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

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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...
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).
We reviewed patient demographics and tumor characteristics including age, body weight (kg), height (m), body surface area (BSA, m²), 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/m²], cyclophosphamide [500 mg/m²], and docetaxel [75 mg/m²]) 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/mm³. 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/mm³. 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.
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 $\chi^2$ 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%
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).
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 prophylaxis.

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

| Variables                   | Patients          | p-value | p-value |
|-----------------------------|-------------------|---------|---------|
| Neutropenia (grades 3 and 4)| No (n = 107)      | 0.002   |         |
|                             | Yes (n = 132)     |         |         |
| Febrile neutropenia         | 58 (54.2)         | < 0.001 | < 0.001|
| Patients experienced FN     | 1st cycle         | < 0.001 |         |
|                             | 2nd cycle         |         |         |
|                             | 3rd cycle         |         |         |
|                             | 4th cycle         |         |         |
|                             | 5th cycle         |         |         |
|                             | 6th cycle         |         |         |
| Number of cycles experienced FN| 1 cycle           | < 0.001 | < 0.001|
|                             | 2 cycles          |         |         |
|                             | 3 cycles          |         |         |
|                             | 4 cycles          |         |         |
|                             | 5 cycles          |         |         |
|                             | 6 cycles          |         |         |
| Treatment-related toxicity  | Anemia            | 0.038   |         |
|                             | Thrombocytopenia  | 0.008   |         |
|                             | Transfusion       | < 0.001 | 0.008   |
|                             | AST/ALT elevation | 0.425   |         |
|                             | Acute kidney injury| 0.987   |         |
| Weight gain (kg)            | 3.51±4.55         | 3.52±3.03| 0.321   |
| Neutropenic infection       | 15 (14.0)         | 0.321   |         |
| Hospitalization             | 107 (100)         | < 0.001 |         |
| Dose reduction              | 41 (38.3)         | 0.001   |         |
| Treatment delay             | 10 (9.3)          | 0.341   |         |
| RDI (%)                     | 93.85 (70–100)    | 0.001   |         |
| RDI < 85.0%                 | 13 (12.1)         | 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 | p-value |
|-----------------------------|-----------------|---------|---------|
| Neutropenia (grade 3)       | No (n = 642)    | < 0.001 |         |
|                             | Yes (n = 792)   |         |         |
| Neutropenia (grade 4)       | 639 (99.5)      | < 0.001 |         |
| Recovery from neutropenia   | 4.15 ± 0.72     | < 0.001 |         |
| Febrile neutropenia         | 232 (36.1)      | < 0.001 |         |
| Treatment-related toxicity  | Anemia          | 0.029   |         |
|                             | Thrombocytopenia| < 0.001 |         |
|                             | Transfusion     | 0.008   |         |
|                             | AST/ALT elevation| 0.426   |         |
|                             | Acute kidney injury| 0.986   |         |
| Hospitalization             | 639 (99.5)      | < 0.001 |         |
| Dose reduction              | 119 (18.5)      | < 0.001 |         |
| Treatment delay             | 11 (17.7)       | 0.096   |         |

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

### 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    |          |             |
| > 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         | 0.43 | 0.05–3.83|             |
| Invasive lobular        | 0.27 | 0.03–2.24|             |
| Others                  |      |          |             |
| 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.
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.
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 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
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 \( (14.0\% \text{ vs. } 3.8\% \text{, } p = 0.109) \), 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.

REFERENCES

1. Dale DC. Colony-stimulating factors for the management of neutropenia in cancer patients. Drugs 2002;62 Suppl 1:1-15. [PUBMED] [CROSSREF]
2. Kuderer NM, Dale DC, Crawford J, Lyman GH. Impact of primary prophylaxis with granulocyte colony-stimulating factor on febrile neutropenia and mortality in adult cancer patients receiving chemotherapy: a systematic review. J Clin Oncol 2007;25:3158-67. [PUBMED] [CROSSREF]
3. Kuderer NM, Dale DC, Crawford J, Cosler LE, Lyman GH. Mortality, morbidity, and cost associated with febrile neutropenia in adult cancer patients. Cancer 2006;106:2258-66. [PUBMED] [CROSSREF]
4. Schilling MB, Parks C, Deeter RG. Costs and outcomes associated with hospitalized cancer patients with neutropenic complications: a retrospective study. Exp Ther Med 2011;2:859-66. [PUBMED] [CROSSREF]
5. Lalami Y, Klastersky J. Impact of chemotherapy-induced neutropenia (CIN) and febrile neutropenia (FN) on cancer treatment outcomes: an overview about well-established and recently emerging clinical data. Crit Rev Oncol Hematol 2017;120:163-79. [PUBMED] [CROSSREF]
6. Chirivella I, Bermejo B, Insa A, Pérez-Fidalgo A, Magro A, Rosello S, et al. Optimal delivery of anthracycline-based chemotherapy in the adjuvant setting improves outcome of breast cancer patients. Breast Cancer Res Treat 2009;114:479-84. [PUBMED] [CROSSREF]
7. Colleoni M, Price K, Castiglione-Gertsch M, Goldhirsch A, Coates A, Lindner J, et al. Dose-response effect of adjuvant cyclophosphamide, methotrexate, 5-fluorouracil (CMF) in node-positive breast cancer. Eur J Cancer 1998;34:1693-700. [PUBMED] [CROSSREF]
8. Chilcott J, Lloyd Jones M, Wilkinson A. Docetaxel for the adjuvant treatment of early node-positive breast cancer: a single technology appraisal. Health Technol Assess 2009;13 Suppl 1:7-13.
PUBMED | CROSSREF

9. Lee SG, Jee YG, Chung HC, Kim SB, Ro J, Im YH, et al. Cost-effectiveness analysis of adjuvant therapy for node positive breast cancer in Korea: docetaxel, doxorubicin and cyclophosphamide (TAC) versus fluorouracil, doxorubicin and cyclophosphamide (FAC). Breast Cancer Res Treat 2009;114:589-95.
PUBMED | CROSSREF

10. Lupichuk S, Tilley D, Kostaras X, Joy AA. Real-world adjuvant TAC or FEC-D for HER2-negative node-positive breast cancer in women less than 50 years of age. Curr Oncol 2016;23:164-70.
PUBMED | CROSSREF

11. Mackey JR, Martin M, Pienkowski T, Rolski J, Guastalla JP, Sami A, et al. Adjuvant docetaxel, doxorubicin, and cyclophosphamide in node-positive breast cancer: 10-year follow-up of the phase 3 randomised BCIRG 001 trial. Lancet Oncol 2013;14:72-80.
PUBMED | CROSSREF

12. Barcenas CH, Niu J, Zhang N, Zhang Y, Buchholz TA, Elting LS, et al. Risk of hospitalization according to chemotherapy regimen in early-stage breast cancer. J Clin Oncol 2014;32:2010-7.
PUBMED | CROSSREF

13. Bennett CL, Djulbegovic B, Norris LB, Armitage JO. Colony-stimulating factors for febrile neutropenia during cancer therapy. N Engl J Med 2013;368:1131-9.
PUBMED | CROSSREF

14. Aapro MS, Bohlius J, Cameron DA, Dal Lago L, Donnelly JP, Kearney N, et al. 2010 update of EORTC guidelines for the use of granulocyte-colony stimulating factor to reduce the incidence of chemotherapy-induced febrile neutropenia in adult patients with lymphoproliferative disorders and solid tumours. Eur J Cancer 2011;47:8-32.
PUBMED | CROSSREF

15. Smith TJ, Khatcheressian J, Lyman GH, Ozer H, Armitage JO, Balducci L, et al. 2006 update of recommendations for the use of white blood cell growth factors: an evidence-based clinical practice guideline. J Clin Oncol 2006;24:3187-205.
PUBMED | CROSSREF

16. Mitchell S, Li X, Woods M, Garcia J, Hebard-Massey K, Barron R, et al. Comparative effectiveness of granulocyte colony-stimulating factors to prevent febrile neutropenia and related complications in cancer patients in clinical practice: a systematic review. J Oncol Pharm Pract 2016;22:702-16.
PUBMED | CROSSREF

17. Almenar D, Mayans J, Juan O, Bueno JM, Lopez JI, Frau A, et al. Pegfilgrastim and daily granulocyte colony-stimulating factor: patterns of use and neutropenia-related outcomes in cancer patients in Spain--results of the LEARN Study. Eur J Cancer Care (Engl) 2009;18:280-6.
PUBMED | CROSSREF

18. Woo HD, Kim HS, Lee JH, Kim HM, Han SW, Kim SY, et al. Toxicity and tolerability study of adjuvant TAC regimen chemotherapy in Korean patients with breast cancer. J Breast Cancer 2011;14:544-9.
PUBMED | CROSSREF

19. Lee J, Ahn MH, Jang YH, Lee EJ, Park JH, Rho J, et al. Toxicity and quality of life of Korean breast cancer patients treated with docetaxel-containing chemotherapy without primary G-CSF prophylaxis. Breast Cancer 2014;21:670-6.
PUBMED | CROSSREF

20. Park BK, Gwak HK, Lim ST, Suh YJ, Jeon YW. Incidence of febrile neutropenia in advanced breast cancer patients receiving adjuvant docetaxel-doxorubicin-cyclophosphamide chemotherapy in Korea and its impact on prognosis. J Breast Dis 2019;7:97-104.
CROSSREF

21. Lee J, Lee JE, Kim Z, Han SW, Hur SM, Kim SY, et al. Pegfilgrastim for primary prophylaxis of febrile neutropenia in breast cancer patients undergoing TAC chemotherapy. Ann Surg Treat Res 2018;94:223-8.
PUBMED | CROSSREF

22. Weycker D, Barron R, Edelsberg J, Kartashov A, Lyman GH. Incidence of reduced chemotherapy relative dose intensity among women with early stage breast cancer in US clinical practice. Breast Cancer Res Treat 2012;133:301-10.
PUBMED | CROSSREF

23. Eiermann W, Pienkowski T, Crown J, Sadeghi S, Martin M, Chan A, et al. Phase III study of doxorubicin/cyclophosphamide with concomitant versus sequential docetaxel as adjuvant treatment in patients with human epidermal growth factor receptor 2-normal, node-positive breast cancer: BCIRG 005 trial. J Clin Oncol 2011;29:3877-84.
PUBMED | CROSSREF
24. Hor SY, Lee SC, Wong CI, Lim YW, Lim RC, Wang LZ, et al. PXR, CAR and HNF4alpha genotypes and their association with pharmacokinetics and pharmacodynamics of docetaxel and doxorubicin in Asian patients. Pharmacogenomics J 2008;8:139-46.

25. Onoue H, Yano I, Tanaka A, Itohara K, Hanai A, Ishiguro H, et al. Significant effect of age on docetaxel pharmacokinetics in Japanese female breast cancer patients by using the population modeling approach. Eur J Clin Pharmacol 2016;72:703-10.

26. Naeim A, Henk HJ, Becker L, Chia V, Badre S, Li X, et al. Pegfilgrastim prophylaxis is associated with a lower risk of hospitalization of cancer patients than filgrastim prophylaxis: a retrospective United States claims analysis of granulocyte colony-stimulating factors (G-CSF). BMC Cancer 2013;13:11.

27. Fortner BV, Okon TA, Zhu L, Tauer K, Moore K, Templeton D, et al. Costs of human resources in delivering cancer chemotherapy and managing chemotherapy-induced neutropenia in community practice. Community Oncol 2004;1:23-8.