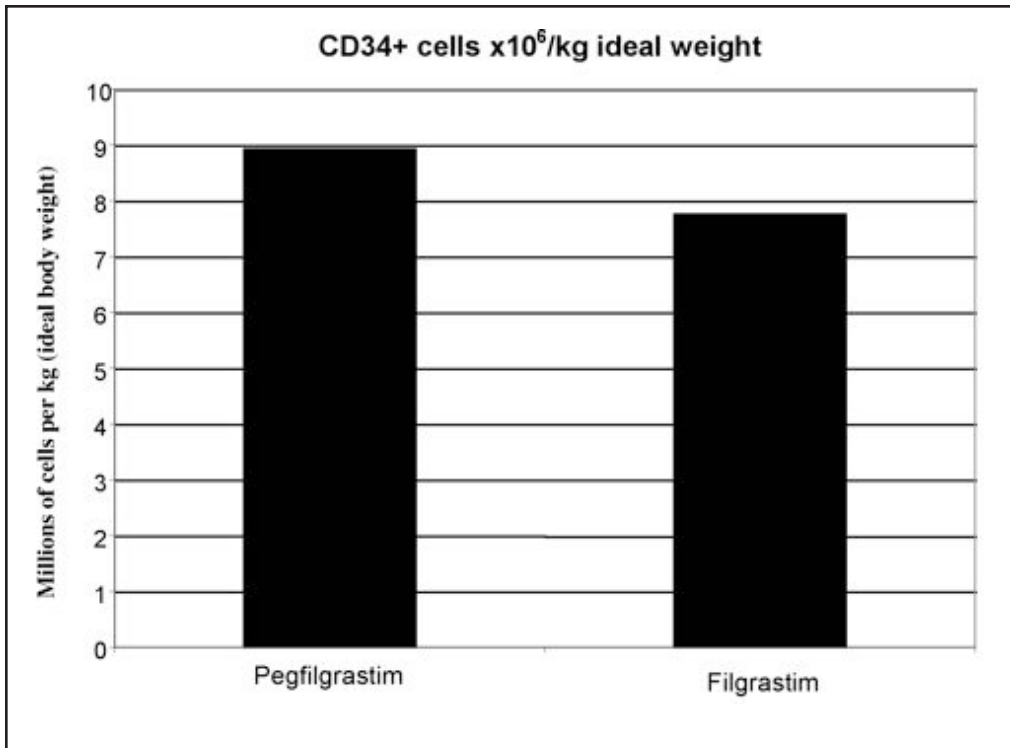


Figure 1. Mean number of mobilized CD34+ cells/kg ideal body weight.

the number of apheresis procedures required did not differ significantly (although the mean was lower in the pegfilgrastim group) with a mean of 1.5 for the pegfilgrastim group compared with 1.8 for the filgrastim group ($P=0.27$).

Cytokine Cost

The cytokine cost in the pegfilgrastim group was the same for all patients, \$3,250 for a single 6-mg dose. The filgrastim group received a median of 20 injections (range 4 to 36 injections) with an average cost of \$4,245 (range \$2,290 to \$8,760). There was a statistically significant difference in cost between the groups ($P=0.05$) favoring the pegfilgrastim group.

DISCUSSION

As PBSC mobilization is a common stem cell collection strategy, maximizing

efficacy, patient comfort, and cost need to be studied. Here 13 patients with hematologic malignancies who were mobilized with a single injection of pegfilgrastim after chemotherapy priming are discussed.

The data here established in a variety of hematologic malignancies that pegfilgrastim can successfully mobilize stem cells and that these cells engraft in a timely fashion. The single dosing obviates the need for patients to perform self-injections, and in 1 study was shown to reduce patient visits and increase quality of life.⁵

Three patients failed to mobilize with pegfilgrastim. Two of these patients who had advanced NHL subsequently received filgrastim, and in both cases, again failed to mobilize. These 2 patients were extensively pretreated for their malignancies and the failure likely represents accumulated marrow toxicity.

The third patient suffered from AML. Previous studies using filgrastim mobilization in AML have shown that up to 21% of patients fail to respond effectively.⁶

These data demonstrate the feasibility of using a single low-dose injection of pegfilgrastim as part of a mobilization strategy. This regimen has several advantages including increased patient compliance and comfort as well as decreased cost.

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