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# Randomized Phase III Trial of Pegfilgrastim versus Filgrastim after Autologus Peripheral Blood Stem Cell Transplantation

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Nonrandomized trials suggest that pegfilgrastim, a pegylated granulocyte colony-stimulating factor, could be used in lieu of filgrastim after autologus peripheral blood stem cell transplantation. This phase III, randomized, double-blinded, placebo-controlled trial compared the efficacy, costs, and safety of single-dose pegfilgrastim (single 6 mg dose) versus daily filgrastim (5 μg/kg/day) for this indication. Seventy-eight patients, matched for age, sex, underlying disease, stage, and CD34/kg transplant dose were enrolled. Cytokines were started on day +1 posttransplant and continued to an absolute neutrophil count (ANC) of $5 \times 10^9$/L for 3 days or $10 \times 10^9$/L for 1 day. The median time to neutrophil engraftment (ANC >1.5 $\times 10^9$/L for 3 days or $5 \times 10^9$/L for 1 day) was the same in both groups (12 days). No differences in platelet engraftment (11 versus 13 days), number of platelet transfusions (5 versus 4), percent with positive cultures for bacterial pathogens (23% versus 15%), days of fever (1 versus 2), deaths prior to engraftment (1 versus 1), or duration of hospital stay (19 versus 19 days) were seen between the pegfilgrastim and filgrastim groups, respectively. Using the average wholesale price for doses used in this trial, there was a per-patient savings of $961 for the pegfilgrastim group ($P < .001$). This phase III study failed to demonstrate a difference in time to neutrophil engraftment or any clinical sequelae between pegfilgrastim and filgrastim when given post-APBSCT, with pegfilgrastim achieving a cost savings over filgrastim.

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**KEY WORDS:** Autologous stem cell transplantation, Pegfilgrastim, Hematopoietic engraftment

## INTRODUCTION

High-dose chemotherapy/radiotherapy followed by autologus peripheral blood stem cell transplantation (APBSCT) is a potentially curative therapy for a number of chemosensitive malignancies. As high-dose therapy regimens produce severe pancytopenia for 7-14 days posttransplant, febrile neutropenia and infection can develop, which are associated with a significant risk of morbidity and mortality [1-3]. Recombinant hematopoetic colony-stimulating factors (CSF), such as granulocyte colony-stimulating factor (G-CSF), have been shown to accelerate engraftment following APBSCT, decrease the number of bacterial infections, number of days on antibiotics, and shorten the length of hospital stay [4-9]. Three studies have additionally shown nonsignificant trends toward lower overall costs in patients receiving these cytokines [6,7,10].

Filgrastim (r-met Hu-G-CSF), a human G-CSF produced by recombinant DNA technology is 1 such FDA agent approved for this indication [11]. Covalently bonding a 20-kD polyethylene glycol (PEG) molecule to filgrastim decreases its plasma clearance, which leads to an increased half-life of 33.2 hours compared to the 3.5 hours for G-CSF [12]. Despite the difference in half-life, this compound, pegfilgrastim, possesses similar clinical activity when used to prevent infections in the neutropenic patient [13,14]. Although small nonrandomized trials have suggested that pegfilgrastim could be used in lieu of filgrastim to speed hematopoietic reconstitution after APBSCT, the data are inconsistent as to whether this agent shortens the period of neutropenia posttransplant compared to G-CSF, and no large phase III trial data exist [15-19]. This phase III, randomized, double-blinded,

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placebo-controlled comparative trial of pegfilgrastim versus filgrastim after APBSCT was therefore undertaken to compare the efficacy, costs, and safety of the 2 treatments in patients receiving myeloablative preparative regimens.

## PATIENTS AND METHODS

### Patients

Adults undergoing an APBSCT for multiple myeloma (MM), lymphoma, testicular, or ovarian carcinoma were candidates for this phase III, prospective, randomized, double-blinded, placebo-controlled comparative trial of pegfilgrastim versus filgrastim. Patients were eligible if they were greater than the age of 18 years, had a SWOG performance status of $\leq 2$, a creatinine clearance $\geq 50$ mL/min, as well as a total bilirubin level $<1.5$ mg/dL and aspartate aminotransferase (AST) $<2$ times the upper limit of normal. In addition, a minimum of $>2 \times 10^6$ $CD34^+$cells/kg needed to be collected for transplant. All patients provided written informed consent by completing a form approved by the institutional review board.

### PBSC Collection and Transplantation

PBSC were mobilized for collection using cytokines alone as previously described by daily 12-liter aphereses starting on day 5 of mobilization [20,21]. The goal was to collect a maximum of $4 \times 10^6$ $CD34^+$/kg from a maximum of 5 consecutive daily apheresis procedures. The stem cells were cryopreserved in low molecular weight hydroxyethyl starch and dimethylsulfoxide and held at $-80$ °C [22].

Conditioning regimens included total body irradiation (TBI) (12 Gy in 8 fractions over 4 days) with etoposide (60 mg/kg) and cyclophosphamide (Cy) (100 mg/kg; TBI/VP/Cy), TBI + Cy (60 mg/kg; TBI/Cy), Ifosfamide (10 g/$m^2$, Carboplatin [area under the curve, AUC 28], and Etoposide (2.4 g/$m^2$; ICE), busulfan (Bu) (16 mg/kg), and Cy (120 mg/kg; Bu/Cy), paclitaxel (700 mg/$m^2$), mitoxantrone (90 mg/$m^2$), and carboplatin (AUC 28; TANC), and BCNU (15 mg/kg), etoposide (60 mg/kg), and Cy (100 mg/kg; BCV), BCNU (300 mg/$m^2$), and etoposide(0.8 g/$m^2$), Ara-C (1.6 g/$m^2$), melphalan (Mel; 140 mg/$m^2$; BEAM), and Mel (200 mg/$m^2$). On the day of transplantation (designated as day 0), the PBSC were rapidly thawed and infused through a central venous catheter.

### Clinical Management

Microbial prophylaxis consisted of acyclovir 5 mg/kg orally every 12 hours from day +1, fluconazole 200 mg orally every 12 hours starting on day +1, and prophylactic norfloxacin 400 mg orally twice daily, beginning on the same day as their conditioning regimen, and continued until complete engraftment [23-25]. Neutropenic fever was defined as a fever above 38.4°C once or above 38.2°C on 3 consecutive readings with an absolute neutrophil count (ANC) $<0.5 \times 10^9$/L, and was treated with imipenem/cilastatin 500 mg intravenously every 8 hours [26]. Packed red blood cell and platelet transfusions were given when hemoglobin or platelet levels were below 8 g/dL or $15 \times 10^9$/L, respectively. All blood products were irradiated and filtered prior to infusion [27].

### Protocol Therapy

Patients were randomized on day 0 in a 1:1 ratio to receive either a single 6 mg subcutaneous injection of pegfilgrastim along with daily filgrastim placebo, or daily subcutaneous filgrastim injections at 5 μg/kg daily plus a singe injection of pegfilgrastim placebo on day +1, starting approximately 24 hours after the completion of the PBSC infusion. Filgrastim or pegfilgrastim placebo was continued until sustained engraftment, as defined in prior Phase III trials as ANC $5 \times 10^9$/L for 3 days, or $10 \times 10^9$/L for 1 day, or through day +25 posttransplant. Patients not achieving an ANC of $>0.5 \times 10^9$/L by day +19 after transplant were permitted to receive opened-label filgrastim.

### Statistical Methods

The primary endpoint for this study was a comparison to the time to a neutrophil engraftment of $\geq 1.5 \times 10^9$/L $\times$ 3 days or $5 \times 10^9$/L $\times$ 1 day. Secondary endpoints included time to resolution of severe neutropenia (of $\geq 0.5 \times 10^9$/L $\times$ 3 days), length of hospital stay, incidence of infections, time to a platelet engraftment as measured by count recovery to $>20 \times 10^9$/L for 7 days, the number of platelet and packed red blood cell (PRBC) transfusions, the average number of filgrastim doses in the filgrastim arm, number of doses of rescue filgrastim, costs, and overall survival (OS).

A sample size of 78, 39 per treatment group, was required to provide a statistical power of 95% to detect a clinically significant difference between the 2 groups of 2 days in engraftment, assuming a standard deviation of 2.4 days and a 1-sided $\alpha$ of .05. To control for differences in speed of engraftment resulting from differing $CD34^+$/kg stem cell doses, patients were stratified based on the $CD34^+$/kg cell dose received ($<5.0 \times 10^6$/kg versus $\geq 0.5 \times 10^6$/kg). Patients were also stratified by preparative regimen (TBI containing or non-TBI containing) to account for differences in mucotoxic potential. Within a stratum, enrolled patients were randomized in a 1:1 fashion into the 2 study groups. The filgrastim and pegfilgrastim groups were compared using the Student's *t*-test for continuous variables, and categoric variables were

examined with the chi-square test. A linear regression model was used to examine confounders on time to engraftment. A 2-sided $p$ value of $<.05$ was considered to be significant. Survival analyses were plotted as Kaplan-Meier curves and compared using the log-rank test.

## RESULTS

### Patient Characteristics

In all, 78 patients were enrolled in this study at our institution between November of 2003 and May of 2007 (Figure 1). Patients were consecutively enrolled, if eligible for this trial, and there was no requirement for specified posttransplant cytokine administration mandated by the disease therapy trial the patient was also enrolled on. Thirty-nine patients each were randomized to the pegfilgrastim and filgrastim groups. The clinical characteristics are shown in Table 1. The mean $CD34^+$ stem cell doses infused were 4.1 and 4.7 $\times$ $10^6$/kg ($P = .68$) for the pegfilgrastim and filgrastim groups, respectively. The groups were matched for age, sex, weight, and underlying disease. All patients received protocol therapy and were evaluable for the endpoints.

### Engraftment Data

The median time to an ANC of 1.5 $\times$ $10^9$/L for 3 days or 5.0 $\times$ $10^9$/L for 1 day was 12 days in both groups (Table 2 and Figure 2). The median time to resolution of severe neutropenia (ANC $\geq$0.5 $\times$ $10^9$/L $\times$ 3 days) was 9 and 10 days, respectively, for the pegfilgrastim and filgrastim groups ($P = .15$). When adjusted for stem cell dose and conditioning regimens with TBI there was no significant difference in time to engraftment ($P = .11$). In addition to the primary endpoint, we examined several other measures of hematopoietic recovery. Patients in either arm received a mean of 12 injections, either filgrastim placebo or filgrastim, to reach the primary endpoint engraftment level. However, the protocol defined cytokine discontinuation engraftment endpoint of an ANC of 5.0 $\times$ $10^9$/L for 3 days or 10 $\times$ $10^9$/L for 1 day was reached in only 44% of the patients in the pegfilgrastim group compared to 95% in the filgrastim group. The median number of doses to reach this endpoint was 25 for the

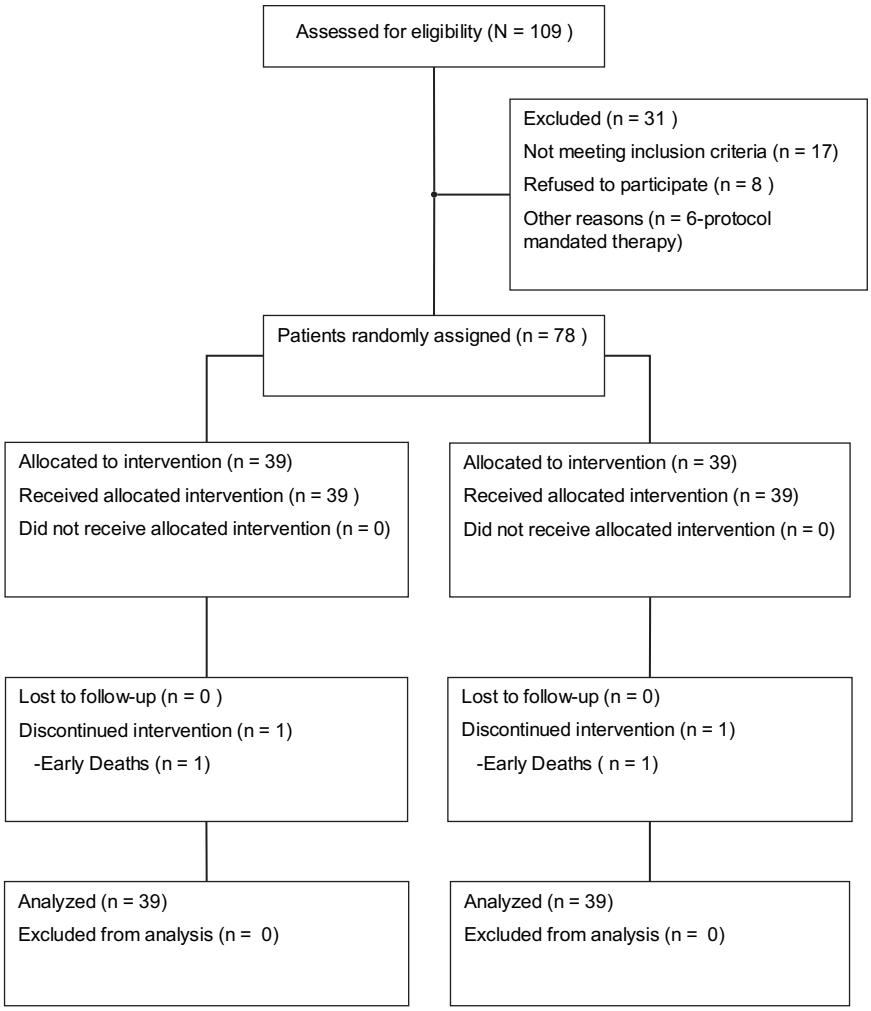


**Figure 1.** Patient enrollment and movement through the study.

**Table 1. Patient Characteristics**

| | Filgrastim | Pegfilgrastim | *p* value |
|---|---|---|---|
| Number of patients | 39 | 39 | |
| Age (median, range) | 56 (20-80) | 56 (22-79) | 0.7374 |
| Sex | | | |
| Male (%) | 12 (31) | 12 (31) | 1.00 |
| Female (%) | 27 (69) | 27 (69) | 1.00 |
| Weight (mean, kg) | 75.799 | 82.211 | 0.053 |
| *Disease* | | | |
| Hodgkin lymphoma | 7 (18%) | 6 (15%) | |
| Non-Hodgkin lymphoma | 14 (36%) | 21 (54%) | |
| Multiple myeloma | 15 (38%) | 8 (21%) | |
| Solid tumor (testicular, ovarian) | 3 (8%) | 4 (10%) | |
| *Remission Status* | | | |
| Complete remission 1 | 10 (26%) | 9 (23%) | |
| Greater than complete remission 1 | 11 (28%) | 10 (26%) | |
| Partial remission 1 or greater | 12 (31%) | 15 (38%) | |
| Disease progression or relapse | 5 (13%) | 5 (13%) | |
| Nummber of prior regimens (median, range) | 2 (1-5) | 2 (1-5) | 0.67 |
| Time to transplant in months (median, range) | 20 (4-168) | 15.5 (4-242) | 0.91 |
| Prior radiation to marrow | 2 (5%) | 4 (10%) | |
| *Conditioning Regimen* | | | |
| TBI/VP/Cy or TBI/Cy | 13 (33%) | 12 (31%) | |
| ICE | 2 (5%) | 1 (3%) | |
| Bu/Cy | 14 (36%) | 5 (13%) | |
| TANC | 1 (3%) | 3 (8%) | |
| BCV | 7 (18%) | 10 (26%) | |
| BEAM | 0 (0%) | 4 (10%) | |
| Melphalan | 2 (5%) | 4 (10%) | |
| TBI containing | 13 (33%) | 12 (31%) | |
| Non-TBI containing | 26 (67%) | 27 (69%) | |
| *Graft data* | | | |
| Mobilization | | | |
| G-CSF | 32 (82%) | 29 (74%) | |
| GM-CSF and GCSF | 7 (18%) | 6 (15%) | |
| AMD 3100 | 0 (0%) | 4 (10%) | |
| $CD34^+$ cells x $10^6$/kg infused (median, range) | 4.13 (1.82-12.11) | 4.21 (1.78-18.99) | 0.75 |

TBI indicates total body irradiation; VP, etoposide; Cy, cyclophosphamide; Bu, busulfan; G-CSF, granulocyte colony-stimulating factor; GMCSF, granulocyte macrophage colony-stimulating factor.

pegfilgrastim group and 13 for the filgrastim group ($P < .0001$). No patient required opened-label, rescue filgrastim to achieve engraftment.

When examining the mean ANC over the first 25 days after transplant, there is a sharp increase in the ANC on day +2 in both groups followed by a decline starting on day +5. The ANC of both groups followed a similar recovery pattern except for days +12 to day +16, when the median ANC for the filgrastim group was significantly higher than that of pegfilgrastim.

There was no significant difference in the platelet engraftment between the pegfilgrastim and filgrastim study arms (11 versus 13 days, $P = .29$). Each arm also received the similar amount of platelet (5 versus 4, $P = .30$) and RBC transfusions (2 versus 2, $P = .052$) (Table 3). The mean platelet counts for each group declined from day 0 to day +7, then steadily increased to pretransplant levels until engraftment. There was no significant difference in the mean platelet counts for either group in the first 25 days after transplant (Figure 3).

## Toxicities

There were no grade III or IV toxicities, including bone pain, which could be specifically attributed to either of the study drugs. Two patients (one from each arm) died while on the study. Both patients died from infection-related sepsis prior to neutrophil engraftment (on day +7 and day +13). The median number of days with febrile neutropenia of the pegfilgrstim arm was 1 (range: 0-7 days), and 2 for the filgrastim arm (range: 0-12 days). There was no significant difference in the incidence of positive

**Table 2. Hematologic Recovery**

| | Filgrastim | Pegfilgrastim | *p* value |
|---|---|---|---|
| Days to ANC 0.5x$10^9$/L (median, range) | 10 (8-15) | 9 (8-13) | 0.15 |
| Days to ANC 1.5 x $10^9$/L (median, range) | 12 (9-16) | 12 (9-24) | 0.21 |
| Days to ANC 5 x $10^9$/L (median, range) | 13 (9-22) | 25 (10-18) | 0.001 |
| Days to platelets 20 x $10^9$/L (median, range) | 10 (8-68) | 11 (7-21) | 0.29 |

ANC indicates absolute neutrophil count.

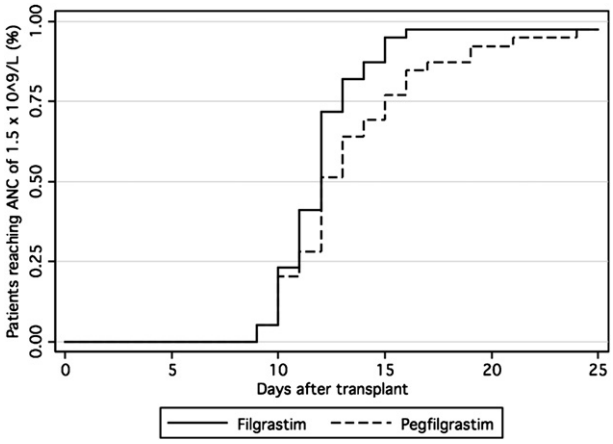


**Figure 2.** Neutrophil engraftment after transplant. Kaplain-Meier plot of time to an ANC of $1.5 \times 10^9$/L for 3 days, or $5 \times 10^9$/L for 1 day in the filgrastim group compared to the pegfilgrastim group.

cultures for bacterial pathogens between the 2 arms as well (23% in pegfilgrastim versus 15% in filgrastim, $P = .39$).

The median hospital duration was the same for each of the groups (19 days). The median follow-up of survivors was 14 months. At the time of analysis, there was no significant difference in survival at day +100 ($P = .67$) or at 1 year ($P = .97$) (Figure 4).

### Cost Analysis

In the pegfilgrastim arm, patients received a single, fixed dose of 6 mg on day +1 after APBSCT. In the filgrastim arm, the study drug was given daily at 5 μg/kg daily for a median number of 12 days (range: 9-16 days) starting on day +1 after APBSCT to reach an ANC of $1.5 \times 10^9$/L for 3 or $5.0 \times 10^9$/L x1 day. Considering the average wholesale price in U.S. dollars for the actual doses used in this trial, the cost per patient was a mean of $3547.40 USD with pegfilgrastim and $4508.20 USD with filgrastim. This resulted in a per-patient savings of $960.80 USD for the pegfilgrastim group compared to the filgrastim group using this engraftment endpoint ($P < .001$).

## DISCUSSION

We present data from the first randomized double blinded trial of pegfilgrastim versus filgrastim following APBSCT. In this study, we demonstrated that the outcomes in both groups were similar in terms of times to ANC engraftment and all potential sequelae of prolonged neutropenia. Other endpoints examined also yielded similar results in the 2 groups examined, in particular, with respect to transfusions and hospital stay as well as posttransplant mortality. We demonstrated that because pegfilgrastim is cleared by neutrophil absorption [13,28], our patients were able to achieve ANC engraftment despite their receiving only a single dose posttransplant rather than repeated daily doses of filgrastim.

Pegfilgrastim has been used before in the postautotransplant setting but the results have been conflicting. Farese et al. [29] first studied pegfilgrastim after autologous transplant in rhesus macaques, and showed that a single dose was as effective as daily filgrastim in neutrophil recovery. Subsequently, Musto et al. [30] looked at an 11-patient cohort with MM, non-Hodgkin lymphoma, and acute myelogenous leukemia conditioned with Mel, BEAM, or TBI/Cy. Patients received pegfilgrastim on day +3 post-ABPSCT and were compared retrospectively to matched historical controls who received standard doses of filgrastim starting on day +5 posttransplant. The median time to neutrophil engraftment in the pegfilgrastim group was 2 days shorter compared to the filgrastim group (10 versus 12). There was also a suggestion of cost benefit in this small study. Jagasia et al. [15] conducted a larger study in which 38 patients with MM and lymphoma, conditioned with Mel or BCV, who received pegfilgrastim on day +1. Again, these patients were compared to a historical cohort in which filgrastim was started on either day +1 or day +4. Engraftment times were found to be shorter in the pegfilgrastim group than the filgrastim group (10 versus 13.7 days; $P < .05$). However Martino et al. [16] treated 37 patients with multiple myeloma, who were also conditioned with melphalan, and given pegfilgrastim on day +1, and showed no significant difference in engraftment versus a group of historic controls given filgrastim on day +5. Likewise Vanstraelen et al. [18] conducted a study comparing 20 patients with lymphoma and MM conditioned with TBI/Cy, BEAM, or Mel, receiving pegfilgrastim versus historical controls receiving filgrastim, both starting on day +1, and again found no difference in neutrophil recovery (9 versus 8 days). More recently, Ballestrero et al. [19] looked at 44 patients undergoing autologus

**Table 3. Transfusions, Infectious Complications, and Toxicity**

| | Filgrastim | Pegfilgrastim | *p* value |
|---|---|---|---|
| Number of platelet transfusions (median, range) | 4 (0-14) | 5 (1-15) | 0.30 |
| Number of RBC transfusion (median, range) | 1 (0-4) | 2 (0-5) | 0.052 |
| Duration of hospital stay (median, range) | 19 (12-26) | 19 (10-36) | 0.32 |
| Days of febrile neutropenia (median, range) | 2 (0-12) | 1 (0-7) | 0.13 |
| Nummber of documented infections | 6 | 9 | 0.16 |
| Days with grade III or VI mucocitis (median, range) | 0 (0-14) | 1 (0-19) | 0.44 |

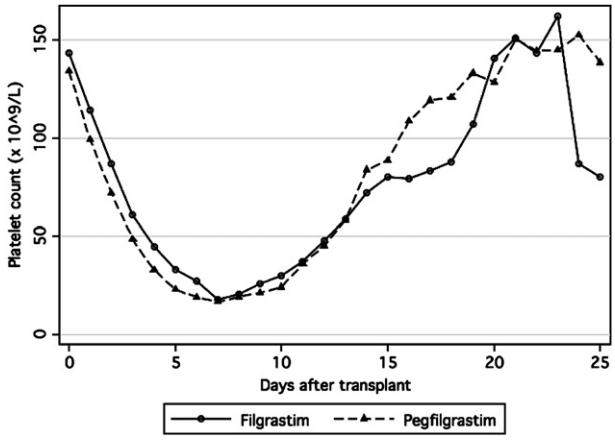


**Figure 3.** Platelet count ($\times 10^9$/L) in the first 25 days after transplant.

transplant for lymphoma and solid tumors compared to 25 historic controls. These patients were conditioned with thiotepa in combination with Mel or mitoxantrone, ICE, or BEAM, and again were found to have no difference in time to neutrophil recovery (10 versus 9.5 days) when starting both pegfilgrastim and filgrastim on day +5.

A nonblinded, randomized, controlled study by Staber et al. [31] showed a significant trend to shorter engraftment with pegfilgrastim versus filgrastim (8.3 versus 9.5 days). Patients with acute leukemia, MM, non-Hodgkin and Hodgkin lymphoma were conditioned with TBI/Cy, BEAM, BCVM, or Mel, with pegfilgrastim given on day +5 and filgrastim was on day +7. Our study, the first randomized, placebo-controlled study comparing the 2 agents as well as the studies conducted by Vanstraelen et al. [18] and Ballestrero et al. [19], started each growth factor on the same day, where the other studies listed started each growth factor on different days. The delay in starting filgrastim after that of pegfilgrastim may explain the earlier engraftment times for pegfilgrastim

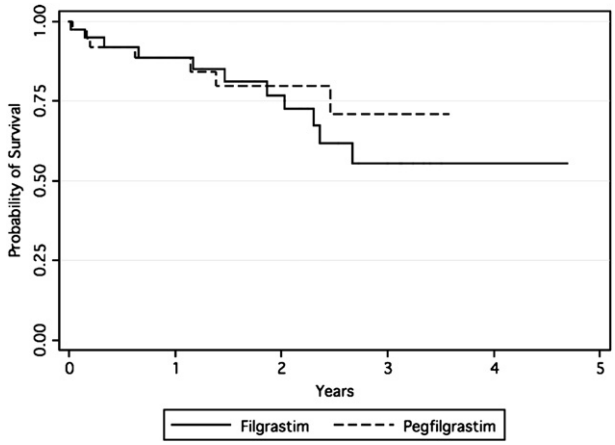


**Figure 4.** Kaplan-Meier plot of OS in the in the filgrastim and pegfilgrastim groups.

in these studies, and potentially why we did not see a difference in engraftment times for the 2 arms.

We did, however, see a significant difference in count recovery to the traditional Phase III trial endpoint for filgrastim cessation, that is, an ANC of $5.0 \times 10^9$/L for 3 days or $10 \times 10^9$/L for 1 day. Although only 44% of the patients in the pegfilgrastim group compared to 95% in the filgrastim group reached this endpoint, there was no subsequent fall off our neutrophil counts nor any sequelae of this relatively lower ANC period in rates of infection, febrile neutropenia, treatment-related mortality, or 100-day survival in the pegfilgrastim group. The significantly higher ANC from day +12 to day +16 between the 2 arms indeed was most likely due to the receptor-mediated clearance of pegfilgrastim as the white count recovered, leading to lowered serum cytokine levels.

We also found no differences in other measures of hematologic recovery, that is, time to platelet engraftment, platelet transfusions, or packed red cell transfusions. These results were similar to those seen in the various pilot studies [15,17-19]. Because pegfilgrastim, once given, maintains constant serum levels until recovery, and may have shunted hematopoietic stem cells away from the megakaryocytic lineage to the granulocytic lineage, we investigated the pattern of platelet count recovery in our patients. Similar to neutrophil recovery, we found no difference in the speed of platelet count recovery. This likely is because of the ability of pegfilgrastim to upregulate the expression of primitive transcription factors such as HOXA9 and GATA3, leading to a robust multilineage engraftment despite the lower peak ANC engraftment seen in our patients [32]. Our speculation that recipients of pegfilgrastim might also have superior lymphocyte and immune reconstitution and that this might have clinical implications can not be proven considering the small numbers of a relatively heterogenous population [33,34].

With apparent equivalency between the 2 groups, the choice of 1 versus the other therapy then would depend on quality of life and costs. No one would dispute the improvement in the quality of life afforded by a single dose of pegfilgrastim given on day +1 posttransplant versus repeated subcutaneous daily doses of filgrastim. Although we did not see a difference in the amount of grade I-II bony pain in the 2 groups, it is likely that the narcotic use for mucositis and pharyngits obscured any potential differences between the 2 arms. Although a single dose of pegfilgrastim costs substantially more than a single dose of filgrastim, using the drug discontinuation endpoint that has been traditionally used in previous clinical trials, we found a cost benefit in the pegfilgrastim group of $960.85 USD for the pegfilgrastim arm. However, multiple studies have demonstrated that delaying the initiation of filgrastim until day +5 posttransplant

does not significantly delay neutrophil recovery and engraftment [35,36]. If one assumes that this would have occurred in our study, then delaying the filgrastim until day +5, patients on this arm would have received only 7 doses of drug to full engraftment thereby leading to an average cost savings for the filgrastim arm of $1212.56 USD per patient over the cost of the pegfilgrastim arm. However, considering the delayed onset studies of Jagasia et al., Musto et al., and Staber et al. [15,30,31], it would need to be proven that this altered strategy led not only to similar engraftment times but also no difference in downstream events as well. Nevertheless, given the overall costs of transplantation this additional cost may be appropriate to consider in those who have previously experienced severe discomfort from repeated daily doses of filgrastim.

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