



Single Center Experiences with Pegfilgrastim as Secondary Prophylaxis

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OBJECTIVE

Pegfilgrastim is a new generation on granulocyte-colony stimulating factors (G-CSF) with different pharmacokinetic properties. In this study, we aimed to evaluate the results of the use of pegfilgrastim as secondary prophylaxis.

METHODS

Between November 2016 and June 2019, a retrospective analysis of the patients who used pegfilgrastim with solid malignancies treated in the University of Health Sciences, Dr. A. Y. Ankara Oncology Hospital Department of Medical Oncology was performed.

RESULTS

A total of 148 patients were evaluated, and 33 (22.2%) of them were in the geriatric population (age>65). The majority of the patients (n=97, 65.5%) were diagnosed with breast carcinoma, and 93.2% (n=138) of all patients were treated with the intermediate-risk chemotherapy regimen. Pegfilgrastim was used as secondary prophylaxis for all of the patients. Despite pegfilgrastim prophylaxis, febrile neutropenia (FN) developed in four (2.7%) patients. Chemotherapy delay due to afebrile neutropenia occurred in eight patients (5.4%), and neutrophil counts returned to normal in mean 4.0 (3-5) days. When side effects were evaluated, 31 patients (20.9%) had pegfilgrastim-induced bone pain and two patients (1.3%) had redness in the injection site.

CONCLUSION

The low incidence of FN and chemotherapy delay, even in secondary prophylaxis with pegfilgrastim, suggests that pegfilgrastim is an effective agent in neutropenia prophylaxis.

Keywords: Febrile neutropenia; granulocyte colony-stimulating factors; pegfilgrastim.

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Introduction

Although it may vary depending on the chemotherapy regimen, up to 80% neutropenia and 20-40% febrile neutropenia (FN) may occur due to cytotoxic chemotherapies.[1-4] Dose reduction and delaying due to

neutropenia reduce the efficacy of chemotherapy. FN can be fatal and increases the costs of treatment due to hospitalizations and antibiotic use.[5,6]

The use of G-CSF significantly reduces the rates of neutropenia and the presence of FN due to chemotherapy. Filgrastim is a widely-used recombinant human

Received: November 28, 2019

Accepted: December 16, 2019

Online: February 20, 2020

Accessible online at:

www.onkder.org

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G-CSF, which lasts longer than 25 years in the treatment of neutropenia. Pegfilgrastim is a new generation G-CSF with different pharmacokinetic properties. [5-8] Pegfilgrastim, which is formed by pegylation of filgrastim with polyethylene glycol, has less renal clearance due to its large molecular structure. In addition, pegfilgrastim binds to the surface receptors of neutrophil precursors and does not separate from the cell surface until the number of neutrophils increases. Due to these two properties, pegfilgrastim is long-acting. In clinical trials, pegfilgrastim administered as a single dose was compared with daily injections of filgrastim and similar efficacy on neutropenia and FN has been shown.[9-13]

In this report, we aimed to evaluate the results of the use of pegfilgrastim as secondary prophylaxis in patients who were diagnosed with solid malignancy and treated in our center.

Materials and Methods

Between November 2016 and June 2019, a retrospective analysis of the patients who used pegfilgrastim with solid malignancies treated at the University of Health Sciences, Dr. A. Y. Ankara Oncology Hospital Department of Medical Oncology, was performed.

Patients with solid malignancy, >18 years old and who used pegfilgrastim at least once for FN prophylaxis were included in this study. Patients with hematologic malignancies were excluded from this study. Due to the regulations in our country, all patients who received pegfilgrastim had a neutrophil count <500 or FN at least once after previous chemotherapy cycles.

Patients' demographic characteristics, comorbidity, Eastern Cooperative Oncology Group (ECOG) performance score, type and stage of the malignancy, chemotherapy regimen, previous radiotherapy, number of cycles the pegfilgrastim applied, chemotherapy delayed due to neutropenia, history of FN, hospitalization due to FN, duration of grade 4 neutropenia and pegfilgrastim related side effects were recorded.

Chemotherapy regimens were grouped according to the guidelines of the National Comprehensive Cancer Network (NCCN) 2.2018 for the risk of FN.

Neutropenia was defined as an absolute neutrophil count of <1500 mcL. The fever ($\geq 38.3^{\circ}\text{C}$ or 38.0°C over 1 hour) with grade 4 neutropenia (neutrophil <500 mcL) was accepted as FN.

Descriptive statistics were performed using the SPSS 23 statistical program.

Results

The clinical characteristics of the 148 patients included in this study are shown in Table 1. Thirty-three (n=33, 22.2%) patients were in the geriatric population (age>65). The majority of patients had a diagnosis of breast carcinoma (n=97, 65.5%), and 92 (62.2%) of all patients received adjuvant chemotherapy. Only one patient at the metastatic stage had bone marrow metastasis.

The most commonly used chemotherapy regimen was the combination of doxorubicin and cyclophosphamide (n=81, 54.7%). According to the risk of FN of the given chemotherapies, 10 patients (6.7%) had high-risk chemotherapy, and the other patients received intermediate-risk chemotherapy. In our study, there was no patient who received neoadjuvant

Table 1 Patients characteristics

	n=148	%
Age		
Median	56 (22-75)	
Sex		
Female	120	81.1
Male	28	18.9
Comorbidity		
Yes	67	45.3
No	81	54.7
Performance score		
0	99	66.9
1	45	30.4
2	4	2.7
Malignancy		
Breast	97	65.5
Colorectal	27	18.3
Lung	5	3.4
Gynecologic	5	3.4
Gastric	4	2.7
Others	10	6.7
Stage		
Localized (Stage I-II-III)	92	62.1
Stage IV	56	37.8
Chemotherapy regimen		
AC	81	54.7
FOLFOX+/-biologic agents	24	16.2
Docetaxel	13	8.7
FOLFIRI+biologic agents	8	5.4
Cisplatin+etoposid	4	2.7
Others	18	12.1

AC: Doxorubicin/cyclophosphamide; FOLFOX: 5-Fluorouracil/leucovorin/oxaliplatin; FOLFIRI: 5-Fluorouracil/leucovorin/Irinotecan

chemotherapy or used pegfilgrastim simultaneously with radiotherapy.

A single dose of 6 mg pegfilgrastim was administered subcutaneously 24 hours after chemotherapy, during median 3 (1-12), a totally of 425 chemotherapy cycles.

Despite pegfilgrastim prophylaxis, FN developed in four (2.7%) patients. One patient was over 65 years of age, and the other patient had high-risk chemotherapy. All of these patients were hospitalized, and the mean duration of grade 4 neutropenia was two (1-3) days. No additional dose of G-CSF (filgrastim, lenograstim) was applied to patients after the development of FN.

One patient with metastatic breast carcinoma who had previously undergone multiple-line chemotherapy was died due to sepsis. This patient was being treated with eribulin at the sixth line for metastatic breast cancer. Before the third cycle of eribulin mesylate administration, the patient's ECOG performance score was 1, white blood cell (WBC) and neutrophil was 7500 mL/3500 mL, respectively. Although pegfilgrastim was administered 24 hours after chemotherapy, septic shock developed after 10 days.

Chemotherapy delay due to afebrile neutropenia occurred in eight patients (5.4%), and neutrophil counts returned to normal in mean 4.0 (3.0-5.0) days.

When the side effects were evaluated, pegfilgrastim-induced bone pain was present in 31 patients (20.9%), and redness in the injection site was 2 (1.3%). Median 18.3 (3.5-30.5) months follow-up, no secondary malignancy occurred. There was no patient whose pegfilgrastim prophylaxis was stopped due to side effects.

Discussion

Despite advances in cancer treatment and prevention, neutropenia due to chemotherapy remains a common complication. Chemotherapy delays due to neutropenia may lead to a decrease in treatment efficacy, and FN can be fatal. There is a clear relationship between the intensity of the chemotherapy regimen and the risk of FN. In some regimens, the risk of FN may exceed 20%. The use of G-CSF significantly reduces the risk of FN and prevents the chemotherapy delay due to neutropenia. In this way, the effectiveness of chemotherapy is preserved.[14] In this study, we aimed to evaluate the efficacy of new generation long-acting pegfilgrastim as secondary prophylaxis.

In this study, despite the pegfilgrastim prophylaxis, the incidence of development of FN was 2.7%. In phase 3, randomized trial, which compared pegfilgras-

tim with filgrastim in patients with breast carcinoma, the incidence of FN was seen 13% in the pegfilgrastim arm after combination chemotherapy of docetaxel and doxorubicin.[9] In another study conducted in the similar group with a same chemotherapy regimen, the incidence of FN was reported as 7%.[12] A study of 943 patients from nine European countries evaluated the efficacy of pegfilgrastim in high-risk chemotherapy.[15] The majority of the patients in this study were diagnosed with breast carcinoma (77%), and the incidence of FN with pegfilgrastim prophylaxis was 3%. A slightly higher incidence of FN was reported in these studies compared to our study. In our study 93.3% of the patients were administered intermediate-risk chemotherapy regimen. In the other studies, all patients were administered a high-risk chemotherapy regimen. Thus, the FN rate is higher than the FN rate in our study.

A lower incidence of FN has been reported in patients receiving intermediate-risk chemotherapy with pegfilgrastim prophylaxis. In patients with colorectal cancer, the efficacy of pegfilgrastim after the 5-fluorouracil, leucovorin and oxaliplatin combination (FOLFOX)/5-fluorouracil, leucovorin and irinotecan combination (FOLFIRI) regimen was evaluated, and the FN rate was found 3.2%.[16] In another study that compared placebo and pegfilgrastim after docetaxel in breast carcinoma, the ratio of FN was 17% and 1%, respectively.[11] In these two studies, which were performed with intermediate-risk chemotherapy regimens, the FN rates were similar to our study.

In Vogel et al.'s study, the rate of hospitalization due to FN was reported as 1% in the pegfilgrastim arm. [11] In our study, all patients who developed FN were hospitalized. In our daily practice, the low socio-cultural level of our patients, and that they live in other cities make us more liberal in the decision of hospitalization, which might have led to a change in hospitalization rates.

In our study, the mean duration of grade 4 neutropenia was two (1-3) days. Similar to our study, Holmes et al. reported that the mean duration of grade 4 neutropenia for the patients who developed FN was 1.7 days.[12] In Salmon et al.'s study, chemotherapy delay due to neutropenia was also in 3% of the patients. [15] The incidence of FN and chemotherapy delay in this study is similar to our study.

In the previous studies, it was reported that the frequency of bone pain due to pegfilgrastim was 18-37%. [17,18] Similarly, these adverse effects were observed in 17.1% of our patients.

One of the limitations of this study was the heterogeneous group of patients concerning oncologic diagnoses and chemotherapy regimens. The other limitation was the retrospective feature of our study.

Although all the patients in our study consisted of patients who had previously developed grade 4 neutropenia, it was observed that there was a low incidence of FN and chemotherapy delay in secondary prophylaxis with pegfilgrastim.

Conclusion

In this study, it was clearly seen that pegfilgrastim is an effective agent for neutropenia prophylaxis with a good tolerability profile.

Peer-review: Externally peer-reviewed.

Conflict of Interest: The authors have no conflicts of interest to declare.

Ethics Committee Approval: The authors declare that this research was conducted according to the principles of the World Medical Association Declaration of Helsinki "Ethical Principles for Medical Research Involving Human Subjects" (amended in October 2013).

Financial Support: The authors declare that this study received no financial support.

Authorship contributions: Concept – F.Y., U.D., B.Ö.; Design – F.Y., U.D.; Supervision – B.Ö., U.D.; Funding – None; Materials – F.Y., A.İ., F.A.; Data collection and/or processing – F.Y., A.İ.; Data analysis and/or interpretation – F.Y., E.E., F.A.; Literature search – F.Y., G.T.; Writing – F.Y., G.T., E.E.; Critical review – F.Y., B.Ö., U.D.

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