

An observational, prospective, open label, multicenter study to evaluate the safety and effectiveness of pegfilgrastim as secondary prophylaxis to decrease the incidence of febrile neutropenia in Korean female patients with breast cancer

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A B S T R A C T

Purpose: Pegfilgrastim is a widely used long-acting granulocyte colony-stimulating factor (G-CSF) that prevents febrile neutropenia (FN) in patients with breast cancer receiving chemotherapy. This study aimed to evaluate the incidence of chemotherapy-related FN events and other adverse events (AEs) during chemotherapy in Korean patients with breast cancer treated with pegfilgrastim as secondary prophylactic support.

Materials and methods: This was a multicenter, open-label, prospective, observational study. A total of 1255 patients were enrolled from 43 institutions. The incidence of FN was evaluated as the primary endpoint. The secondary endpoints included (1) incidence of bone pain, (2) proportion of patients with a relative dose intensity (RDI) of $\geq 85\%$, and (3) proportion of patients with AE.

Results: Pegfilgrastim administration reduced FN by 11.8–1.6%. The highest incidence of bone pain was observed at the time point of the 1st day after the administration and mild bone pain was the most common of all bone pain severity. The mean RDI was $98.5 \pm 7.3\%$, and the proportion of the patients with and $RDI \geq 85\%$ was 96.9% (1169/1233). AEs were reported in 52.6% of the patients, and serious drug reactions occurred in only 0.7%.

Conclusion: The use of pegfilgrastim as secondary prophylaxis was effective and safe for preventing FN in patients with breast cancer who were treated with chemotherapy.

1. Introduction

Febrile neutropenia (FN) is a serious adverse event (SAE) encountered in patients undergoing chemotherapy for cancer treatment [1]. Chemotherapy-induced FN is associated with life-threatening infections, prolonged hospitalization, and increased healthcare costs. Furthermore, dose modification or delays in chemotherapy due to chemotherapy-induced treatment results in worsening clinical survival outcomes [1]. It is important to assess the risk of FN and prevent it by administering recombinant granulocyte colony-stimulating factor (G-CSF) during chemotherapy [2].

Current clinical guidelines recommended the primary prophylactic use of G-CSF when the risk of FN is more than 20% during chemotherapy [3]. Primary prophylaxis involves the use of G-CSF in the first and subsequent sessions of chemotherapy, whereas secondary prophylaxis is defined as the administration of G-CSF to patients who experienced neutropenic complications in the prior session of chemotherapy [4]. A previous episode of FN could increase the possibility of FN recurrence; accordingly, it is important to assess the risk of FN and related complications at each cycle and start secondary prophylaxis with G-CSF [3].

G-CSF is divided into short-acting (Filgrastim and Lenograstim) and long-acting (pegfilgrastim) types. Both are beneficial for the prevention of FN in patients with cancer. However, short-acting G-CSF needs relatively more frequent administration and absolute neutrophil count (ANC) evaluation and could be accompanied by more discomfort and higher medical costs compared to pegfilgrastim [1,5]. Therefore, pegfilgrastim treatment may improve patient compliance. In addition, because there is no need for hospitalization or frequent injections, it is expected to improve the quality of life of the patients and save medical costs [1,6,7]. In spite of its usefulness, pegfilgrastim is associated with several side effects. According to previous study, these include bone pain, splenomegaly, thrombocytopenia, osteopenia and osteoporosis, bone pain, vasculitis, skin rash, eosinophilia, monocytosis, and the development of hematologic malignancy [8].

There has been a lack of reports on the actual usage status, safety, and effectiveness of long-acting pegfilgrastim (G-CSF) as a secondary prophylaxis in patients with breast cancer. We evaluated the incidence of chemotherapy related FN events and other AEs including bone pain during chemotherapy in Korean patients with breast cancer, who were treated with long-acting G-CSF (pegfilgrastim, Neulasta®) as a secondary prophylactic support in this study.

2. Materials and methods

2.1. Study design

The purpose of this study was to investigate the use of pegfilgrastim as secondary prophylaxis to reduce the occurrence of FN in Korean female patients with breast cancer who have received chemotherapy covered by the Korean National Health Insurance. This multicenter,

open-label, prospective observational study aimed to evaluate the safety and effectiveness of pegfilgrastim administration in clinical practice.

The applied chemotherapy regimens were classified into five groups as follows: four cycles of neoadjuvant/adjuvant Doxorubicin (A) 60 mg/m² + Cyclophosphamide (C) 600 mg/m² (AC regimen group), four cycles of neoadjuvant/adjuvant Doxorubicin (A) 60 mg/m² + Cyclophosphamide (C) 600 mg/m² which is followed by four cycles of Docetaxel (T) 75 mg/m² (AC-T regimen group), four cycles of neoadjuvant/adjuvant Doxorubicin (A) 60 mg/m² + Cyclophosphamide (C) 600 mg/m² which is followed by four cycles of Docetaxel (T) 75 mg/m² + Trastuzumab (H) 8 mg/kg (loading dose), 6 mg/kg (maintenance dose) (AC-TH regimen group), four cycles of adjuvant Docetaxel (T) 75 mg/m² + Cyclophosphamide (C) 600 mg/m² (TC regimen group), four cycles of adjuvant Doxorubicin (A) 60 mg/m² + Cyclophosphamide (C) 600 mg/m² which is followed by four cycles of Docetaxel (T) 75 mg/m² + Trastuzumab (H) 8 mg/kg (loading dose), 6 mg/kg (maintenance dose) + Pertuzumab (P) 840 mg (loading dose), and 420 mg (maintenance dose) (AC-THP regimen group).

Secondary prophylaxis was administered to all five chemotherapy groups. Secondary prophylaxis involves starting and continuing pegfilgrastim administration 24 h after the end of chemotherapy in all subsequent cycles if there is any neutropenia in the previous cycle in which pegfilgrastim was not administered for prophylactic treatment [9].

This study was conducted from January 2018 to July 2021, and 1255 patients were sequentially enrolled from 43 institutions. Written informed consents were obtained from the patients according to the ethical standards of the institutional review board (IRB) at each institution and the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. The study protocol was approved by the IRB of each institution. This trial was registered at [ClinicalTrials.gov](https://clinicaltrials.gov), number NCT03433560.

2.2. Study population and procedures

2.2.1. Eligibility criteria

The inclusion criteria were as follows: women aged 19–64 years, patients with breast cancer who had received chemotherapy under the coverage of the medical care benefit of the Korean National Health Insurance; patients with a history of FN or dose-limiting neutropenia (ANC < 500) in the previous cycle without prophylactic G-CSF administration. Patients with chronic myelogenous leukemia; myelodysplastic syndrome; or hypersensitivity to E. coli-derived protein, pegfilgrastim, filgrastim were excluded from the study.

2.2.2. Procedures

Since the chemotherapy cycle and treatment duration varied depending on the regimen the patients received, the safety and effectiveness of pegfilgrastim were evaluated by visiting the institution based on the schedule of chemotherapy that patients received. In this observational study, no additional visits were made other than the usual visits

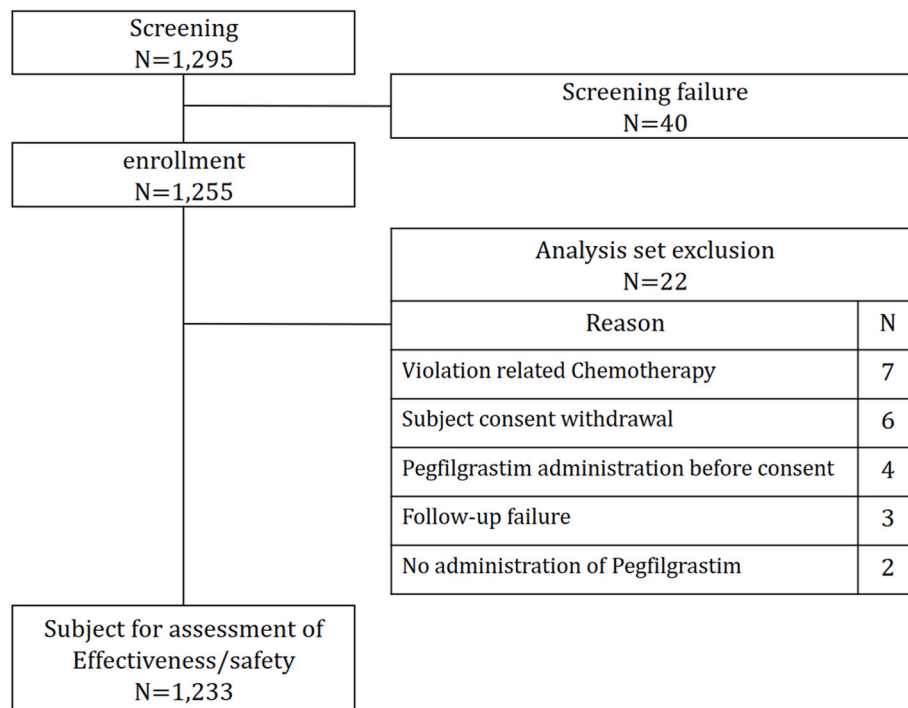


Fig. 1. Flow Diagram of the selection of eligible population.

for treatment purposes. The severity of bone pain was evaluated using a visual analog scale (VAS) questionnaire and was defined as mild, moderate, or severe [10].

2.3. Study endpoints

The primary endpoint was incidence of FN in each patient. FN was

defined as fever and neutropenia as follows: Fever: If the temperature rises above 38.0 °C when measured with a tympanic thermometer or above 37.5 °C when measured with an axillary thermometer, or above 38.3 °C when measured with an oral thermometer, or above 38.0 °C for 1–2 h or more if it persists. Neutropenia: in case that absolute neutrophil count <500/μL or <1000/μL and expected to decrease to <500/μL within 2–3 days [11–13].

Table 1
Baseline characteristics of the study population.

Enrollment 1255 (100%)		Overall	Patients analyzed through chemotherapy regimen				
Demography			AC	AC-T	AC-TH	TC	AC-THP
N (%)		1233 (98.25)	605 (49.07)	511 (41.44)	84 (6.81)	27 (2.19)	6 (0.49)
Age, year		50.36 ± 8.02	50.96 ± 7.87	49.61 ± 8.20	50.23 ± 7.88	51.44 ± 7.98	52.00 ± 4.60
Gender, n (%)	Male	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)
	Female	1233 (100.00)	605 (100.00)	511 (100.00)	84 (100.00)	27 (100.00)	6 (100.00)
Height, cm		158.31 ± 5.59	157.74 ± 5.79	159.10 ± 5.35	157.97 ± 5.39	156.96 ± 4.62	159.50 ± 3.59
Body weight, kg		59.93 ± 10.01	59.16 ± 9.46	60.95 ± 10.69	58.41 ± 9.34	61.79 ± 9.65	64.10 ± 5.99
BSA, m²		1.62 ± 0.15	1.61 ± 0.14	1.64 ± 0.15	1.60 ± 0.14	1.64 ± 0.14	1.70 ± 0.06
pregnancy	No	1233 (100.00)	605 (100.00)	511 (100.00)	84 (100.00)	27 (100.00)	6 (100.00)
	Yes	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)
Comorbidity	Hypertension	153 (12.41)	75 (12.40)	60 (11.74)	11 (13.10)	5 (18.52)	2 (33.33)
	Diabetes	49 (3.97)	23 (3.80)	21 (4.11)	4 (4.76)	1 (3.70)	0 (0.00)
	Cardiac disorder	9 (0.73)	5 (0.83)	2 (0.39)	2 (2.38)	0 (0.00)	0 (0.00)
	Hepato-biliary disorder	11 (0.89)	6 (0.99)	4 (0.78)	0 (0.00)	1 (3.70)	0 (0.00)
	Renal disorder	6 (0.49)	3 (0.50)	1 (0.20)	2 (2.38)	0 (0.00)	0 (0.00)
Chemotherapy cycle before pegfilgrastim	(N) Mean ± SD	(1233) 2.65 ± 1.42	(605) 2.08 ± 0.33	(511) 3.20 ± 1.80	(84) 3.58 ± 1.94	(27) 2.00 ± 0.00	(6) 3.17 ± 2.04
	Median [Min - Max]	2.00 [1.00–8.00]	2.00 [2.00–4.00]	2.00 [1.00–8.00]	2.00 [2.00–8.00]	2.00 [2.00–2.00]	2.00 [2.00–7.00]

AC, Doxorubicin + Cyclophosphamide; **AC-T**, Doxorubicin + Cyclophosphamide → Docetaxel; **AC-TH**, Doxorubicin + Cyclophosphamide → Docetaxel + Trastuzumab; **TC**, Docetaxel + Cyclophosphamide; **AC-THP**, Doxorubicin + Cyclophosphamide → Docetaxel + Trastuzumab + Pertuzumab; **BSA**, body surface area.

¹Data were presented as mean ± SD or number (percentage).

²Age (years) = year of consent (YYYY) – year of birth (YYYY).

³Details of chemotherapy regimens: AC, T, TH, and TC were administered as secondary prophylaxis.

⁴Chemotherapy cycle before pegfilgrastim 1st.

Table 2

Febrile neutropenia incidence according to chemotherapy regimen.

FN incidence (%)	AC N = 605	TC N = 27	AC-T N = 511	AC-TH N = 84	AC-THP N = 6	Overall N = 1,233 ^a
Before pegfilgrastim	64 (10.58)	5 (18.52)	64 (12.52)	12 (14.29)	0 (0.00)	145 (11.76)
post 1st pegfilgrastim	N = 602	N = 27	N = 510	N = 83	N = 6	N = 1,228 ^b
N (%)	5 (0.83)	0 (0.00)	4 (0.78)	0 (0.00)	0 (0.00)	9 (0.73)
95% CI	[0.27, 1.93]	[0.00, 12.77]	[0.21, 2.00]	[0.00, 4.35]	[0.00, 45.93]	[0.34, 1.39]
post 2nd pegfilgrastim	N = 584	N = 27	N = 494	N = 82	N = 5	N = 1192
N (%)	5 (0.86)	0 (0.00)	1 (0.20)	0 (0.00)	0 (0.00)	6 (0.50)
95% CI	[0.28, 1.99]	[0.00, 12.77]	[0.01, 1.12]	[0.00, 4.40]	[0.00, 52.18]	[0.18, 1.09]
post 3rd pegfilgrastim	N = 531	N = 27	N = 461	N = 79	N = 5	N = 1103
N (%)	6 (1.13)	0 (0.00)	2 (0.43)	0 (0.00)	0 (0.00)	8 (0.73)
95% CI	[0.42, 2.44]	[0.00, 12.77]	[0.05, 1.56]	[0.00, 4.56]	[0.00, 52.18]	[0.31, 1.42]
post 4th pegfilgrastim			N = 374	N = 54	N = 5	N = 433
N (%)	–	–	1 (0.27)	0 (0.00)	0 (0.00)	1 (0.23)
95% CI	–	–	[0.01, 1.48]	[0.00, 6.60]	[0.00, 52.18]	[0.01, 1.28]
post 5th pegfilgrastim			N = 364	N = 52	N = 4	N = 420
N (%)	–	–	1 (0.27)	0 (0.00)	0 (0.00)	1 (0.24)
95% CI	–	–	[0.01, 1.52]	[0.00, 6.85]	[0.00, 60.24]	[0.01, 1.32]
post 6th pegfilgrastim			N = 345	N = 49	N = 4	N = 398
N (%)	–	–	1 (0.29)	0 (0.00)	0 (0.00)	1 (0.25)
95% CI	–	–	[0.01, 1.60]	[0.00, 7.25]	[0.00, 60.24]	[0.01, 1.39]
post 7th pegfilgrastim			N = 285	N = 39	N = 4	N = 328
N (%)	–	–	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)
95% CI	–	–	[0.00, 1.29]	[0.00, 9.03]	[0.00, 60.24]	[0.00, 1.12]
post 8th pegfilgrastim						
N (%)	–	–	–	–	–	–
95% CI	–	–	–	–	–	–
Overall	N = 602	N = 27	N = 510	N = 83	N = 6	N = 1228
N (%)	11 (1.83)	0 (0.00)	9 (1.76)	0 (0.00)	0 (0.00)	20 (1.63)
95% CI	[0.92, 3.25]	[0.00, 12.77]	[0.81, 3.32]	[0.00, 4.35]	[0.00, 45.93]	[1.00, 2.50]

AC, Doxorubicin + Cyclophosphamide; AC-T, Doxorubicin + Cyclophosphamide → Docetaxel; AC-TH, Doxorubicin + Cyclophosphamide → Docetaxel + Trastuzumab; TC, Docetaxel + Cyclophosphamide; AC-THP, Doxorubicin + Cyclophosphamide → Docetaxel + Trastuzumab + Pertuzumab.

¹Data were presented as number (percentage). The percentage is calculated based on the data collected at each time point.

²CI: confidence interval.

³Analyzed for each time point after administration of Neulasta.

⁴Details of chemotherapy regimens: AC, T, TH, and TC were administered as secondary prophylaxis.

^a total of 1233 patients were included in effectiveness and safety evaluation.

^b A total of 1228 patients were included in the analysis of FN incidence.

The secondary endpoints were (1) the incidence of bone pain, (2) the proportion of the patients with relative dose intensity (RDI) ≥ 85%, and (3) the proportion of the patients with AE. Bone pain was the most frequently reported AEs associated with the study drug. In this study, the incidence rate and pattern of bone pain after pegfilgrastim administration were investigated. RDI was defined as the amount of chemotherapy administered over a specific time compared to what was planned and was calculated using the following equation [14]: For the RDI calculation, the information on the planned dose and the planned injection duration and the administered dose and injection duration for each pegfilgrastim cycle were collected.

$$RDI = \left(\frac{\text{Actual total dose}}{\text{Actual total injection days}} \div \frac{\text{Planned total dose}}{\text{Planned total injection days}} \right) \times 100\%.$$

The occurrence of AE in clinical practice was recorded for this study. All AEs, regardless of whether they were related to the administration of pegfilgrastim, were recorded within 2 weeks after pegfilgrastim administration.

2.4. Statistical analysis

All data analyses were performed using the SAS software version 9.4. Categorical variables are reported as the number of patients (n), proportions (%), and 95% confidence interval (CI), and continuous variables are presented as the mean and the standard deviation (SD).

The effectiveness and safety analyses included all patients whose data were collected according to the study protocol, without any significant violations of the study protocol. Demographic data and baseline

characteristics were investigated in the chemotherapy group. Continuous variables were presented as descriptive statistics (mean, standard deviation [SD], median, minimum, and maximum), and categorical variables were presented as frequencies and percentages. Differences in the categorical variables among the chemotherapy groups were compared using the Pearson's chi-square test (Fisher's exact test when cells with an expected frequency below 5 were greater than 20%). Patients who did not revisit within the timeline or were not investigated were regarded as missing data. Missed data were not imputed, and a two-sided p -value ≤ 0.05 was considered significant.

3. Results

3.1. Baseline characteristics of the study population

Of the 1295 patients with breast cancer who were screened, 1255 were enrolled in this study from January 2018 to July 2021. After excluding 22 patients, the effectiveness and safety of pegfilgrastim were analyzed in 1233 patients (Fig. 1). The mean age of all patients was 50.4 ± 8.0 years (range 23–64).

Among the 397 patients (32.2%) with comorbidities, hypertension was the most common. 'AC regimen' was the most commonly used regimen (605 patients) and 'AC-T regimen' was the next commonly used regimen (511 patients). The baseline characteristics of the patients and the median chemotherapy cycle before pegfilgrastim are presented in Table 1.

Table 3

Occurrence of bone pain according to chemotherapy regimen.

Chemo type	AC	AC-T	AC-TH	TC	AC-THP	Overall
G-CSF order	N = 605	N = 511	N = 84	N = 27	N = 6	N = 1233
post 1st pegfilgrastim	510	479	79	27	5	1100
Bone pain	125 (24.51)	154 (32.15)	33 (41.77)	16 (59.26)	1 (20.00)	329 (29.91)
post 2nd pegfilgrastim	493	462	74	27	4	1060
Bone pain	111 (22.52)	145 (31.39)	24 (32.43)	17 (62.96)	1 (25.00)	298 (28.11)
post 3rd pegfilgrastim	446	425	72	27	4	974
Bone pain	83 (18.61)	144 (33.88)	25 (34.72)	12 (44.44)	2 (50.00)	266 (27.31)
post 4th pegfilgrastim	0	344	50	0	3	397
Bone pain	–	135 (39.24)	17 (34.00)	–	2 (66.67)	154 (38.79)
post 5th pegfilgrastim	0	332	45	0	3	380
Bone pain	–	110 (33.13)	12 (26.67)	–	2 (66.67)	124 (32.63)
post 6th pegfilgrastim	0	314	41	0	4	359
Bone pain	–	102 (32.48)	12 (29.27)	–	1 (25.00)	115 (32.03)
post 7th pegfilgrastim	0	264	35	0	4	303
Bone pain	–	77 (29.17)	10 (28.57)	–	1 (25.00)	88 (29.04)

AC, Doxorubicin + Cyclophosphamide; **AC-T**, Doxorubicin + Cyclophosphamide → Docetaxel; **AC-TH**, Doxorubicin + Cyclophosphamide → Docetaxel + Trastuzumab; **TC**, Docetaxel + Cyclophosphamide; **AC-THP**, Doxorubicin + Cyclophosphamide → Docetaxel + Trastuzumab + Pertuzumab.

¹Data were presented as number (percentage). The percentage is calculated based on the data collected at each time point.

²Analysis was conducted on participants whose bone pain was recorded as “yes” at each time point. (However, the overall result was analyzed in patients whose bone pain was felt at least once and pain medication was used.)

³Details of chemotherapy regimens: AC, T, TH, and TC were administered as secondary prophylaxis.

Table 4

Comparison of use of pain killers according to pain intensity.

Use of pain killer, N (%)	Mild (1–3)	Moderate (4–6)	Severe (7–10)	Overall	p-value
post 1st pegfilgrastim	N = 141	N = 117	N = 71	N = 329	<0.0001 ^a
Bone pain	74 (52.48)	83 (70.94)	57 (80.28)	214 (65.05)	
post 2nd pegfilgrastim	N = 134	N = 103	N = 60	N = 297	<0.0001 ^a
Bone pain	69 (51.49)	80 (77.67)	48 (80.00)	197 (66.33)	
post 3rd pegfilgrastim	N = 128	N = 97	N = 41	N = 266	<0.0001 ^a
Bone pain	68 (53.13)	72 (74.23)	40 (97.56)	180 (67.67)	
post 4th pegfilgrastim	N = 58	N = 54	N = 42	N = 154	0.0004 ^a
Bone pain	42 (72.41)	50 (92.59)	41 (97.62)	133 (86.36)	
post 5th pegfilgrastim	N = 59	N = 41	N = 24	N = 124	0.0021 ^a
Bone pain	42 (71.19)	40 (97.56)	21 (87.50)	103 (83.06)	
post 6th pegfilgrastim	N = 58	N = 32	N = 25	N = 115	0.0141 ^a
Bone pain	39 (67.24)	28 (87.50)	23 (92.00)	90 (78.26)	
post 7th pegfilgrastim	N = 48	N = 27	N = 13	N = 88	0.1685 ^b
Bone pain	37 (77.08)	25 (92.59)	12 (92.31)	74 (84.09)	
post 8th Pegfilgrastim	N = 0	N = 0	N = 0	N = 0	–
Bone pain	–	–	–	–	

¹Data were presented as number (percentage).

²Pain killer was administered at least once among patients who have ever experienced bone pain during the period of Neulasta administration.

^a Chi-square test.

^b Fisher's exact test.

3.2. Incidence of febrile neutropenia (FN)

The incidence of FN before G-CSF administration was 11.8% (145/1233). The overall incidence of FN during all cycles of the five regimens was 1.6% (20/1228). After pegfilgrastim administration, the incidence of FN decreased to less than 1.0% for most regimens. The efficacy of

pegfilgrastim as FN prophylaxis treatment is shown in Table 2.

3.3. Incidence of bone pain

Table 3 presents the occurrence of bone pain according to chemotherapy regimens. Among all cycles, the highest incidence of bone pain was observed at the time point of the 1st day after the pegfilgrastim administration. Pain intensity was classified as mild (1–3), moderate (4–6), or severe (7–10). Mild bone pain was the most common pain in all cycles. The proportion of patients who used painkillers (65%–86.4%) was higher than that of patients who did not use painkillers (15.9–35.1%) in all cycles, and most of them (84.2–94.6%) answered ‘effective’ when they used painkillers (Table 4). The mean duration of bone pain was 4.4 days. The duration of bone pain was longest at 5.0 ± 3.4 days after the 7th pegfilgrastim administration and shortest at 4.0 ± 3.2 days after the 1st pegfilgrastim administration.

3.4. RDI

The mean RDI was $98.5 \pm 7.3\%$, and the proportion of patients with $RDI \geq 85\%$ was 96.9% (1169/1207). The mean RDI by chemotherapy regimen was the highest in ‘AC-T regimen’ ($98.8 \pm 8.9\%$), and the proportion of patients with an $RDI \geq 85\%$ was also the highest in ‘AC-T regimen’ (97.8%, 492/503) (Table 5).

3.5. Adverse events (AE)

A total of 2035 cases of AEs occurred in 649/1233 (52.6%) patients, whereas 1317 cases of adverse drug reactions (ADRs) occurred in 494/1233 (40.1%) patients. Seventy one SAEs were reported in 46 of the 1233 (3.7%) patients. The incidence of serious ADRs (SADR) was as low as 12 cases in 9/1233 (0.7%) patients and included three cases of pyrexia, two cases of FN, and one case of neutropenia based on the Preferred Term of Medical Dictionary for Regulatory Activities (MedDRA) Version 24.1 (Table 6).

4. Discussion

This is the first real-world study about pegfilgrastim for secondary prophylaxis in patients with breast cancer. In this study, the incidence rate of total FN before pegfilgrastim administration was 11.8% (145/1233), and the incidence rate of total FN after pegfilgrastim

Table 5Proportion of patients with RDI $\geq$ 85%(N = 1233).

RDI (%)	AC (N = 605)	AC-T (N = 511)	AC-TH (N = 84)	TC (N = 27)	AC-THP (N = 6)	Overall (N = 1233)
post 1st pegfilgrastim	(N = 589)					
(N) Mean $\pm$ SD	(589) 99.18 $\pm$ 9.35	(503) 97.85 $\pm$ 8.47	(82) 97.12 $\pm$ 9.97	(27) 95.65 $\pm$ 12.11	(6) 99.83 $\pm$ 22.70	(1207) 98.41 $\pm$ 9.23
$\geq$ 85%, N (%)	543 (92.19)	456 (90.66)	73 (89.02)	25 (92.59)	5 (83.33)	1102 (91.30)
95% CI	[89.72, 94.23]	[87.77, 93.05]	[80.18, 94.86]	[75.71, 99.09]	[35.88, 99.58]	[89.57, 92.83]
post 2nd pegfilgrastim	(N = 549)	(482)	(80)	(27)	(5)	(1143)
(N) Mean $\pm$ SD	98.84 $\pm$ 4.74	96.76 $\pm$ 9.76	97.56 $\pm$ 9.13	98.49 $\pm$ 4.57	98.05 $\pm$ 15.47	97.86 $\pm$ 7.68
$\geq$ 85%, N (%)	521 (94.90)	435 (90.25)	71 (88.75)	26 (96.30)	4 (80.00)	1057 (92.48)
95% CI	[92.71, 96.58]	[87.24, 92.75]	[79.72, 94.72]	[81.03, 99.91]	[28.36, 99.49]	[90.79, 93.94]
post 3rd pegfilgrastim	(N = 363)	(380)	(56)	–	(5)	(441)
(N) Mean $\pm$ SD	–	98.79 $\pm$ 6.16	99.30 $\pm$ 3.60	–	107.25 $\pm$ 13.59	98.95 $\pm$ 6.06
$\geq$ 85%, N (%)	–	363 (95.53)	55 (98.21)	–	5 (100.00)	423 (95.92)
95% CI	–	[92.93, 97.37]	[90.45, 99.95]	–	[47.82, 100.00]	[93.63, 97.56]
post 4th pegfilgrastim	(N = 343)	(365)	(52)	–	(4)	(421)
(N) Mean $\pm$ SD	–	98.63 $\pm$ 5.97	95.79 $\pm$ 8.58	–	82.79 $\pm$ 7.39	98.13 $\pm$ 6.59
$\geq$ 85%, N (%)	–	343 (93.97)	43 (82.69)	–	1 (25.00)	387 (92.12)
95% CI	–	[91.02, 96.18]	[69.67, 91.77]	–	[0.63, 80.59]	[89.90, 94.34]
post 5th pegfilgrastim	(N = 326)	(348)	(50)	–	(4)	(402)
(N) Mean $\pm$ SD	–	98.35 $\pm$ 6.81	96.28 $\pm$ 7.49	–	65.43 $\pm$ 29.79	97.76 $\pm$ 8.04
$\geq$ 85%, N (%)	–	326 (93.68)	43 (86.00)	–	0 (0.00)	369 (91.79)
95% CI	–	[90.58, 96.00]	[73.26, 94.18]	–	[0.00, 60.24]	[88.66, 94.28]
post 6th pegfilgrastim	(N = 297)	(304)	(44)	–	(4)	(352)
(N) Mean $\pm$ SD	–	99.31 $\pm$ 4.22	98.06 $\pm$ 7.40	–	63.85 $\pm$ 28.95	98.75 $\pm$ 6.59
$\geq$ 85%, N (%)	–	297 (97.70)	39 (88.64)	–	0 (0.00)	336 (95.45)
95% CI	–	[95.31, 99.07]	[75.44, 96.21]	–	[0.00, 60.24]	[92.72, 97.38]
post 7th pegfilgrastim	(N = 297)	–	–	–	–	–
(N) Mean $\pm$ SD	–	–	–	–	–	–
$\geq$ 85%, N (%)	–	–	–	–	–	–
95% CI	–	–	–	–	–	–
post 8th pegfilgrastim	(N = 297)	–	–	–	–	–
(N) Mean $\pm$ SD	–	–	–	–	–	–
$\geq$ 85%, N (%)	–	–	–	–	–	–
95% CI	–	–	–	–	–	–
Overall	(N = 566)	(503)	(82)	(27)	(6)	(1207)
(N) Mean $\pm$ SD	98.58 $\pm$ 5.72	98.78 $\pm$ 8.94	97.46 $\pm$ 5.04	97.20 $\pm$ 6.53	94.97 $\pm$ 10.30	98.54 $\pm$ 7.25
$\geq$ 85%, N (%)	566 (96.10)	492 (97.81)	80 (97.56)	26 (96.30)	5 (83.33)	1169 (96.85)
95% CI	[94.20, 97.51]	[96.12, 98.90]	[91.47, 99.70]	[81.03, 99.91]	[35.88, 99.58]	[95.70, 97.76]

AC, Doxorubicin + Cyclophosphamide; AC-T, Doxorubicin + Cyclophosphamide $\rightarrow$ Docetaxel; AC-TH, Doxorubicin + Cyclophosphamide $\rightarrow$ Docetaxel + Trastuzumab; TC, Docetaxel + Cyclophosphamide; AC-THP, Doxorubicin + Cyclophosphamide $\rightarrow$ Docetaxel + Trastuzumab + Pertuzumab.

¹Analyzed for each time point after administration of Neurasta.

²RDI (Relative Dose Intensity) was calculated according to the formula below: Relative Dose Intensity (RDI) = (DDI/SDI) $\times$ 100. Delivered Dose Intensity (DDI) = (total dose administered, mg/m²)/(actual time to complete chemotherapy, including replacement days for missed cycles, days). Standard Dose Intensity (SDI) = (Standard Dose, mg/m²)/(standard time to complete chemotherapy, days).

³Data were presented as mean $\pm$ SD or number (percentage), 95% CI.

⁴Details of chemotherapy regimens: AC, T, TH, and TC were administered as secondary prophylaxis.

administration was reduced to 1.6% (20/1228). This was an observational study and the results should be considered in the context of several similar studies on the effects of long-acting G-CSFs. Our result is similar to those of previous studies [15–17]. A Japanese study suggested that the incidence rate of FN was 1.2% in the test group (pegfilgrastim, n = 173) and 68.8% in the control group (placebo, n = 173) [15]. Recent studies in the US and Argentina have also reported that the incidence rate of FN decreased to 1.0% and 1.7%, respectively, after pegfilgrastim (G-CSF) administration [16,17]. Some studies have compared the prophylactic effects of pegfilgrastim and filgrastim on FN. Most of these studies reported that the risk of FN was lower in the pegfilgrastim group, except for one study that reported no difference in the incidence rate of FN between the two groups. In these studies, the incidence rate of FN in the pegfilgrastim group ranged from 1% to 11.9% [18–22].

According to Massimo et al. (2020), RCTs provide the highest level of evidence for defining the efficacy of treatments before their adoption in clinical practice. However, in oncology, as in other fields of medicine, the analysis of real-world evidence (RWE) has been rapidly highlighted in recent years to answer clinical and policy-relevant questions that cannot be answered directly or completely using RCT data. It is clear that data obtained from the health records, cancer registries, and other RWE sources can provide valuable insights into treatments and their outcomes in routine daily oncology practice. Although the description of AE in real-world practice could be less accurate than that in RCTs due to

the lack of close monitoring and randomization, the RWE can be useful to describe treatment tolerability and collect AE in a larger population with more heterogeneity compared with the clinical trials [23]. Furthermore, our study is a large-scale prospective observational study which examined the safety and effectiveness of pegfilgrastim as a secondary prophylaxis for FN in patients with breast cancer in actual clinical practice.

Bone pain is the most common AE caused by G-CSF and it can be induced by various mechanisms, including inflammatory processes, expansion of the bone marrow, stimulation of osteoclasts and osteoblasts, and afferent nerve stimulation [24]. According to a systematic review, long-acting G-CSF significantly decreased the rate of bone pain (RR 0.75; 95% CI 0.58–0.98) compared to short-acting G-CSF [25]. The bone pain events associated with pegfilgrastim were reported 20–45% in RCTs, while 59–71% in post-marketing surveys [24]. In this observational study, the bone pain incidence rate related to pegfilgrastim was similar to the RCT results of 27.3–38.8%. Meanwhile, when reviewing the safety data of pegfilgrastim, the overall incidence rate of ADRs was 41.3%, of which bone pain was 6.9% from the European Eudra Vigilance database [26]. There were differences in race, the range of age, and the amount of the data between two databases. In our study, the incidence rate of all the AEs and ADRs was 52.6% and 40.1%, respectively, and that of SADR was 0.7%. There were no events of bone pain which are evaluated as the SAE or SADR in our study. As the SADR, there were

Table 6

AE in patients during this study (n = 1233).

Classification	N (%) [E]	95% CI
Adverse event	649 (52.64)	[49.80, 55.45]
Adverse drug reaction	494 (40.06)	[37.32, 42.86]
Serious adverse event	46 (3.73) [71]	[2.74, 4.95]
Serious adverse drug reaction	9 (0.73) [12]	[0.33, 1.38]
SAE based on MedDRA (SOC, PT)		
Blood and lymphatic system disorders	28 (2.27)	[42]
Febrile neutropenia	13 (1.05) [18]	
Neutropenia	11 (0.89) [14]	
Leukopenia	7 (0.57) [9]	
Pancytopenia	1 (0.08) [1]	
Infections and infestations	11 (0.89)	[12]
Pneumonia	2 (0.16) [2]	
Atypical pneumonia	1 (0.08) [1]	
Breast abscess	1 (0.08) [1]	
Device related bacteraemia	1 (0.08) [1]	
Device related infection	1 (0.08) [1]	
Influenza	1 (0.08) [1]	
Pyelonephritis acute	1 (0.08) [1]	
Systemic candida	1 (0.08) [1]	
Upper respiratory tract infection	1 (0.08) [1]	
Urinary tract infection	1 (0.08) [1]	
Wound infection	1 (0.08) [1]	
General disorders and administration site conditions	6 (0.49)	[6]
Pyrexia	4 (0.32) [4]	
Asthenia	2 (0.16) [2]	
Gastrointestinal disorders	4 (0.32)	[5]
Abdominal pain	1 (0.08) [1]	
Diarrhoea	1 (0.08) [1]	
Haemorrhoids thrombosed	1 (0.08) [1]	
Nausea	1 (0.08) [1]	
Vomiting	1 (0.08) [1]	
Investigations	2 (0.16)	[2]
Neutrophil count decreased	2 (0.16) [2]	
Metabolism and nutrition disorders	1 (0.08)	[1]
Hypophagia	1 (0.08) [1]	
Musculoskeletal and connective tissue disorders	1 (0.08)	[1]
Myalgia	1 (0.08) [1]	
Neoplasms benign, malignant and unspecified (including cysts and polyps)	1 (0.08)	[1]
Uterine leiomyoma	1 (0.08) [1]	
Nervous system disorders	1 (0.08)	[1]
Syncope	1 (0.08) [1]	
SADR based on MedDRA (SOC, PT)		
General disorders and administration site conditions	4 (0.32)	[4]
Pyrexia	3 (0.24) [3]	
Asthenia	1 (0.08) [1]	
Blood and lymphatic system disorders	3 (0.24)	[5]
Febrile neutropenia	2 (0.16) [2]	
Neutropenia	1 (0.08) [3]	
Investigations	1 (0.08)	[1]
Neutrophil count decreased	1 (0.08) [1]	
Metabolism and nutrition disorders	1 (0.08)	[1]
Hypophagia	1 (0.08) [1]	
Musculoskeletal and connective tissue disorders	1 (0.08)	[1]
Myalgia	1 (0.08) [1]	

SOC, system organ class; PT, preferred term.

¹MedDRA version 24.1.²Data were presented as number (percentage).³[E], number of AE.

three events of pyrexia, two events of FN, and one event of asthenia, neutropenia, neutrophil count decreased, hypophagia and myalgia, respectively. Ten AEs of leukocytosis which was included in warning and precautions in label of pegfilgrastim were reported in our study [27]. There was no unusual AE in comparison with the European Eudra Vigilance database [26].

During chemotherapy, the dose and administration time are critical to the survival rate of patients. A decrease in RDI is an important factor in assessing the impact of secondary prophylaxis with pegfilgrastim on breast cancer chemotherapy because it is related to poor clinical survival outcomes. In this study, the data were collected by setting the optimal RDI cutoff to 85% or higher for the best overall survival result. The proportion of patients with RDI $\geq$ 85% was 96.9%, which was comparable with previous results, indicating excellent secondary prophylaxis results with pegfilgrastim [28]. In a prospective cohort study on primary prophylaxis with pegfilgrastim, the proportion of patients with RDI $\geq$ 85% was maintained at > 93.2% [2]. According to a systematic review of the impact of primary prophylaxis, the RDI of all G-CSF-treated arms was over 90%, but the mean RDI of the placebo or no-treatment arm was less than 90% or 85% [29].

This study had a few limitations. First, this was an observational single arm study. Because of this reason, the safety and effectiveness of pegfilgrastim could not be compared directly with control group, although this was a prospective study. Second, there is the lack of diversity in chemotherapy regimen. Korean National Health Insurance program provides coverage for pegfilgrastim only in some regimen. For this reason, we could not include doxorubicin + cyclophosphamide followed by weekly or three weeks interval paclitaxel group in our study. Finally, mean age of patients in this study was relatively young compared to some recent studies [16,17]. Considering this, we could not completely rule out that this had an impact on our results.

The use of pegfilgrastim as secondary prophylaxis was effective in preventing chemotherapy-induced FN in patients with breast cancer. Furthermore, the AEs, including bone pain, were tolerable in patients treated with pegfilgrastim. This is the first study to demonstrate the effectiveness and safety of pegfilgrastim as secondary prophylaxis for the prevention of chemotherapy-induced FN in patients with breast cancer.

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Declaration of competing interests

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