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Clinical Impact of Primary Prophylactic Pegfilgrastim in Breast Cancer Patients Receiving Adjuvant Docetaxel-Doxorubicin-Cyclophosphamide Chemotherapy

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Conflict of Interest
The authors declare that they have no competing interests.

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Conceptualization: Jeon YW, Suh YJ; Data curation: Jeon YW; Formal analysis: Jeon YW,

ABSTRACT

Purpose: The regimen including concurrent docetaxel, doxorubicin, and cyclophosphamide (TAC) has been categorized as an important risk factor for febrile neutropenia (FN). This comparative study examined the clinical impact of long-acting granulocyte colony-stimulating factor (G-CSF) (pegfilgrastim) during adjuvant TAC chemotherapy in Korean patients with advanced breast cancer.
Methods: We analyzed data from 239 patients who received 6 cycles of adjuvant TAC chemotherapy. We categorized patients into 2 groups according to the use of primary prophylactic pegfilgrastim and compared the incidence and risk of FN, hospital care costs, and survival in the 2 groups.
Results: The incidence of FN decreased from 54.2% to 21.2% in all patients, after the use of pegfilgrastim. The analysis of a total of 1,432 chemotherapy cycles showed that the incidence of FN decreased from 36.1% to 9.1% after the use of pegfilgrastim. Moreover, the decrease in the incidence of FN with the use of pegfilgrastim resulted in a significant decrease in the mean duration of neutropenia (4.15 to 1.29 days), the risk of hospitalization (99.5% to 29.7%) and the mean total hospital care cost (USD 3,038 to USD 2,347). High relative dose intensity (RDI) in patients treated with pegfilgrastim than in those not treated with pegfilgrastim (99.18% vs. 93.85%) was associated with a better overall survival ($p = 0.033$).
Conclusions: The use of pegfilgrastim during adjuvant TAC chemotherapy was significantly associated with a decrease in the incidence and risk of FN, hospital care costs, and risk of death compared to the use of adjuvant TAC without primary prophylaxis.

Keywords: Breast neoplasms; Drug therapy; Febrile neutropenia; Granulocyte colony-stimulating factor

INTRODUCTION

Febrile neutropenia (FN) is a serious adverse effect in patients undergoing adjuvant chemotherapy for breast cancer [1]. Chemotherapy-induced FN may predispose patients to life-threatening infections and prolonged hospitalization, may require modifications of the chemotherapy dose or schedule, and may even be fatal [2]. In practice, these complications

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significantly contribute to increased medical and financial costs for breast cancer patient care [3,4]. Furthermore, a decrease in the relative dose intensity (RDI) of the chemotherapy regimen due to chemotherapy-induced FN prevents the achievement of optimal clinical survival outcomes [5-7].

Previous studies comparing various chemotherapy regimens have reported the effectiveness of a concurrent anthracycline-taxane regimen (docetaxel, doxorubicin, and cyclophosphamide [TAC]) for locally advanced breast cancer patients [8-10]. However, this regimen is associated with a significant risk of FN and hospitalization, particularly in the absence of primary granulocyte colony-stimulating factor (G-CSF) administration [11,12]. Despite the known effectiveness, the efficacy of this regimen is often restricted by FN. Therefore, clinical guidelines have categorized this regimen as conferring a high risk (> 20%) for FN, and have recommended the use of prophylactic recombinant G-CSF in patients receiving this regimen [13-15].

Short- and long-acting recombinant G-CSFs are helpful for reducing the incidence of chemotherapy-induced FN [13]. However, the data suggest that long-acting G-CSF is more effective than short-acting G-CSF in terms of the incidence of FN and FN-related complications [16,17]. Furthermore, long-acting G-CSF is also less burdensome to administer than short-acting G-CSF (once per cycle with long-acting G-CSF vs. up to 11 injections with short-acting G-CSF) [16,17]. Therefore, pegfilgrastim (a type of long-acting G-CSF) has been approved for primary prophylactic therapy during adjuvant TAC chemotherapy use since 2015 in the Korean guidelines for cost reimbursement.

Previous studies conducted in Korea reported that the overall frequency of FN during adjuvant TAC chemotherapy was significantly higher than that observed in previous studies conducted in Western countries (42.5%–63.4% vs. 17%–26%) [18-20]. However, only 1 study with a small sample size reported the clinical effect of primary prophylactic therapy using pegfilgrastim on the incidence of FN during adjuvant TAC chemotherapy in Korea [21]. Therefore, the aim of the current study was to evaluate not only the difference in the incidence of FN but also the difference in the risk of FN-related complications and hospitalization according to whether Korean patients with advanced breast cancer received primary prophylactic support with pegfilgrastim during adjuvant TAC chemotherapy. Additionally, comparative data on the costs incurred during adjuvant TAC chemotherapy were examined.

METHODS

Study population

The relevant Institutional Review Boards have approved this study (VC18RESI0162). All procedures in the study which involved human participants were performed in accordance with the ethical standards of the institutional and/or national research committee, and also in accordance with the 1964 Declaration of Helsinki and its later amendments or comparable ethical standards. Written informed consent was obtained from all patients. Electronic medical records of breast cancer patient who received adjuvant TAC chemotherapy from January 2010 to December 2018 at the Department of Surgery of St. Vincent's Hospital at the Catholic University of Korea, were reviewed. To minimize confounding factors in the analysis, patients with bilateral breast cancer or distant metastases at the time of diagnosis, and those who received neoadjuvant chemotherapy were excluded. Patients who did not complete 6 cycles of adjuvant TAC chemotherapy were also excluded (**Figure 1**).

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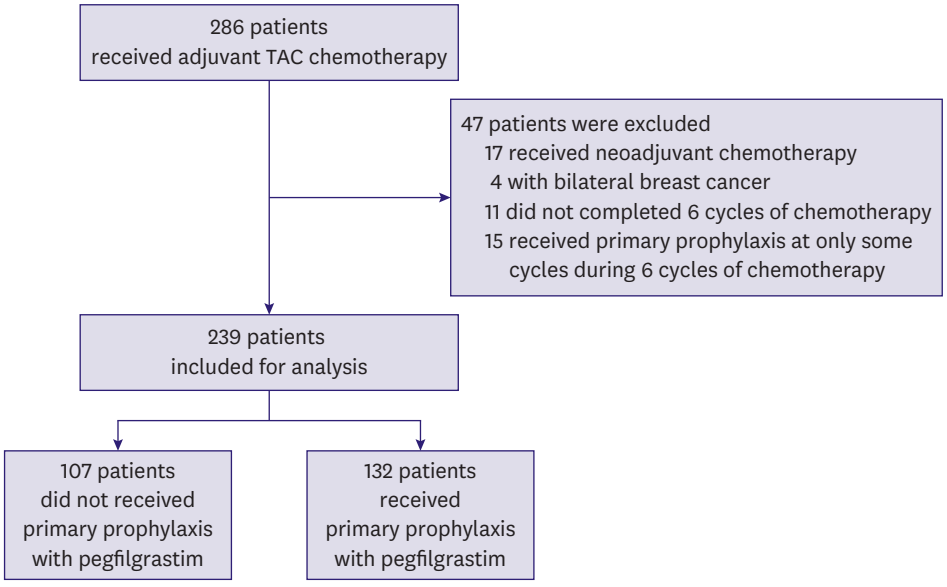

Figure 1. Consort diagram showing the patient inclusion and exclusion criteria.
TAC = docetaxel, doxorubicin, and cyclophosphamide.

We reviewed patient demographics and tumor characteristics including age, body weight (kg), height (m), body surface area (BSA, m^2), menopausal status, type of surgery, pathological staging, histologic type and grade, hormone receptor (HR) and human epidermal growth factor receptor 2 (HER2) expression, comorbidities, and smoking history. HR status determined using an enzyme immunoassay was obtained from patient medical records. Immunohistochemistry (IHC), fluorescence *in situ* hybridization (FISH), or silver *in situ* hybridization (SISH) were used to evaluate HER2 status. Samples with an IHC score of 0 or +1, or those with an IHC score of +2 and a negative FISH/SISH were defined as negative for HER2 overexpression.

Treatment

All patients received 6 cycles of TAC chemotherapy (doxorubicin [50 mg/m^2], cyclophosphamide [500 mg/m^2], and docetaxel [75 mg/m^2]) on day 1, every 3 weeks. Pegfilgrastim (Neulasta®, Amgen, Thousand Oaks, USA) has been covered by the National Health Insurance program since 2015. Since then, it has been used as a primary prophylactic in breast cancer patients undergoing TAC chemotherapy treatment in Korea. Pegfilgrastim was subcutaneously administered at 24 to 48 hours after the administration of chemotherapy, starting in January 2015. Before using pegfilgrastim, short-acting recombinant G-CSF (filgrastim) was administered daily for patients with at least grade 3 neutropenia after each cycle until the absolute neutrophil count (ANC) was restored to 1,000/mm^3. Laboratory tests including complete blood counts (CBCs) with differential and biochemistry assays were performed before each chemotherapy cycle, and on day 6. After chemotherapy, the nadir CBC was measured from day 6 until the ANC was restored to 1,000/mm^3. All patients with FN received prophylactic antibiotic therapy comprised of 1 g intravenously cefoperazone twice daily, and 200 mg tobramycin sulfate once daily, unless their use was contraindicated.

Outcome assessment

The incidence of FN, FN-related hospitalization, and FN-related complications according to the Common Terminology Criteria for Adverse Events (CTCAE) version 4.02, were investigated. FN was defined as neutropenia (< 500 neutrophils/μL or < 1,000 neutrophils/μL

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for over 48 hours) with a febrile event (oral temperature ≥ 38.3°C or ≥ 38.0°C for over 1 hour) observed by medical staff.

Dose reduction was defined as a reduction in the delivered dosage(s) of agent(s) administered relative to the standard values. If FN occurred, the doses of the TAC regimen were reduced by 1 dose level in the next cycle. A second dose reduction was allowed if FN still occurred after the first dose reduction. Of the patients who did not receive primary prophylaxis, those with grade 4 neutropenia were hospitalized for recovery from neutropenia. Of the patients who received primary prophylaxis, those who took more than 2 days to recover from grade 4 neutropenia were hospitalized. The chemotherapy RDI was estimated based on the ratio of the delivered dose intensity (DDI) and the reference standard dose intensity (SDI) [22].

The total hospital care cost was calculated as the sum of the costs associated with all medical claims during the entire cycle. Outpatient hospital visit costs, hospitalization costs, chemotherapy costs, and G-CSF costs were included in the total hospital care cost measure. The costs represented the reimbursed amount paid for the patient as identified by the electronic medical records.

Statistical analysis

The χ^2 test was used to compare categorical variables, and the 2-sample *t*-test was used to compare continuous variables. The logistic regression model was used to evaluate the odds ratio (OR) of FN among patients treated with primary prophylactic pegfilgrastim. The Kaplan-Meier method and log-rank tests were used for the comparison of survival curves. Disease-free survival (DFS) was calculated as the time from surgery to diagnosis of recurrent disease in the ipsilateral breast or at a local, regional, or distant site. Overall survival (OS) was defined as the time from initial diagnosis of primary breast cancer to death from any cause. The Cox proportional hazard regression model was used to evaluate the correlation of primary prophylaxis with DFS and OS. All tests were 2-sided, and a p-value < 0.05 was considered as statistically significant. The analyses were performed using SPSS version 18.0 for Windows (IBM Corp., Armonk, USA).

RESULTS

Between January 2010 and December 2018, 239 Korean patients (1,432 cycles of chemotherapy) with advanced breast cancer who received adjuvant TAC chemotherapy were enrolled for the analysis (**Figure 1**). A total of 107 patients did not receive prophylactic treatment with pegfilgrastim, and 132 patients received primary prophylactic support with pegfilgrastim during adjuvant TAC chemotherapy. The demographics and clinical characteristics of the study population according to primary prophylactic support with pegfilgrastim during adjuvant TAC chemotherapy are shown in **Table 1**. The median age was 51 years (range, 30–70 years). The mean body weight, body mass index (BMI), and BSA were 59.90 ± 8.63 kg, 24.09 ± 3.39 kg/m^2, and 1.60 ± 0.13 m^2, respectively.

The incidence of neutropenia, including that of grades 3/4, was 100% in patients who did not receive primary prophylaxis, and 91.7% in patients treated with prophylactic pegfilgrastim (p = 0.002). FN occurred in 54.2% of patients who did not receive primary prophylaxis, and in 21.2% of patients who received prophylactic pegfilgrastim (p < 0.001; **Table 2**). In the analysis of a total of 1,432 chemotherapy cycles, the incidence of grades 3 and 4 neutropenia was 0.4%

Table 1. Patients and tumor characteristics

Characteristics	Primary prophylaxis with pegfilgrastim		*p*-value
	No (n = 107)	Yes (n = 132)	
Age (years)	50.17 ± 6.87 (35–66)	52.05 ± 8.34 (30–70)	0.015
BMI (kg/m^2)	24.11 ± 3.40 (16.6–34.7)	24.75 ± 3.36 (18.5–33.9)	0.703
BSA (m^2)	1.58 ± 0.13 (1.19–1.96)	1.62 ± 0.13 (1.32–2.02)	0.762
Menopausal status			0.060
Premenopausal	56 (52.3)	53 (40.2)	
Postmenopausal	51 (47.7)	79 (59.8)	
Type of surgery			0.076
Breast conserving surgery	87 (81.3)	118 (89.4)	
Mastectomy	20 (18.7)	14 (10.6)	
Pathologic T stage			0.440
T1	56 (52.3)	62 (47.0)	
T2	48 (44.9)	66 (50.0)	
T3–T4	3 (2.8)	4 (3.0)	
Pathologic N stage			0.055
N1	68 (63.6)	99 (75.0)	
Higher than N2	39 (36.4)	33 (25.0)	
Histologic grade			0.405
G1 and G2	55 (51.4)	75 (56.8)	
G3	52 (48.6)	57 (43.2)	
Histologic type			0.109
Invasive ductal	101 (94.4)	117 (88.6)	
Invasive lobular	4 (3.7)	6 (4.6)	
Other	2 (1.9)	9 (6.8)	
Hormone receptor			0.248
ER and/or PR positive	73 (68.2)	99 (75.0)	
ER and PR negative	34 (31.8)	33 (25.0)	
HER2			0.190
Negative	72 (67.3)	99 (75.0)	
Positive	35 (32.7)	33 (25.0)	
Comorbidity			0.844
No	82 (76.6)	97 (73.5)	
Diabetes	5 (4.7)	10 (7.6)	
Hypertension	14 (13.1)	19 (14.4)	
Diabetes + Hypertension	6 (5.6)	6 (4.5)	
Smoking			0.045
No	105 (98.1)	122 (92.4)	
Yes	2 (1.9)	10 (7.6)	

Data are expressed as n (%) or the median (range).
BMI = body mass index; BSA = body surface area; ER = estrogen receptor; PR = progesterone receptor; HER2 = human epidermal growth factor receptor 2.

and 99.5%, respectively, in all cycles without primary prophylaxis. However, with prophylactic pegfilgrastim, the incidence of grades 3 and 4 neutropenia decreased to 15.4% and 69.4%, respectively. FN occurred in 36.1% of all cycles without primary prophylaxis and in 9.1% of all cycles with prophylactic pegfilgrastim ($p < 0.001$; **Table 3**). To identify risk factors for the occurrence of FN despite the use of primary prophylactic pegfilgrastim, logistic regression analysis was used to analyze data of patients treated with primary prophylactic pegfilgrastim (n = 132) (**Table 4**). However, there were no significant risk factors for the occurrence of FN among patient demographic characteristics and tumor characteristics.

Compared with patients who did not receive primary prophylaxis, most patients treated with prophylactic pegfilgrastim experienced FN starting on the first cycle and during only 1 cycle (**Table 2**). Furthermore, the mean duration of neutropenia significantly decreased after using prophylactic pegfilgrastim (4.15 ± 0.72 days vs. 1.29 ± 0.89 days, $p < 0.001$; **Table 3**).

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Table 2. Incidence of neutropenia and chemotherapy-related adverse events in all patients according to primary prophylaxis

Variables	Patients		*p*-value
	Primary prophylaxis with pegfilgrastim		
	No (n = 107)	Yes (n = 132)	
Neutropenia (grades 3 and 4)	107 (100.0)	121 (91.7)	0.002
Febrile neutropenia	58 (54.2)	28 (21.2)	< 0.001
Patients experienced FN			< 0.001
1st cycle	37/58 (63.8)	20/28 (71.5)	
2nd cycle	10/58 (17.3)	2/28 (7.1)	
3rd cycle	2/58 (3.4)	1/28 (3.6)	
4th cycle	3/58 (5.2)	1/28 (3.6)	
5th cycle	5/58 (8.6)	2/28 (7.1)	
6th cycle	1/58 (1.7)	2/28 (7.1)	
Number of cycles experienced FN			< 0.001
1 cycle	9/58 (15.6)	20/28 (71.5)	
2 cycles	16/58 (27.6)	1/28 (3.6)	
3 cycles	13/58 (22.4)	1/28 (3.6)	
4 cycles	10/58 (17.2)	1/28 (3.6)	
5 cycles	6/58 (10.3)	2/28 (7.1)	
6 cycles	4/58 (6.9)	3/28 (10.6)	
Treatment-related toxicity			
Anemia	15 (14.0)	8 (6.1)	0.038
Thrombocytopenia	3 (2.8)	16 (12.1)	0.008
Transfusion	34 (31.8)	15 (11.4)	< 0.001
AST/ALT elevation	1 (0.9)	3 (2.3)	0.425
Acute kidney injury	0 (0)	0 (0)	
Weight gain (kg)	3.51±4.55	3.52±3.03	0.987
Neutropenic infection	15 (14.0)	13 (9.8)	0.321
Hospitalization	107 (100)	68 (51.5)	< 0.001
Dose reduction	41 (38.3)	6 (4.5)	< 0.001
Treatment delay	10 (9.3)	8 (6.1)	0.341
RDI (%)	93.85 (70–100)	99.18 (88.4–100)	< 0.001
RDI < 85.0%	13 (12.1)	2 (1.5)	0.001

Data are expressed as number (%) or the median (range).
FN = febrile neutropenia; AST = aspartate transaminase; ALT = alanine aminotransferase; RDI = relative dose intensity.

Table 3. Incidence of neutropenia and chemotherapy-related adverse events in all chemotherapy cycles according to primary prophylaxis

Variables	Cycles		*p*-value
	Primary prophylaxis with pegfilgrastim		
	No (n = 642)	Yes (n = 792)	
Neutropenia (grade 3)	3 (0.4)	122 (15.4)	< 0.001
Neutropenia (grade 4)	639 (99.5)	550 (69.4)	< 0.001
Recovery from neutropenia (days)	4.15 ± 0.72	1.29 ± 0.89	< 0.001
Febrile neutropenia	232 (36.1)	72 (9.1)	< 0.001
Treatment-related toxicity			
Anemia	22 (3.4)	13 (1.6)	0.029
Thrombocytopenia	6 (0.9)	39 (4.9)	< 0.001
Transfusion	40 (6.2)	26 (3.3)	0.008
AST/ALT elevation	1 (0.1)	3 (0.4)	0.426
Acute kidney injury	0 (0)	0 (0)	
Hospitalization	639 (99.5)	235 (29.7)	< 0.001
Dose reduction	119 (18.5)	16 (2.0)	< 0.001
Treatment delay	11 (1.7)	6 (0.7)	0.096

Data are expressed as number (%) or the median (range).
AST = aspartate transaminase; ALT E= alanine aminotransferase.

We investigated other treatment-related toxicities in the 2 groups. Although patients treated with prophylactic pegfilgrastim were more likely to experience grades 3/4 thrombocytopenia, anemia and transfusion occurred more frequently in patients who did not receive primary

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Table 4. Logistic regression analysis for the odds of febrile neutropenia among patients with primary prophylactic pegfilgrastim (n = 132)

Variable	OR	95% CI	*p*-value
Age			0.842
< 60 years	1		
≥ 60 years	1.10	0.45–2.68	
BMI (kg/m^2)			0.130
Normal (18.5–24.9)	1		
Overweight (> 25.0)	1.79	0.84–3.81	
Menopausal status			0.519
Premenopausal	1		
postmenopausal	1.30	0.60–2.79	
Pathologic T stage			0.215
T1	1		
T2	0.92	0.42–1.98	
T3–T4	7.33	0.71–75.27	
Pathologic N stage			0.582
N1	1		
More than N2	1.27	0.54–2.95	
Histologic grade			0.406
G1, G2	1		
G3	1.37	0.65–2.92	
Histologic type			0.372
Invasive ductal	1		
Invasive lobular	0.43	0.05–3.83	
Others	0.27	0.03–2.24	
Hormone receptor			0.741
ER and/or PR positive	1		
ER and PR negative	0.86	0.36–2.08	
HER2			0.741
Negative	1		
Positive	0.86	0.36–2.08	
Co-morbidity			0.992
No	1		
Diabetes	1.06	0.26–4.38	
Hypertension	1.14	0.39–3.29	
Diabetes + Hypertension	1.23	0.21–7.11	
Smoking			0.974
No	1		
Yes	1.02	0.25–4.18	

BMI = body mass index; ER = estrogen receptor; PR = progesterone receptor; HER2 = human epidermal growth factor receptor 2; OR = odds ratio; CI = confidence interval.

prophylaxis (**Tables 2** and **3**). Among the 107 patients who did not receive primary prophylaxis, 15 (14.0%) patients developed neutropenic infections, which included 3 cases of chemoport infections, 9 cases of wound infections, and 3 cases of pneumonia. Neutropenic infections were observed in 13 (9.8%) of the 132 patients treated with prophylactic pegfilgrastim; among these, 8 cases of chemoport infections, 4 cases of wound infections, and 1 case of a perianal abscess were recorded (**Table 2**). Most patients did not experience severe hepatotoxicity or nephrotoxicity.

Dose reductions during adjuvant TAC chemotherapy were more frequently observed in patients who did not receive primary prophylaxis than in patients who received prophylactic pegfilgrastim (38.3% vs. 4.5%, $p < 0.001$, respectively); the RDI was lower in patients who did not receive primary prophylaxis than in those who received prophylactic pegfilgrastim (93.85% vs. 99.18%, $p < 0.001$, respectively). Furthermore, an RDI below 85.0% during adjuvant TAC chemotherapy was observed in 13 (12.1%) of the 107 patients who did not receive primary prophylaxis, but in only 2 patients (1.5%) treated with prophylactic pegfilgrastim ($p < 0.001$) (**Table 2**).

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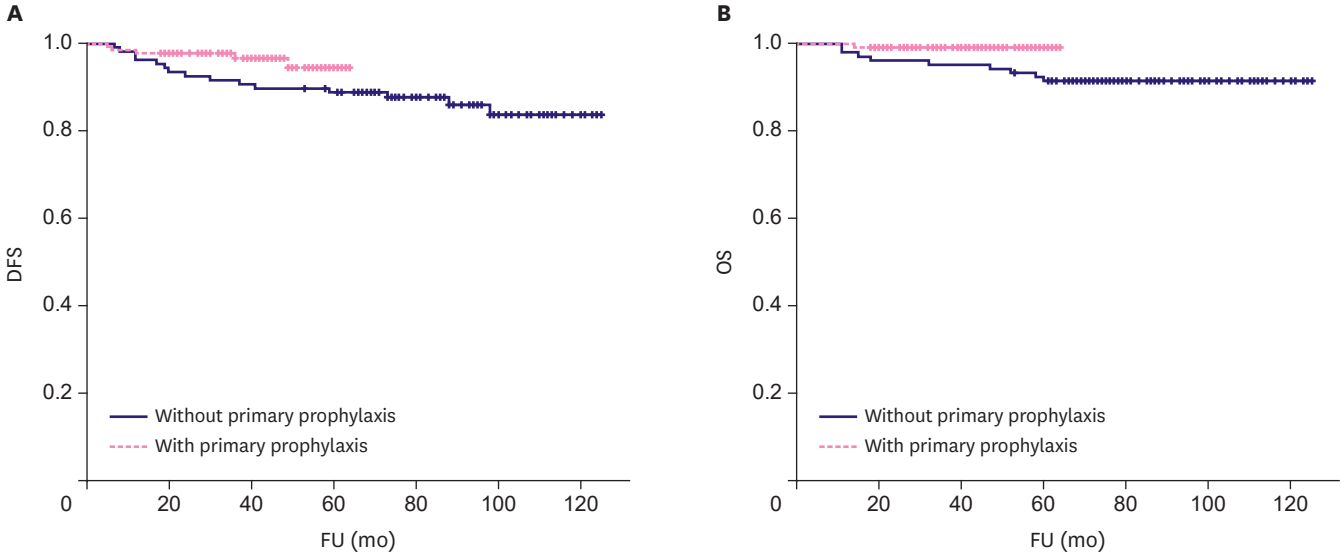

Figure 2. (A) DFS (p = 0.109) and (B) OS (p = 0.033), according to the primary prophylaxis with pegfilgrastim.
DFS = disease-free survival; OS = overall survival; FU = follow-up.

Compared with patients who did not receive primary prophylaxis, patients who received prophylactic pegfilgrastim showed a reduction in the risk of hospitalization (100.0% vs. 51.5%, p < 0.001) (**Table 2**). The incidence of hospitalization in each chemotherapy cycle was 99.5% in patients who did not receive primary prophylaxis and 29.7% in patients treated with prophylactic pegfilgrastim (p < 0.001) (**Table 3**). The mean total hospital care cost for all chemotherapy cycles was greater for patients who did not receive primary prophylaxis than for patients treated with prophylactic pegfilgrastim (USD 3,038 vs. USD 2,347, p < 0.001). The high total hospital care cost in patients who did not receive primary prophylaxis might have been affected by the high neutropenia-related hospitalization cost compared with patients treated with prophylactic pegfilgrastim.

The median length of follow-up was 57 months (range, 11–125). During follow-up, recurrence developed in 20 (8.4%) patients including 15 (14.0%) patients who did not receive primary prophylaxis and 5 (3.8%) patients treated with primary prophylaxis (hazard ratio [HR], 2.32; 95% confidence interval [CI], 0.81–6.89; p = 0.105). No significant differences in DFS (p = 0.109; **Figure 2A**) were found after Kaplan-Meier modeling. Overall, 10 (4.2%) patients died, including 9 (8.4%) patients who did not receive primary prophylaxis and 1 (0.8%) patient who received primary prophylaxis (HR, 7.22; 95% CI, 0.89–58.84; p = 0.022). Kaplan-Meier modeling showed that patients treated with primary prophylaxis had a better OS than did those who did not receive primary prophylaxis (p = 0.033; **Figure 2B**).

DISCUSSION

This study provides a summary of the comparative effectiveness of pegfilgrastim versus short-acting G-CSF in Korean breast cancer patients receiving adjuvant TAC chemotherapy in real-world clinical practice. Primary prophylactic support with pegfilgrastim during adjuvant TAC chemotherapy was significantly associated with a decrease in the incidence of FN, risk of FN-related complications and hospitalization, and total hospital care cost, compared to adjuvant TAC without primary prophylaxis.

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A treatment regimen with 6 cycles of adjuvant TAC chemotherapy has an obvious advantage compared to that with 4 cycles of AC followed by 4 cycles of docetaxel (AC followed by T). This is because the TAC regimen has a shorter treatment period than does the AC followed by T regimen, while showing similar efficacy with regard to DFS and OS [23]. However, treatment with the TAC regimen results in a significantly higher incidence of FN than does treatment with the AC followed by T regimen, which has limited the use of the TAC regimen in breast cancer patients [23]. Previous studies conducted in Western countries reported that the overall incidence of FN during adjuvant TAC chemotherapy was 17%–26% [8,10,11,23], and clinical guidelines have categorized this regimen as conferring a high risk (> 20%) of FN [13-15]. However, the overall frequency of FN in Korean breast cancer patients receiving adjuvant TAC chemotherapy was a significantly higher than that in patients in previous studies conducted in Western countries (42.5%–63.4% vs. 17%–26%) [18-20]. Ethnic differences in hematologic toxicity from the TAC regimen are associated with inter-individual and inter-ethnic variations of docetaxel and doxorubicin pharmacokinetics or pharmacodynamics due to genetic differences [24,25]. Previous studies reported that a greater degree of docetaxel- and doxorubicin-induced myelosuppression was observed in Asian patients than in Western patients [24,25]. Therefore, efforts to reduce the incidence of FN and FN-related complications in Korean breast cancer patients receiving adjuvant TAC chemotherapy are very important.

The use of long-acting G-CSF is the most important way to overcome the limitations caused by the hematologic toxicity of the TAC regimen. Treatment with long-acting G-CSF reduces FN and results in better supportive care and an improved quality of life in breast cancer patients [13,16,17,21]. In our study, the incidence of FN decreased from 54.2% to 21.2% in patients, and from 36.1% to 9.1% in all chemotherapy cycles, after the use of primary prophylactic pegfilgrastim. Moreover, a decrease in the incidence of FN resulted in a significant decrease in the mean duration of neutropenia (4.15 to 1.29 days) and the risk of hospitalization (99.5% to 29.7%). Although the rate of hospitalization decreased after the use of pegfilgrastim as the primary prophylactic, the rate of hospitalization in our current study was much higher than that observed in previous studies conducted in Western countries (10%–24.2%) [12,26]. In Korea, because most medical expenses for cancer patients are covered by National Health Insurance, cancer patients can access medical facilities more easily than can patients in Western countries. Therefore, we believe that the high incidence of hospitalization in our current study is not due to disease severity but because of the different healthcare environments.

One distinct aspect of this study is that comparative costs were reported for short-acting (filgrastim) and long-acting recombinant G-CSF (pegfilgrastim). In cancer patients, FN-related complications and hospitalization following chemotherapy significantly contribute to the costs of supportive care. According to a study from 115 medical centers in the United States between 1995 and 2000, the average cost per hospitalization due to FN was reported to be $12,372 for breast cancer [3]. Another retrospective single-time-point survey study reported that the total time and human resource cost with filgrastim (14.8 hours and $364.66) in a 21-day chemotherapy cycle were higher than those with pegfilgrastim (2.4 hours and $57.30) [27]. In this study of real-world clinical practice, the total hospital care cost for all chemotherapy treatments was greater for filgrastim than that for pegfilgrastim (USD 3,038 vs. USD 2,347, $p < 0.001$) because of the greater costs of inpatient care during filgrastim cycles.

Furthermore, the use of long-acting G-CSF results in the preservation of the RDI of chemotherapy [5-7]. Several retrospective and prospective studies have reported that a decrease in the chemotherapy RDI, which commonly caused by FN, is a key factor in the

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assessment of adjuvant chemotherapy efficacy (e.g., DFS and OS) [5-7]. In our study, the RDI was significantly lower in patients who did not receive primary prophylaxis (93.85% vs. 99.18%, $p < 0.001$). Furthermore, an RDI below 85.0% during adjuvant TAC chemotherapy was observed in 12.1% of patients who did not receive primary prophylaxis but in only 1.5% of patients who received prophylactic pegfilgrastim ($p < 0.001$). As a result, patients treated with primary prophylaxis had a better OS than did those who did not receive primary prophylaxis ($p = 0.033$). Although DFS was not significantly different between the 2 groups (14.0% vs. 3.8%, $p = 0.109$), there was an observed difference of 10.2%.

Our study had some limitations, such as its retrospective nature. The number of patients was small because only patients who received adjuvant TAC chemotherapy at a single institution were included. In addition, the follow-up period of our study may not have been sufficient to evaluate patients with late recurrences or death, which can occur 10 years after the initial treatment. However, we believe that this study has clinical value because it is the first study comparing the clinical effectiveness of pegfilgrastim versus filgrastim in Korean breast cancer patients receiving adjuvant TAC chemotherapy.

In conclusion, primary prophylaxis with pegfilgrastim during adjuvant TAC chemotherapy was significantly associated with a decrease in the incidence of FN and the risk of FN-related complications (including the mean duration of neutropenia, the risk of hospitalization, total hospital care cost, and RDI) compared to those during adjuvant TAC without primary prophylaxis. As the incidence of FN is much higher in Korean breast cancer patients than in Western breast cancer patients, primary prophylaxis with pegfilgrastim is not optional; on the contrary, it is an essential part of treatment to improve the quality of life and oncologic outcomes of Korean breast cancer patients receiving adjuvant TAC chemotherapy.

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