in vivo *32*: 899-903 (2018)
doi:10.21873/invivo.11326

Effectiveness and Safety of Pegfilgrastim in BEP Treatment for Patients with Germ Cell Tumor

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Abstract. *Background: The effectiveness and safety of pegfilgrastim during bleomycin, etoposide and cisplatin (BEP) chemotherapy have not yet been investigated. Patients and Methods: Patients with germ cell tumors (GCTs) who received pegfilgrastim during BEP at the Kanazawa University Hospital between January 2014 and December 2016 were retrospectively analyzed. The frequency of adverse events and effectiveness in inhibiting neutropenia were compared between cycles using pegfilgrastim and those using filgrastim. Results: Pegfilgrastim and filgrastim were administered in 13 and 22 cycles, respectively. The absolute neutrophil count at the nadir was significantly lower in patients receiving pegfilgrastim than in those receiving filgrastim (p=0.003). The duration of grade 2-4 neutropenia in cycles using filgrastim was significantly longer than that in those pegfilgrastim (p=0.01). No significant differences in the incidence of febrile neutropenia and serious adverse events were observed. Conclusion: Pegfilgrastim can be safely and effectively administrated during BEP for patients with GCT.*

Germ cell tumor (GCT) is a common malignancy that affects adolescent and young adult males. The development of an effective combined chemotherapy, specifically bleomycin, etoposide and cisplatin (BEP), has dramatically improved the prognosis of patients with advanced GCT (1, 2). However, BEP induces severe myelosuppression. When administering the standard BEP regimen without granulocyte-colony stimulating factor (G-CSF), 30-50% of treated patients are generally unable to receive full-dose treatment as scheduled because of myelosuppression (3). Because worse outcomes are reported with insufficient BEP dose intensity, G-CSF, such as filgrastim, is administered daily during BEP in most cases (4). Filgrastim allows the timely delivery of cytotoxic chemotherapy at an adequate dose (5-7). Pegfilgrastim, a sustained-release form of filgrastim, reduces the number of injections required to one per cycle of chemotherapy. Many studies have demonstrated the noninferiority of pegfilgrastim compared to filgrastim in terms of the duration of severe neutropenia and risk of febrile neutropenia (FN) (8, 9). However, to our knowledge, no study has reported on the use of pegfilgrastim during the standard BEP treatment for GCT. In this study, the effectiveness and safety of pegfilgrastim compared to filgrastim during BEP for GCT were investigated.

Patients and Methods

Between January 2014 and December 2016, 16 patients with GCT were treated at Kanazawa University Hospital. Six patients who had not received BEP were excluded from the study. Consequently, 10 patients met the inclusion criterion and were retrospectively analyzed. The demographic, surgical, pathological, and follow-up data were collected from their medical charts. Patients received a BEP regimen, composed of 30 mg (30,000 international units) intravenous bleomycin (*i.v.*) injection on days 1, 8, and 15; 100 mg/m^2 etoposide *i.v.* on days 1, 2, 3, 4, and 5; and 20 mg/m^2 cisplatin *i.v.* on days 1, 2, 3, 4, and 5. Treatment was repeated every 3 weeks for two to four cycles. Pegfilgrastim (3.6 mg) was administered subcutaneously on day 7. The administration of filgrastim (75 μg) was at the discretion of each attending physician. Leukopenia, neutropenia, thrombocytopenia, anemia, FN, and other adverse events were analyzed. Statistical analyses were performed using commercially available software Prism (GraphPad, San Diego, CA, USA). Comparisons among different groups were performed using the chi-squared test and the Mann–Whitney *U*-test. In all analyses, *p*-values of less than 0.05 indicated statistical significance.

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Key Words: BEP, germ cell tumor, neutropenia, pegfilgrastim.

Table I. *Patient background characteristics.*

No.	Age, years	Pathology	IGCC	Distant metastasis	No. of cycles	
					Peg	Filg
1	28	Non-seminomatous	Poor	LN, lung	3	1
2	47	Mixed	Good	None	1	1
3	56	Mixed	Intermediate	None	2*	2
4	48	Mixed	Good	None	4	0
5	30	Seminoma	Good	None	3	0
6	48	Seminoma	Good	None	0	3
7	19	Non-seminomatous	Poor	LN, lung	0	4
8	44	Seminoma	Good	None	0	3
9	32	Non-seminomatous	Poor	LN	0	4
10	37	Mixed	Poor	LN, lung	0	4

*Filgrastim was administered following pegfilgrastim in one cycle. Mixed: Non-seminomatous and seminoma; IGCC: International Germ Cell Classification; BEP: bleomycin + etoposide + cisplatin; Peg: pegfilgrastim; Filg: filgrastim; LN: lymph node.

Table II. *Hematological adverse events of therapy with bleomycin, etoposide and cisplatin, according to administration of granulocyte-colony stimulating factor.*

	Pegfilgrastim (3.6 mg)	Filgrastim (75 μg)	*p*-Value
Cycles administered, n	13	22	
Median no. of administrations per cycle	1	5 (1-9)	
Median baseline ANC (10^3/μl)	6.31 (2.07-8.99)	5.73 (1.58-24.2)	0.52
ANC at nadir (10^3/μl)	1.99 (0.4-5.1)	0.82 (0.06-2.1)	0.003
Grade 4 adverse event			
Anemia	0	1 (4.5%)	>0.99
Thrombocytopenia	0	0	
Leukopenia	0	5 (22.7%)	0.13
Neutropenia	1 (14.3%)	8 (36.4%)	0.11
Grade 3 or more			
Febrile neutropenia	0	2 (9.1%)	0.51

ANC: Absolute neutrophil count.

Results

Of 10 patients who met the inclusion criterion, pegfilgrastim and filgrastim were administered to five and eight patients, respectively. Three patients received both pegfilgrastim and filgrastim during BEP treatment. One patient received both pegfilgrastim and filgrastim in the same cycle. In total, pegfilgrastim and filgrastim were administered in 13 and 22 cycles, respectively. The median age at GCT diagnosis was 40.5 years. Three patients were found to have seminoma, four had mixed tumors of seminoma and nonseminoma, and three had nonseminoma. According to International Germ Cell Classification (10), five, one, and four patients were classified with good, intermediate, and poor prognosis, respectively (Table I).

Hematologic adverse events are shown in Table II. There was no significant difference in baseline absolute neutrophil count (ANC) between cycles using pegfilgrastim and those using filgrastim (p=0.52); nevertheless, the nadir ANC value was significantly lower in those using filgrastim (p=0.003). The line graphs of the number of neutrophils in all cycles using both agents are shown in Figure 1. Although there was no significant difference, FN occurred in two cycles using filgrastim and did not occur in any cycles using pegfilgrastim. The duration of grade 2-4 neutropenia in cycles using filgrastim was significantly longer than in those using pegfilgrastim (p=0.01, median of 0 and 2 days, respectively, Figure 2). Serious adverse events, such as interstitial pneumonia and splenic rupture, were not observed. However, more severe neutrophilia was observed in cycles using

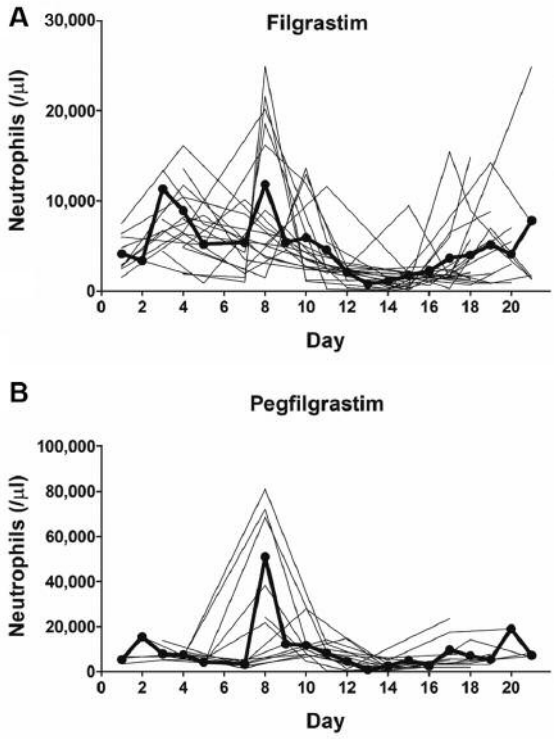

Figure 1. *The number of neutrophils in all cycles in individual patients treated with bleomycin, etoposide and cisplatin, according to administration of pegfilgrastim (A) and filgrastim (B), respectively. Bold lines indicate the average values each day.*

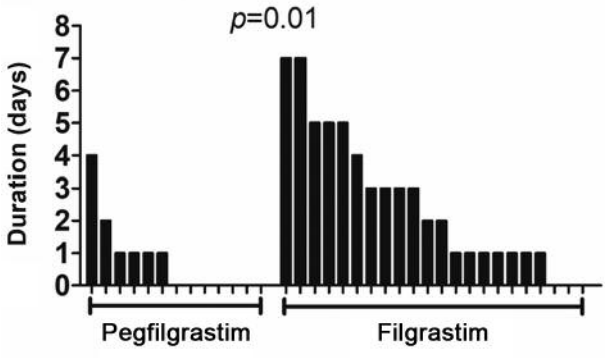

Figure 2. *The duration of grade 2-4 neutropenia in individual patients treated with bleomycin, etoposide and cisplatin, according to administration of granulocyte-colony stimulating factor.*

pegfilgrastim than in those using filgrastim (median 21,800 and 13,500/μl, respectively, p=0.006; Figure 3A). The median number of days to maximum neutrophil count (MNC) in cycles using pegfilgrastim and those using filgrastim was 8 and six, respectively (Figure 3B). Although there was no significant difference, MNC most frequently occurred after pegfilgrastim injection (11 out of 13, 85%). MNC was recorded before the initiation of filgrastim injection in 50% (11 out of 22) of filgrastim-used cycles (Figure 3C). Advanced GCT is sometimes associated with systemic inflammation with high baseline ANC before the induction of BEP treatment. The cycle which included the day of MNC before the initiation of pegfilgrastim and filgrastim was recorded for each patient. The percentage of patients with MNC before the initiation of filgrastim injection in the first cycle and subsequent cycles was 27% and 73%, respectively (not significantly different, Figure 3D).

Discussion

Pegfilgrastim is generally administered between 14 days before and 24 h after the administration of chemotherapy agents. In this study, patients receive pegfilgrastim on day 7 in the BEP regimen, that is, 2 days after etoposide and cisplatin administration. This shows the effect of pegfilgrastim during days 8 and 15 when bleomycin is administered, because pegfilgrastim is a sustained-release form of filgrastim. Theoretically, simultaneous administration of exogenous G-CSF and chemotherapy leads to an increased pool of neutrophil precursors susceptible to destruction by chemotherapy, which paradoxically leads to an increased risk of neutropenia (11, 12). In a retrospective study, Weycker *et al*. analyzed 45,592 patients who received pegfilgrastim. They reported that FN incidence was found to be significantly higher in patients who received pegfilgrastim prophylaxis on the same day as chemotherapy completion compared to those who received it several days after the completion of chemotherapy (13). In contrast, Burris *et al*. reviewed three randomized double-blind studies comparing same-day and next-day pegfilgrastim and showed a statistically insignificant trend toward longer duration of severe neutropenia for the same-day group (14). Bleomycin was reported to lead to minimal or no myelosuppression and leukopenia *in vitro*, and neutropenia rarely occurred when it was used as a single-agent treatment (15, 16). The simultaneous use of bleomycin and G-CFS was reported to increase the risk of interstitial pneumonia in patients with lymphoma; however, an increase in bleomycin-induced pulmonary toxicity has not been reported when using G-CSF in GCT chemotherapy regimens containing bleomycin (3, 17, 18). These results may support the use of pegfilgrastim during BEP treatment, particularly when bleomycin is administered under the lasting effect of sustained-release pegfilgrastim.

Interestingly, the MNC was recorded most frequently after pegfilgrastim injection in 85% (11 out of 13) of cycles using pegfilgrastim. In contrast, it was recorded before the initiation of filgrastim injection in 50% (11 out of 22) of cycles using filgrastim. These results indicate that filgrastim injection may

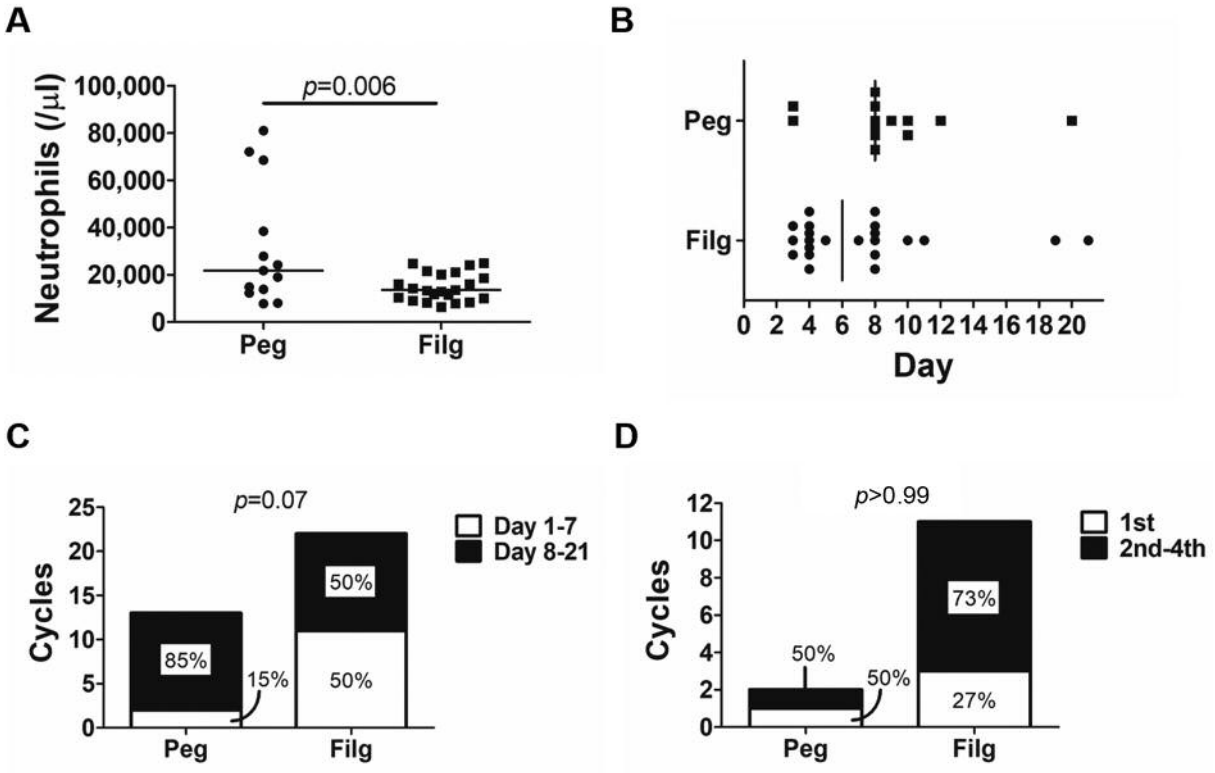

Figure 3. *Changes in neutrophil count in patients treated with bleomycin, etoposide and cisplatin during cycles using pegfilgrastim (Peg) and filgrastim (Fil). A: Maximum neutrophil count for individual patients. Bars represent median values. B: The number of days to the maximum neutrophil count for individual patients. C: The percentage of patients with maximum neutrophil count before and after initiation of granulocyte-colony stimulating factor (G-CSF) is shown. Most maximum neutrophil counts were recorded on days after pegfilgrastim injection in cycles administering pegfilgrastim; however, only half of the maximum neutrophil counts were recorded after filgrastim injection in cycles administering filgrastim. D: Of cycles with maximum neutrophil count recorded before initiation of G-CSF, the percentage of cycles with maximum count before G-CSF initiation in the first and subsequent (second, third, and fourth) cycles in the therapy series of bleomycin, etoposide, and cisplatin is shown.*

not be efficacious for increasing the neutrophil count in patients under BEP treatment. Furthermore, the proportion of the median number of days to MNC before the initiation of filgrastim injection in the first cycle is only 27%, indicating that MNC early in the filgrastim cycle is not due to the systemic inflammation caused by active GCT before BEP treatment, that is, filgrastim may not be able to increase the neutrophil count sufficiently beyond the baseline number of neutrophils before the initiation of filgrastim injection. In contrast, even in pegfilgrastim-induced neutrophilia, the number of leukocytes was less than 100,000/μl, which is borderline grade 3 neutrophilia. Moreover, neither interstitial pneumonia nor splenic rupture were observed. Splenic rupture secondary to G-CSF use most commonly occurs in patients and healthy donors in the hematopoietic cell transplantation setting (19-22).

This study had several limitations. The median number of administrations of filgrastim was five, while administration of pegfilgrastim once per cycle is equivalent to a daily injection of filgrastim for 11 days (9). This difference potentially leads to differences between cycles using pegfilgrastim and those using filgrastim. The small sample size may have prevented determination of the precise statistical significance of differences between cycles using the two different forms of G-CSF. Larger prospective studies with longer follow-up periods and data from other ethnic backgrounds are needed to confirm the findings of this study. In conclusion, this study showed that pegfilgrastim during BEP for patients with GCT may be a potential treatment to effectively reduce the severity and duration of neutropenia with minimal toxicity.

Conflicts of Interest

The Authors declare that they have no conflicts of interest.

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Received April 2, 2018
Revised May 2, 2018
Accepted May 3, 2018