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ORIGINAL ARTICLE

Pegfilgrastim: More Cost Effective and Equally Efficacious Option as Compared to Filgrastim in Autologous Stem Cell Transplant

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Abstract Use of growth factor after high-dose chemotherapy (HDC) and autologous peripheral blood stem cell (PBSC) support is current standard in reducing days of neutropenia. This retrospective study aims to compare the efficacy of two standard growth factors, pegfilgrastim (PEG) and filgrastim (FIL) after HDC. We collected data on 195 consecutive adult patients who received an autotransplant (myeloma, lymphoma and others) between January 2004 and December 2014 at two tertiary care centres. The primary end point was the duration of neutropenia in terms of days to reach an ANC $> 0.5 \times 10^9$/L. Filgrastim was given to 110 patients and PEG was given to 85 patients. Time to engraftment, defined as the time to reach an ANC of 0.5×10^9/L on 2 consecutive days after the day of auto-SCT, was 12.6 days with FIL compared with 12.1 days with PEG group ($p = 0.126$). When comparing the total days of severe neutropenia (WBC $< 0.1 \times 10^9$/L), there were 5.5 days of severe neutropenia with FIL compared with 5.8 days with PEG group ($p = 0.7$). The duration of febrile neutropenia was an average of 5.3 days with FIL and 4.6 days with PEG ($p = 0.029$). The total number of antibiotic days was shorter for the patients who received PEG, being 11.08 days with PEG and 12.1 days with FIL ($p = 0.184$).The average cost savings per person in terms of number of days of hospitalization and number of days of total parental nutrition was 582 Rs ($p = 0.512$) and 6003 Rs ($p = 0.018$) respectively in favour of PEG arm. PEG is similar to FIL in hematological reconstitution, however it is more cost effective alternative after HDC and PBSC.

Keywords Pegfilgrastim · Filgrastim · Autologous stem cell transplantation

Introduction

High-dose chemotherapy (HDC) with autologous stem cell support (SCT) is the current standard of care in relapsed lymphomas and myeloma. Peripheral blood stem cell (PBSC) has been the preferred stem cell source, with a significant advantage in large randomized studies [1, 2].

Growth factor administration, mainly granulocyte colony-stimulating factor [G-CSF, filgrastim (FIL) or lenograstim], after PBSC has been shown to significantly reduce the time to reach a safe neutrophil count [3–6]. However, this has not yet translated into reduction of clinically significant events, such as infections, mortality, or extra-hematological toxic effects in other studies [7–9]. The American Society of Clinical Oncology (ASCO) guidelines recommends the use of growth factor after autologous stem cell transplant [10].

Pegfilgrastim (PEG) is synthesized by adding a 20 kDa polyethylene glycol moiety to FIL. Thus it tends to have a longer half-life and subsequently attains higher plasma concentration [11]. It usually maintains a higher level during the period of neutropenia and subsequently its level falls during the period of engraftment in view of neutrophil mediated clearance. It has been shown to have similar

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efficacy whether given weight based or in fixed doses [12]. One single dose of PEG (6 mg) was shown to be as effective as FIL (5 mcg/kg) in reducing the length of severe neutropenia and clinical complications associated with it, in animal models [13] and in patients undergoing conventional dose chemotherapy [14–18].

PEG after HDC and PBSC has been effective in various retrospective and prospective studies. Randomised phase 3 [19, 20] studies have shown that the PEG provided a similar efficacy in hematological reconstitution as compared to FIL but is more cost effective.

The purpose of this study was to compare the engraftment kinetics and supportive care requirement of a fixed-dose PEG (6 mg) compared with daily FIL (5 mcg/kg), in our set of population, and in resource limited setting, as well as to compare its effects and benefits in engraftment.

Patients and Methods

Study Design

We collected data on 202 consecutive adult patients who received an auto-transplant (myeloma, lymphoma and others) between January 2004 and December 2014 at two tertiary care centres. During the first half of the study period, 110 consecutive patients received filgrastim (5 mcg/kg) beginning day 1 after transplant. For the second half of the study we collected data from 85 consecutive patients (2008/2009 onwards) who received pegfilgrastim 6 mg on day 1 after transplant (since there was a greater trend of using this after 2008). Institutional guidelines allowed patients receiving a single dose of pegfilgrastim to receive additional doses of filgrastim based on physician discretion.

Data collection included baseline characteristics, time to neutrophil recovery with ANC of $> 0.5 \times 10^9$/L, incidence of febrile neutropenia, number of days of severe neutropenia (WBC $< 0.1 \times 10^9$/L), number of doses of filgrastim and pegfilgrastim given, and days of intravenous antibiotics, number of days of hospitalsation and number of days of total parenteral nutrition. We also conducted a cost analysis between the two groups.

Primary endpoint was to study difference in engraftment kinetics between filgrastim and pegfilgrastim.

Secondary endpoints were number of days of severe neutropenia, difference in number of days of febrile neutropenia, number of hospital days, blood product support, and cost difference between the two.

White blood cells (WBC) engraftment was taken as day with two consecutive values of ANC $> 0.5 \times 10^9$/L and platelet engraftment was taken as first day of unsupported platelets $> 20{,}000$ (maintained for 7 days).

Cost Analysis

We conducted cost analysis in terms of average cost saved per person in terms of days of antibiotics, days of hospitalization (room and professional charges), additional days of blood products and additional days of total parenteral nutrition, between both the groups. Inflation was not taken into account. For this we calculated the average cost of each of this variable in every individual in pegfilgrastim and filgrastim arm.

Statistical Analysis

Mann–Whitney test was used to compare various variables amongst the two groups. We compared engraftment kinetics of WBC (Kaplen Meier, event was WBC $> 1.5 \times 10^9$/L as a function of day to achieve it) and platelet (event was unsupported platelet count was more than 20,000 as a function of day to achieve it or the day of discharge if platelets had not engrafted yet) between the pegfilgrastim and filgrastim arms (p value using log-rank test). We compared demographics using descriptive statistics using Chi square.

Results

Demographic Profile

A total of 202 patients receiving auto-SCT from January 2004 to December 2014 were retrospectively reviewed. 7 patients that died during the course of transplant were excluded from the study. There were 110 patients in the filgrastim and 85 patients in pegfilgrastim arms of the study. Baseline characteristics of the patients were well balanced in both study groups with detailed demographics presented in Table 1.

Neutrophil Recovery

Time to engraftment, defined as the time to reach an absolute neutrophil count (ANC) of 0.5×10^9/L on 2 consecutive days after the day of auto-SCT, was 12.6 days with filgrastim compared with 12.1 days with pegfilgrastim cohort ($p = 0.126$) (Table 2). Total days of severe neutropenia (WBC $< 0.1 \times 10^9$/L), as well as number of days required to reach WBC $> 1 \times 10^9$/L between the two groups were also comparable ($p = 0.5$), as shown in Table 2.

Time to engraftment of platelets, defined as the time to reach a platelet count of 20×10^9/L at least for 7 unsupported consecutive days (starting at least 48 h of last platelet transfusion), was 14.5 days with filgrastim compared

Table 1 Demographics of study group in pegfilgrastim and filgrastim arm

	Filgrastim (n = 110)	Pegfilgrastim (n = 85)	*p* value
Age (years)	40 (36%)	44 (51%)	0.09
Gender			
Male	80 (72%)	56 (66%)	0.382
Female	30 (28%)	29 (34%)	
Disease treated			
Multiple myeloma	46 (41%)	45 (54%)	0.37
Hodgkins lymphoma	32 (30%)	21 (25%)	
Non-Hodgkins Lymphoma	20 (19%)	14 (16%)	
Others	4 (3%)	2 (2.5%)	
Acute Leukemia	8 (7%)	2 (2.5%)	
Median CD34	3.2	3.3	0.82

Table 2 Comparison of engraftment variables amongst two groups using Mann–Whitney test

	Filgrastim mean (SD)	Pegfilgrastim mean (SD)	*p* value
Days of WBC $< 0.1 \times 10^9$/L	5.5 (4.01)	5.8 (3.9)	0.4
Time to reach WBC $> 1.0 \times 10^9$/L (days)	12.7 (4.4)	12.8 (4.9)	0.5
Days to platelets platelet engraftment (mean, range)	14.5 (6.1)	13.7 (5.03)	0.4
Days neutrophil engraftment	12.6 (4.2)	12.1 (4.4)	0.126

with 13.7 days with pegfilgrastim group ($p = 0.4$). Ninety-two (83%) patients in filgrastim cohort and 72 (84%) in pegfilgrastim cohort showed stable platelet engraftment at the time of discharge.

Infection Risk and Use of Anti-microbials

The duration of febrile neutropenia was an average of 5.3 days with filgrastim and 4.6 days with pegfilgrastim group ($p = 0.029$). The total number of antibiotic days was shorter for the patients who received pegfilgrastim, being 11.08 days with pegfilgrastim and 12.1 days with filgrastim ($p = 0.184$). The duration of hospital stay was 18.4 days for pegfilgrastim as compared to 19.6 days in filgrastim group ($p = 0.123$) (Table 3).

Doses of Filgrastim and Pegfilgrastim

Patients in the filgrastim cohort received an average of 14.6 daily injections. In total, 63 (74%) of the 85 patients in the pegfilgrastim cohort received only the single dose of pegfilgrastim, while 22 (25%) patients received additional filgrastim. The average number of days of additional filgrastim was 5.8 days and the average starting day was 14.1 days. Even after censoring patients who received additional filgrastim in pegfilgrastim cohort, the primary end-point (days to engraftment), was comparable between the two groups ($p = 0.45$). However, additional days of filgrastim used in the pegfilgrastim group is a potential bias in this study.

Table 3 Comparison of supportive care between two groups using Mann–Whitney test

	Filgrastim mean (SD)	Pegfilgrastim mean (SD)	*p* value
Number platelet transfusions (mean)	4.5 (4.02)	3.9 (4.3)	0.06
Number of red blood cell transfusion (mean)	2.7 (2.8)	2.1 (2.4)	0.06
Duration hospital (mean)	19.6 (6.9)	18.4 (6.6)	0.123
Febrile neutropenia (days)	5.3 (3.7)	4.6 (4.03)	0.029
Number of days of antibiotics (mean)	12.1 (6.01)	11.08 (6.4)	0.184
Number of days of TPN (mean)	7.6 (5.9)	4.08 (4.9)	0.005

Table 4 Cost analysis between two groups using Mann–Whitney test

Cost savings	Filgrastim (Rs) Mean (SD)	Pegfilgrastim (R) Mean (SD nearest decimal)	Cost savings per person (Rs)	*p* value
Packed cell transfusion charges	10,797.93 (8592)	9470.1 (7284)	1327	0.274
Platelet transfusion charges	29,705.8 (23,736)	25,870.1 (26,176)	3835	0.068
Total parenteral nutrition charges	25,071.4 (14,117)	19,068.7 (10,077)	6003	0.018
Cost of hospital days	2.21.946.1 (93,086)	2,21,364.7 (79,459)	582	0.512

Cost Assessment

The average cost savings per patient was 11,432 rupees (Indian Rupees) in favour of pegfilgrastim arm (Table 4). However, the cost effectiveness might vary depending on different treatment settings.

Discussion

The high doses of chemotherapy before auto-SCT leave patients at risk of neutropenic complications. In our study with 195 patients (7 excluded) we found that patients receiving pegfilgrastim had lesser days with severe neutropenia, WBC $< 0.1 \times 10^9$/L ($p = 0.4$). Patients on pegfilgrastim arm had faster neutrophil engraftment which was statistically non-significant ($p = 0.126$) and decrease in the incidence of febrile neutropenia which was statistically significant ($p = 0.029$). This led to reduction in supportive care (blood products, antibiotics and hospital stay) in patients on pegfilgrastim arm and average cost savings of 11,747 rupees per person. Other factors like conditioning regime and CD34 counts were comparable between the two arms and could not have contributed to this.

The kinetics of neutrophils engraftment showed higher levels of neutrophils in pegfilgrastim group. However towards the end of engraftment period there is a drop in neutrophil levels with use of pegfilgrastim (pegfilgrastim mediated clearance of neutrophils) as has been shown in other studies. However this study and other studies have not studied the monocytic population of cells either morphologically or immunophenotypically).

Pegfilgrastim, once given, maintains constant serum levels until recovery, and may shunt hematopoietic stem cells away from the megakaryocyte lineage to the granulocyte lineage. However we found no difference in platelet kinetics between the two groups. This likely might be 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 [21].

The advantage of various G-CSF schedule, on day + 1 [22, 23] or on days + 3 and + 5 [24] or on day +7 [25] has not yet been shown. Earlier randomized studies have compared pegfilgrastim on day 1 with various schedules of filgrastim but in our study both the groups were given growth factors on day 1 of transplant.

Previously published data comparing the use of pegfilgrastim and filgrastim have generally concluded that pegfilgrastim is a safe and equally efficacious alternative to filgrastim. Jagasia et al. [22] studied the use of pegfilgrastim given on day 1 in 38 multiple myeloma and lymphoma patients after autologous transplantation. They found a relatively lower incidence of febrile neutropenia (49%), and no difference in the time to neutrophil engraftment when compared with a historical filgrastim control group. Vanstraelen et al. [23] found no significant difference in neutrophil engraftment (8 vs. 9 days with pegfilgrastim and filgrastim, respectively) or incidence of fever in 20 patients receiving pegfilgrastim when compared with a filgrastim historical control. However, they found significantly higher values of lymphocytes and neutrophils up to day 100 in the pegfilgrastim group. Other studies have suggested that faster lymphocyte recovery may be associated with improved outcome after autologous transplantation [26]. A study similar to ours by MSKCC group [27] with 164 patients, compared 82 patients who received pegfilgrastim on day + 1 with 82 patients who received filgrastim from day 5 onwards. They showed that Patients who received pegfilgrastim had faster engraftment (9.6 days compared with 10.9 days, $p = 0.0001$), a lower incidence of febrile neutropenia (59% compared with 78%, $p = 0.015$), and fewer days of treatment with i.v. antibiotics (6.3 days compared with 9.6 days, $p = 0.006$), which translated to an estimated total cost savings of over $8000 per patient.

Two large prospective randomized studies were conducted comparing pegfilgrastim with filgrastim. Study from Ilianos [19] group (78 patients). Growth factors were started on day + 1 post transplant. The median time to neutrophil and platelet engraftment was the similar in both groups (9 vs. 10 days and 11 vs. 13 days) respectively. There was no difference in the days of febrile neutropenia

(1 vs. 2), or duration of hospital stay (19 vs. 19 days) between the two groups. There was a per-patient savings of $961 for the pegfilgrastim group ($p = 0.001$).

In an Italian study, eighty patients were assigned to filgrastim at a daily dose of 5 mcg/kg or a single fixed dose of pegfilgrastim (6 mg) 1 day after PBSC. The mean duration of neutropenia similar was (6 and 6.2 days) and the mean time to reach an ANC $> 0.5 \times 10^9$/L was 11.5 and 10.8 in the filgrastim and pegfilgrastim group, respectively. No differences were observed in the incidence of fever (62 vs. 56%) and of documented infections (31 vs. 25%) [20].

This is the largest study in resource limited country comparing role of pegfilgrastim with filgrastim in autologous transplant setting. The limitations of this analysis include its retrospective study design. In addition, toxicities can be difficult to accurately assess through chart review. Nonetheless, patients receiving pegfilgrastim had faster engraftment and lesser incidence of febrile neutropenia. In addition, these patients required fewer days of anti-microbials and hospitalization.

We conclude that a single dose of pegfilgrastim is a safe and efficacious alternative to daily injections of filgrastim and is a cost-effective approach in auto-SCT patients.

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Authors' Contribution VS, RJ and AG contributed equally, wrote manuscript, analyzed data, designed study, treated patients; AG, treated patients; TS, mentored manuscript, treated patients, designed study.

Compliance with Ethical Standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethical Approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.Acknowledgement, Prof Navin Khattry and Prof Arnon Nagler for valuable inputs during preparation of manuscript.

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