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The Optimal Timing and Duration of Daily G-CSF for the Primary Prevention of Febrile Neutropenia in Breast Cancer Patients Undergoing Adjuvant TAC Chemotherapy

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ABSTRACT

Aim: TAC chemotherapy is a standard adjuvant treatment for early-stage breast cancer, with G-CSF recommended for preventing febrile neutropenia (FN). This study investigates the optimal initiation timing for daily filgrastim to prevent FN in patients undergoing TAC chemotherapy, a subject not fully explored in existing guidelines.

Methods: Sixty breast cancer patients receiving adjuvant TAC chemotherapy were randomly assigned to start daily filgrastim either on Day 2 (Day 2 group, $n = 30$) or Day 5 (Day 5 group, $n = 30$). The primary outcome was the incidence of FN. Secondary outcomes included the duration of neutropenia treatment and the neutropenia profile.

Results: Patients underwent 349 cycles of TAC chemotherapy (173 cycles in Day 2 group and 176 cycles in Day 5 group). The incidence of FN was significantly lower in the Day 2 group (6.4%, 11/173) compared to the Day 5 group (22.2%, 39/176, $p < 0.0001$). Additionally, the mean $\pm$ SD duration of filgrastim treatment was longer (8 ± 1 vs. 6 ± 1 days, $p < 0.0001$), and the duration of severe neutropenia was shorter (3 ± 1 vs. 4 ± 1 days, $p = 0.001$) in the Day 2 group.

Conclusion: Initiating filgrastim on Day 2 of TAC chemotherapy significantly enhances its effectiveness in preventing FN compared to starting on Day 5. These findings support early intervention and sustained treatment to optimize toxicity management in adjuvant TAC chemotherapy.

1 | Introduction

Breast cancer remains the most prevalent cancer among women worldwide. In 2022, it accounted for 23.8% of all new female cancer cases and 15.49% of all cancer deaths among women globally, as reported by the World Health Organization [1]. Despite these statistics, survival rates have improved significantly, with a recent Korean study showing a 5-year relative survival

rate of 93.6% from 2015 to 2019, up from 78.3% in 1993–1995 [2]. These improvements are mainly due to advances in understanding breast cancer biology and the development of effective pharmacological treatments.

Chemotherapy, particularly regimens based on anthracycline and taxane formulations, plays a pivotal role in treating lymph node-positive breast cancer as the cornerstone of adjuvant

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therapy. The 10-year follow-up of the Breast Cancer International Research Group (BCIRG) 001 study showed that TAC therapy (docetaxel, doxorubicin, and cyclophosphamide) was superior to FAC therapy (fluorouracil, doxorubicin, and cyclophosphamide), enhancing disease-free survival by 28% and overall survival by 30% in patients with lymph node-positive breast cancer [3]. Subsequent studies have established adjuvant TAC as the standard in breast cancer treatment [4, 5].

However, TAC chemotherapy is associated with hematological toxicities, including bone marrow suppression, edema, and peripheral neuropathy. Notably, febrile neutropenia (FN) is a severe and potentially fatal toxicity that can lead to increased secondary infections, extended hospital stays, reduced drug dosages, and delayed or discontinued treatment, thereby compromising the therapeutic efficacy of the regimen. Previous studies have underscored the importance of maintaining the relative dose intensity (RDI) of anticancer drugs more than 85% to improve disease-free and overall survival rates [6, 7]. Therefore, it is critical to actively prevent and manage severe toxicities such as FN to maintain the appropriate chemotherapy dosage and ensure treatment efficacy after TAC chemotherapy.

Granulocyte colony-stimulating factors (G-CSFs) enhance the production of functional neutrophils by accelerating the maturation process from bone marrow stem cells to mature neutrophils. This is achieved by regulating neutrophil function, lifespan, differentiation, and proliferation within the bone marrow [8]. Clinical studies have demonstrated that G-CSF formulations effectively reduce the frequency, severity, and duration of leukocyte reduction following chemotherapy [9–11]. Consequently, these agents facilitate more consistent dosing, timing of administration, and adherence to planned treatment cycles.

International treatment guidelines from major oncological societies, including the National Comprehensive Cancer Network (NCCN), the American Society of Clinical Oncology (ASCO), and the European Society of Medical Oncology (ESMO), recommend the primary preventive administration of G-CSF formulations when the risk of developing FN after chemotherapy exceeds 20% [12–15]. Following the BCIRG 001 study, which reported an incidence of 65.5% for Common Terminology Criteria for Adverse Events (CTCAE) Grades 3–4 neutropenia and 24.7% for FN in the TAC treatment group [3, 16], the use of daily G-CSF as a secondary prophylaxis was approved. Moreover, primary preventive administration of G-CSF is advocated based on results from the Spanish Breast Cancer Study Group (GEICAM) 9805 trial. This trial found an FN incidence of 25.2% with secondary prophylactic administration and only 5.5% with primary prophylactic administration following TAC chemotherapy [4].

Both the NCCN and ASCO treatment guidelines recommend several G-CSF formulations, including original filgrastim, filgrastim biosimilars, original pegfilgrastim, and pegfilgrastim biosimilars, with the same level of recommendation. They advise choosing the appropriate formulation based on administration convenience, cost, and clinical circumstances [13]. Pegfilgrastim, a long-acting version of filgrastim, has been developed, and its effectiveness in preventing FN is reported to be equivalent to that of daily filgrastim administration [17, 18]. This offers greater convenience for patients and medical staff. However, many countries still use

filgrastim primarily due to cost considerations or other factors affecting accessibility.

According to the FDA label for filgrastim, a daily injection of 5 mcg/kg is initiated 24 h after chemotherapeutic agent administration (Day 2) and continued for 2 weeks, with the treatment ceasing once the absolute neutrophil count (ANC) reaches 10,000/mm³ on blood tests [19]. In contrast, NCCN guidelines advocate for the commencement of daily subcutaneous filgrastim injections of 5 mcg/kg the day after chemotherapy or 3–4 days post-chemotherapy, continuing until the ANC returns to normal levels post-nadir [14]. The GEPARTRIO study compared FN incidence between primary preventive treatment to daily filgrastim (Days 5–10, for 6 days) and pegfilgrastim during TAC chemotherapy, finding FN rates of 18% and 7%, respectively [20]. This suggests that starting daily filgrastim on Day 5 for only 6 days may not provide optimal FN prevention. Additionally, another study indicated that shorter administration periods of G-CSF formulations correlate with decreased effectiveness in preventing FN [21]. Current guidelines do not clearly address the optimal start time and duration of daily G-CSF treatment, reflecting the limited evidence available.

Therefore, this study was designed to evaluate the impact of the timing of filgrastim initiation (Day 2 vs. Day 5) on the incidence of FN in breast cancer patients undergoing TAC chemotherapy. Additionally, it aimed to determine the optimal duration of treatment for maximum protection against FN, where feasible.

2 | Materials and Methods

2.1 | Study Design and Participants

This study was conducted with the approval of the Institutional Review Board (IRB) at each participating hospital, and all patients provided informed consent. Participants were primary breast cancer patients who had undergone surgery at Soonchunhyang University Bucheon Hospital and Soonchunhyang University Cheonan Hospital between June 2013 and September 2014, and were scheduled for six cycles of adjuvant TAC chemotherapy.

Eligible participants were over 18 years old, had an Eastern Cooperative Oncology Group (ECOG) performance status of 0–2, an ANC $\geq$ 1500/mm³, and a platelet count $\geq$ 100,000/mm³. Additional inclusion criteria included appropriate serum creatinine or creatinine clearance (less than 1.5 times the normal upper limit), no liver dysfunction (bilirubin, AST, and ALT less than 1.5 times, and alkaline phosphatase less than 2.5 times the normal upper limits), and no cardiac dysfunction, confirmed by a normal electrocardiogram within the last month or echocardiography showing normal left ventricular ejection fractions (LVEF) within the last 3 months.

Exclusion criteria were prior administration of G-CSF, pregnancy or lactation, antibiotic treatment for active infection within 72 h of anticancer treatment, previous bone marrow stem cell transplants, or radiation treatment within the last 4 weeks.

Participants were quasi-randomized into Day 2 or Day 5 groups for G-CSF administration. The process involved envelopes

containing an equal ratio of treatment group assignments, which were managed centrally at a single clinical trial center to ensure security and prevent identification of their contents. Upon enrollment of each new participant who met the eligibility criteria and provided informed consent, an envelope was sequentially opened in a blinded fashion. The treatment group assignment inside the envelope was then communicated to the relevant hospital.

2.2 | Adjuvant TAC Chemotherapy and G-CSF Treatment

Patients received the TAC chemotherapy regimen on the first day (Day 1) of each cycle. This regimen included 50 mg/m² of doxorubicin, 500 mg/m² of cyclophosphamide, and 75 mg/m² of docetaxel, administered sequentially. Each cycle was repeated every 21 days, with a total of six cycles. Following protocols from GEICAM 9805 study [4], ciprofloxacin 500 mg was administered twice daily from Days 5 to 14 as prophylactic antibiotics post-chemotherapy.

Patients were assigned into two groups for G-CSF treatment with leucostim (filgrastim, Dong-A ST): one group received 5 mcg/kg daily starting on the second day (Day 2 group) and the other from the fifth day (Day 5 group). Filgrastim was administered subcutaneously by medical staff at each participating hospital. The treatment duration continued until the ANC rebounded from its nadir, reaching 1500/mm³ or higher.

Complete blood cell counts were scheduled to measure baseline levels before starting chemotherapy (Day 0) and then daily from the day after chemotherapy until the ANC exceeded 1500/mm³. Body temperature was measured daily from the day before chemotherapy (Day 0) through the end of the cycle (Day 21). Temperature checks were conducted once daily at 9 a.m. using an axillary thermometer, with additional measurements taken if fever-related symptoms such as body aches, headaches, fatigue, chills, or sweating were reported.

2.3 | Study Endpoints

The primary endpoint of this study was the incidence of FN between the two treatment groups (Day 2 group and Day 5 group). Secondary endpoints included the profile of neutropenia, characterized by the duration of severe neutropenia (ANC < 1000/mm³ above CTCAE Grade 3), the depth and period of FN, time to recovery of the ANC to normal ranges, infections resulting from FN, and the rates of chemotherapy dose reduction, delay, or discontinuation.

FN was defined as a single oral temperature measurement of 38.3°C or higher, or a temperature of 38.0°C or higher maintained for more than an hour, accompanied by severe neutropenia (ANC < 1000/mm³) as per CTCAE version 5.0 [14, 22]. Hospitalization criteria were based on clinical assessments, including symptoms like high fever, severe neutropenia (ANC < 500/mm³), or other complications that required inpatient care. Patients diagnosed with FN were admitted for management.

In the event of FN, diagnostic procedures such as blood and urine cultures and chest x-rays were performed to identify the source of infection. Chemotherapy dose reductions were defined as a reduction of more than 15% of the total dose per body surface area [6, 7], and dose delays were defined as a postponement of chemotherapy administration by more than 3 days from the scheduled date.

2.4 | Sample Size and Statistical Analysis

To determine the sample size for this study, we conducted a power analysis based on anticipated effect sizes derived from preliminary data and previous studies in similar settings. Given the scarcity of eligible patients for this specific protocol and financial constraints, achieving the ideal sample size for conventional power (e.g., 80% power to detect a significant difference at an alpha level of 0.05) was not feasible. Therefore, we opted for a sample size of 60, balancing practical limitations with the need to detect a clinically meaningful effect. This sample size was considered sufficient to serve as a pilot, providing valuable preliminary data to justify a more extensive, fully powered study in the future.

All patients receiving at least one TAC chemotherapy cycle were included in the analysis. Results were expressed as mean ± standard deviation (SD) or median (range). The incidence of FN was analyzed using the chi-squared test, and the duration and depth of FN over CTCAE Grade 3 were analyzed using the independent sample *t*-test. Similarly, the period from the lowest point (nadir) of the ANC to recovery to the normal range was also analyzed using the independent sample *t*-test. Statistical significance was established at a *p* value of less than 0.05, and analyses were performed using SPSS version 26.0 (SPSS Inc., Chicago, IL, USA).

3 | Results

3.1 | Patients and Adjuvant TAC Chemotherapy

Sixty breast cancer patients eligible for TAC adjuvant chemotherapy following definitive surgical treatment were included in this study. Patients were divided into two groups: the Day 2 group (*n* = 30), receiving daily filgrastim starting from Day 2, and the Day 5 group (*n* = 30), starting filgrastim on Day 5. Of the planned six cycles of TAC chemotherapy, 28 patients in the Day 2 group and 29 in the Day 5 group completed at least one cycle and were included in the analysis. The Day 2 group underwent a total of 173 cycles (96.1%), and the Day 5 group underwent 176 cycles (97.8%). The baseline characteristics of the patients, which indicate that the two groups were well-balanced, are summarized in Table 1. Further details of the TAC chemotherapy cycles, the duration of daily G-CSF treatment, and the use of preventive antibiotics are provided in Table 2.

3.2 | Incidence of FN

FN occurred in 6.4% of cases (11/173 cycles) in the Day 2 group and 22.2% of cases (39/176 cycles) in the Day 5 group (*p* < 0.0001),

TABLE 1 | Baseline patient characteristics.

	Day 2 group	Day 5 group	<i>p</i> value
Number of patients	30	30	
Age (year)			
Mean $\pm$ SD	49 $\pm$ 8	48 $\pm$ 8	0.548
Median (range)	48 (35-65)	47 (32-65)	0.801
Height (cm, mean $\pm$ SD)	157 $\pm$ 5	157 $\pm$ 4	0.670
Weight (kg, mean $\pm$ SD)	61 $\pm$ 8	59 $\pm$ 9	0.368
BSA (m ² , mean $\pm$ SD)	1.61 $\pm$ 0.11	1.58 $\pm$ 0.13	0.452
ECOG performance status (<i>n</i> , %)			0.500
0	28 (93.3%)	29 (96.7%)	
1	2 (6.7%)	1 (3.3%)	
Stage (<i>n</i> , %)			0.598
Stage II	17 (56.7%)	19 (63.3%)	
Stage III	13 (43.3%)	11 (36.7%)	
Baseline ANC $\times 10^9$ /L (mean $\pm$ SD)	5633 $\pm$ 3594	5403 $\pm$ 4218	0.578

Abbreviations: ANC, absolute neutrophil count; BSA, body surface area; ECOG, Eastern Cooperative Oncology Group.

TABLE 2 | Description of TAC chemotherapy, G-CSF treatment, and antimicrobial prophylaxis.

	Day 2 group	Day 5 group	<i>p</i> value
Total number of TAC cycles (<i>n</i> , %)	173 (96%)	176 (98%)	
Duration of G-CSF treatment per cycle (day)			
Mean $\pm$ SD	8 $\pm$ 1	6 $\pm$ 1	<0.0001
Median (range)	8 (5-11)	6 (3-9)	<0.0001
Cycles with ciprofloxacin prophylaxis (<i>n</i> , %)	173 (100%)	176 (100%)	

demonstrating a statistically significant lower incidence of FN in the group that received daily filgrastim starting from Day 2 (Table 3). The duration (mean $\pm$ SD) of FN was 2 $\pm$ 1 days in both the Day 2 group and the Day 5 group ($p = 0.687$) (Table 3).

3.3 | Characteristics of FN and Severe Neutropenia

The ANC value (mean $\pm$ SD) of CTCAE Grade 3 or higher neutropenia for the first TAC chemotherapy cycle was 282 $\pm$ 198/mm³ in the Day 2 group and 186 $\pm$ 121/mm³ in the Day 5 group ($p = 0.029$). These results indicate that during the first cycle, when severe neutropenia is most prominent, daily filgrastim support from Day 2 maintained higher ANC levels than those from Day 5. The differences in ANC levels between the two groups over time are depicted in Figure 1. Additionally, the duration of CTCAE Grade 3 or higher neutropenia was shorter in the Day 2 group (mean $\pm$ SD: 3 $\pm$ 1 days) compared to the Day 5 group (mean $\pm$ SD: 4 $\pm$ 1 days, $p = 0.001$), indicating a faster recovery period in the Day 2 group as detailed in Table 3.

The duration (mean $\pm$ SD) of CTCAE Grade 4 neutropenia was identical between the two groups (3 $\pm$ 1 days for both, $p = 0.007$),

as shown in Figure 2. However, the nadir ANC (mean $\pm$ SD) was significantly higher in the Day 2 group (115 $\pm$ 232/mm³) compared to the Day 5 group (32 $\pm$ 22/mm³, $p = 0.058$), as depicted in Figure 3. Notably, the depth of neutropenia during cycles 3, 5, and 6 was statistically significantly more profound in the Day 5 group ($p < 0.05$).

Furthermore, the total time required for recovery from the lowest point of ANC to the normal range across all six cycles of TAC chemotherapy was shorter in the Day 2 group (mean $\pm$ SD: 12 $\pm$ 3 days) compared to the Day 5 group (mean $\pm$ SD: 14 $\pm$ 2 days, $p = 0.014$). The time to ANC recovery for each cycle is illustrated in Figure 4.

Details of FN and the grade, depth, and duration of neutropenia between each group are summarized in Table 3.

3.4 | Clinical Outcomes of FN

Patients who agreed to inpatient treatment received intravenous antibiotics and daily filgrastim from the onset of CTCAE Grade 4 neutropenia (ANC < 500/mm³) during adjuvant TAC chemotherapy until their absolute neutrophil levels recovered to more

TABLE 3 | Profile of neutropenia.

	Day 2 group	Day 5 group	p value
Incidence of FN for Cycle 1 (n, %)	2 (6.7%)	4 (13.3%)	0.671
Incidence of FN for all cycles (n, %)	11 (6.4%)	39 (22.2%)	<0.0001
Duration of FN for Cycle 1 (day, mean $\pm$ SD)	2 $\pm$ 1	3 $\pm$ 1	0.381
Duration of FN for all cycles (day, mean $\pm$ SD)	2 $\pm$ 1	2 $\pm$ 1	0.687
CTCAE Grades 3–4 neutropenia for Cycle 1 (/mm ³ , mean $\pm$ SD)	282 $\pm$ 198	186 $\pm$ 126	0.029
CTCAE Grades 3–4 neutropenia for all cycles (/mm ³ , mean $\pm$ SD)	252 $\pm$ 161	234 $\pm$ 121	0.239
Nadir ANC in Cycle 1 (/mm ³ , mean $\pm$ SD)	62 $\pm$ 153	11 $\pm$ 11	0.077
Nadir ANC for all cycles (/mm ³ , mean $\pm$ SD)	115 $\pm$ 232	32 $\pm$ 22	0.058
Time to ANC recovery in Cycle 1 (day, mean $\pm$ SD)	2 $\pm$ 1	2 $\pm$ 1	0.213
Time to ANC recovery for all cycles (day, mean $\pm$ SD)	2 $\pm$ 1	2 $\pm$ 1	<0.0001
Total time to ANC recovery for all cycles (day, mean $\pm$ SD)	12 $\pm$ 3	14 $\pm$ 2	0.014
Duration of Grades 3–4 neutropenia for Cycle 1 (day, mean $\pm$ SD)	4 $\pm$ 1	4 $\pm$ 1	0.068
Duration of Grades 3–4 neutropenia for all cycles (day, mean $\pm$ SD)	3 $\pm$ 1	4 $\pm$ 1	0.001
Duration of Grade 4 neutropenia for Cycle 1 (day, mean $\pm$ SD)	3 $\pm$ 1	3 $\pm$ 1	0.285
Duration of Grade 4 neutropenia for all cycles (day, mean $\pm$ SD)	3 $\pm$ 1	3 $\pm$ 1	0.007

Abbreviations: ANC, absolute neutrophil count; CTCAE, Common Terminology Criteria for Adverse Events; FN, febrile neutropenia.

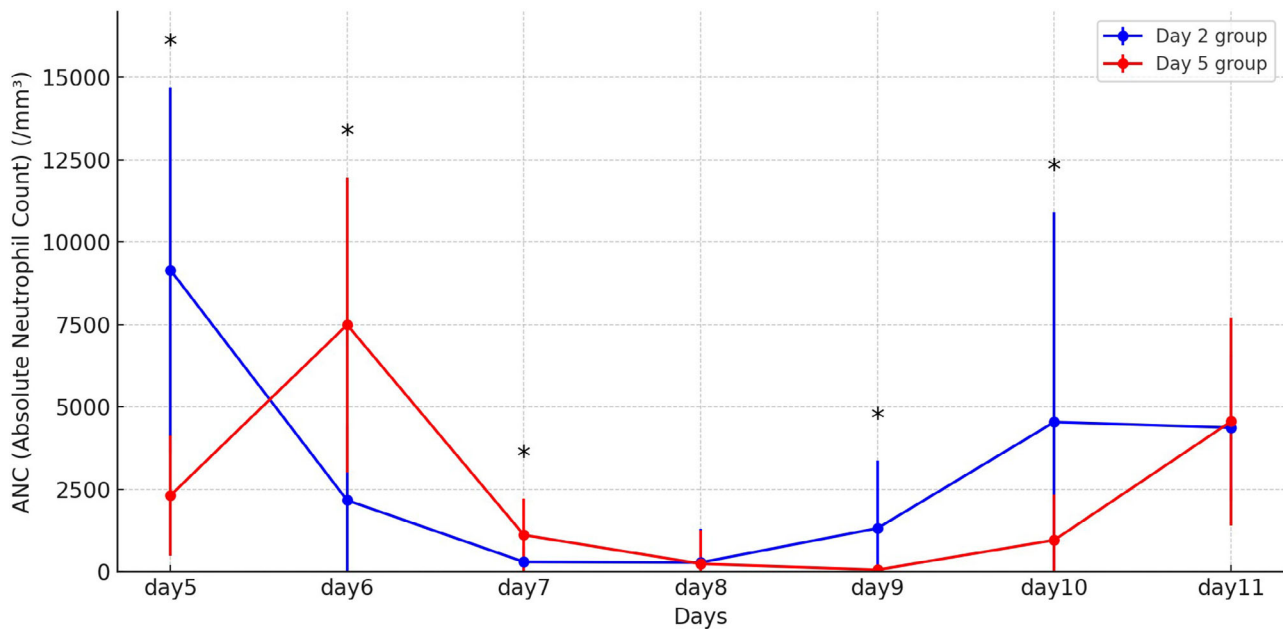


FIGURE 1 | Changes in the absolute neutrophil count across all TAC chemotherapy cycles. Data presented as mean $\pm$ SD; error bars represent SD; * $p < 0.05$.

than 1500/mm³. Consequently, the hospitalization rate was 94.2% (163/173 cycles) in the Day 2 group and 100% (176/176 cycles) in the Day 5 group. The mean $\pm$ SD hospitalization period per chemotherapy cycle was 3 $\pm$ 1 days for both groups ($p = 0.290$) (Table 4).

There were two cases (1.2%) of FN-related infections in the Day 2 group and three cases (1.7%) in the Day 5 group, with no significant difference between the groups ($p > 0.999$). Specific infections included one herpes zoster, one pneumonia, one

Clostridium difficile-associated diarrhea, and two chemoport site infections.

4 | Discussion

Our study confirmed that initiating daily G-CSF from the second day of adjuvant TAC chemotherapy significantly reduces the incidence of FN compared to starting on the fifth day (6.4% vs. 22.2%, $p < 0.0001$). This demonstrates the benefits of early G-CSF

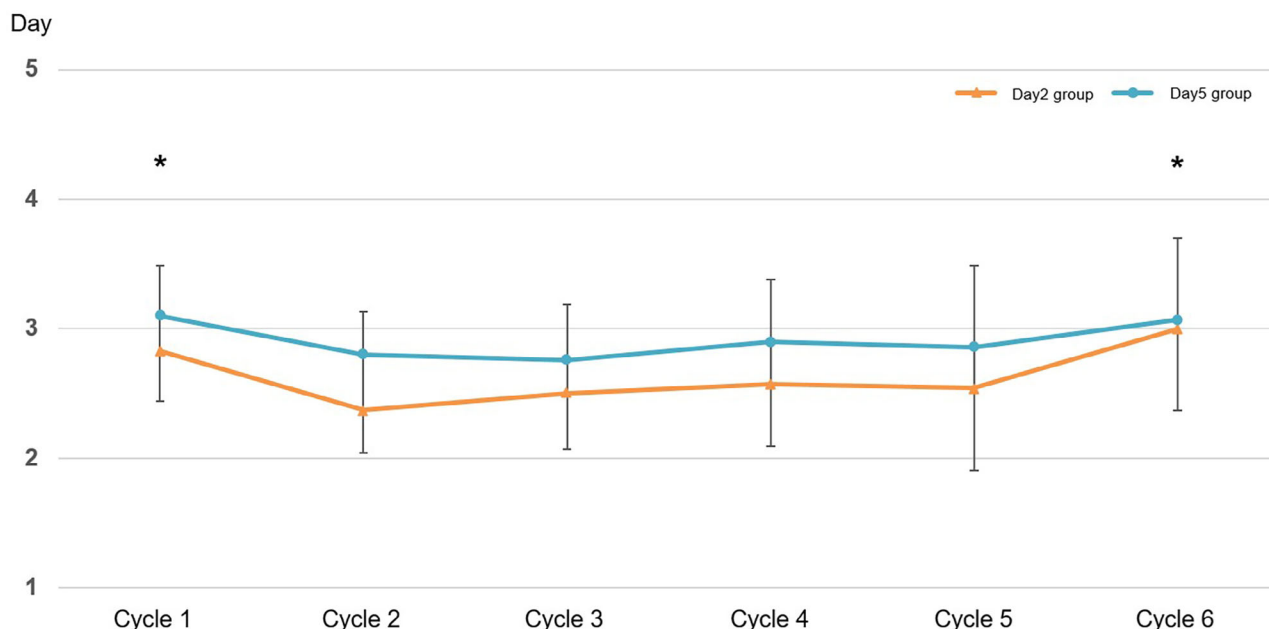


FIGURE 2 | Duration of common terminology criteria for adverse events (CTCAE) Grade 4 neutropenia across all TAC chemotherapy cycles. Data presented as mean $\pm$ SD; error bars represent SD; * $p < 0.05$.

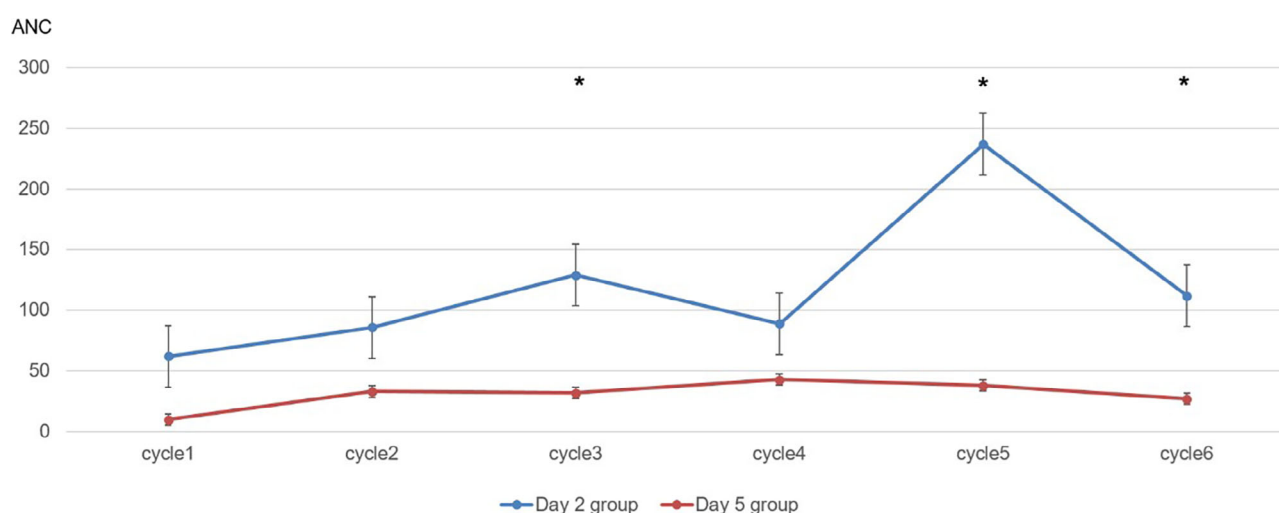


FIGURE 3 | Nadir absolute neutrophil count (ANC) across in all TAC chemotherapy cycles. Data presented as mean $\pm$ SD; error bars represent SD; * $p < 0.05$.

intervention. The treatment duration was also longer in the Day 2 group, averaging more than 7 days (8 ± 1 days), compared to the Day 5 group (6 ± 1 days, $p < 0.0001$), further contributing to reduced severity of neutropenia and lower incidence of FN.

Despite the nonsignificant difference in mean ANC nadir between the groups (115 ± 232 vs. 32 ± 22 ; $p = 0.058$), the higher nadir values in the Day 2 group suggest a more robust neutrophil recovery. Additionally, the shorter duration of severe neutropenia (CTCAE Grades 3–4) in the Day 2 group (3 ± 1 vs. 4 ± 1 days, $p = 0.001$) supports the effectiveness of early filgrastim administration.

These findings suggest that initiating filgrastim administration on the second day mitigates the depth of neutropenia and

shortens the period required for ANC recovery to normal ranges compared to starting on the fifth day. Thus, in the primary prevention of FN in adjuvant TAC chemotherapy, it is more effective to begin daily administration of filgrastim on the second day and maintain it for at least 7 days than to start on the fifth day.

The results of current study demonstrate the importance and effectiveness of starting filgrastim support early and extending the treatment duration to enhance neutrophil recovery, reduce the depth of neutropenia, and minimize the risk and duration of severe complications. This approach can provide practical assistance in clinical practice to optimize the management of FN and chemotherapy-induced neutropenia in patients undergoing adjuvant TAC chemotherapy.

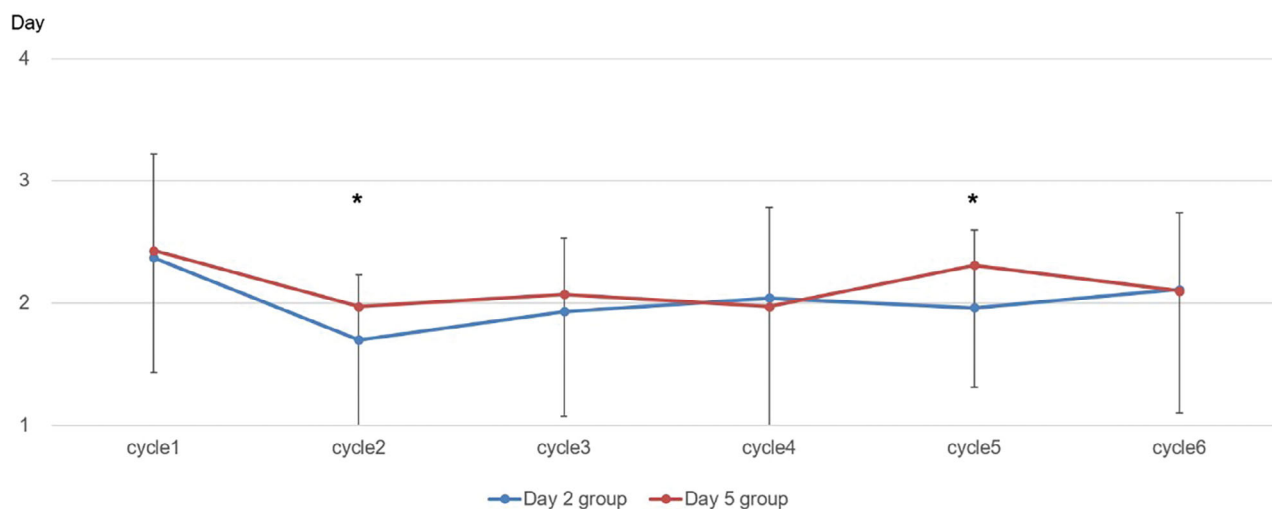


FIGURE 4 | Time to absolute neutrophil count (ANC) recovery across all TAC chemotherapy cycles. Data presented as mean $\pm$ SD; error bars represent SD; * $p < 0.05$.

TABLE 4 | Neutropenia-related outcomes.

	Day 2 group (N = 173)	Day 5 group (N = 176)	p value
Hospitalizations (n, %)	163 (94.2%)	176 (100%)	
Duration of hospitalization for Cycle 1 (day, mean $\pm$ SD)	3 $\pm$ 1	4 $\pm$ 1	0.265
Duration of hospitalization for all cycles (day, median, range)	3 $\pm$ 1	3 $\pm$ 1	0.290
Use of IV antibiotics (n, %)	163 (94.2%)	176 (100%)	
Neutropenic infection (n, %)	2 (1.2%)	4 (2.3%)	>0.999
Herpes zoster		1	
Pneumonia	1		
<i>Clostridium difficile</i> -associated diarrhea (CDAD)		1	
Chemoport site infection	1	2	
Treatment delay (n, %)	4 (2.3%)	1 (0.6%)	>0.999
Dose reduction (n, %)	0 (0%)	0 (0%)	>0.999
Treatment discontinuation	2 (1.2%)	1 (0.6%)	>0.999

TAC chemotherapy is recognized as a standard adjuvant systemic treatment for early breast cancer, noted for its ability to extend both the disease-free and overall survival periods [3–5]. However, according to the 10-year results of the BCIRG 005 study [23], TAC chemotherapy showed no difference in treatment efficacy compared to AC>T (adriamycin, cyclophosphamide, and docetaxel) therapy. A significant drawback of TAC therapy is its higher degree of myelosuppression compared to AC>T. However, when primary prevention with G-CSF formulations is implemented, TAC chemotherapy not only shortens the treatment duration but also demonstrates lower toxicity. Therefore, with proper primary prevention using G-CSF, TAC chemotherapy can be administered effectively and safely while maintaining RDI.

Currently, various G-CSF formulations are employed to prevent or treat FN due to bone marrow toxicity following systemic chemotherapy. Filgrastim, the first G-CSF formulation devel-

oped, initiated this clinical application, followed by several others, including tbo-filgrastim, filgrastim-sndz, filgrastim-aafi, and pegfilgrastim—a pegylated version of G-CSF. Filgrastim is characterized by a short action time, rapid absorption following subcutaneous injection, and a half-life of approximately 33.5 h. Typically, it is injected daily from 1 to 3 days after chemotherapy until the ANC returns to normal levels. Despite over 20 years of clinical use, the optimal timing and duration for the primary prevention of FN with filgrastim remain inconclusive due to a lack of prospective or comparative efficacy studies [13–15].

International treatment guidelines currently need more specific criteria for the appropriate duration of filgrastim treatment, resulting in nonstandardized practices worldwide (Table 5). A Canadian survey involving breast cancer patients and physicians revealed varied prescription durations for filgrastim post-chemotherapy—31.6% prescribed it for 5 days, 47.4% for 7 days,

TABLE 5 | Treatment guidelines for neutropenia prevention.

Organization	Guideline description
ASCO [13]	Filgrastim should be started 1–3 days after administration of myelotoxic chemotherapy and continued until reaching ANC $\geq$ 2000~3000/mm ³ .
NCCN [14]	Start the next day or up to 3~4 days after completion of myelosuppressive chemotherapy and treat through post-nadir recovery.
ESMO [15]	Use 5 μ g/kg of filgrastim subcutaneously 1–3 days after the last day of chemotherapy until sufficient/stable post-nadir ANC recovery (achieving a target ANC of > 10,000/mm ³ is not necessary).

Abbreviations: ASCO, American Society of Clinical Oncology; ESMO, European Society of Medical Oncology; NCCN, National Comprehensive Cancer Network.

13.2% for 10 days, and 7.9% for other durations—indicating a lack of consensus [24]. Given that filgrastim can cause side effects such as bone pain, skin rash, nausea, and thrombocytopenia, determining an optimal administration period is crucial to balance minimizing these adverse effects while maintaining its therapeutic efficacy [25, 26].

Therefore, accurately determining the optimal timing and duration for daily G-CSF administration to prevent serious complications such as FN can enhance patient safety, reduce medical costs, and improve treatment convenience. Moreover, establishing practical treatment guidelines is crucial, especially when pegylated G-CSF is unavailable.

In this study, the duration of filgrastim administration was 8 ± 1 days in the Day 2 group and 6 ± 1 days in the Day 5 group, showing a statistically significant difference ($p < 0.0001$). Prior research and systematic reviews on the duration of G-CSF support during TAC chemotherapy suggest that durations of 1–3 days (odds ratio 2.4 [95% CI 1.6–3.4]) and 4–6 days (odds ratio 1.9 [95% CI 1.3–2.8]) are associated with higher incidences of FN-related complications compared to maintaining treatment for more than 7 days [27, 28]. These findings are consistent with those of this study.

While pivotal trials for TAC chemotherapy, such as the BCIRG 005 trial [3] and the GEICAM 9805 study [4, 16], did not report differences in FN incidence based on the start day or duration of filgrastim treatment, the GEPARTRIO study [20] indirectly suggested that the administration of filgrastim either from Day 2 or Day 5 was suboptimal if daily G-CSF treatment lasted less than 7 days. This aligns with the results observed in our study, highlighting the effectiveness of extending G-CSF treatment to at least 7 days to optimize FN prevention.

The incidence of FN during adjuvant TAC chemotherapy in the BCIRG 005 trial was reported as 17% when primary prevention with G-CSF was implemented [23]. Similarly, Von Minkwitz et al. reported an FN occurrence of 18% in the GEPARTRIO study when daily filgrastim was used after TAC chemotherapy [20]. In this study, the incidence of FN was 14.3%, which aligns with these previous studies. According to our previous research [29], in Korean breast cancer patients, the occurrence of FN was significantly higher at 42.5% when no G-CSF was used for primary prevention. The current study demonstrated a reduction in FN to 14.3% with primary prevention and notably to 6.4% when G-CSF administration commenced on Day 2. This confirms the vital importance of initiating primary prevention therapy at an

appropriate time and maintaining daily G-CSF administration for at least 7 days during adjuvant TAC chemotherapy.

While the relatively small number of patients involved is a limitation of this study, the prospective nature of our research offers more objective outcomes compared to retrospective studies. Another challenge was confirming differences in hospitalization rates due to FN between the two groups. Under Korean medical insurance systems, patients with CTCAE Grade 4 neutropenia, characterized by an ANC less than 500/mm³, are eligible for hospitalization and receive supportive treatment until their neutrophil counts return to normal. This practice may obscure potential differences in complications arising from FN.

Despite these limitations, this study is the first to outline the optimal start time and duration for daily filgrastim treatment in a way that distinguishes it from routine clinical practices.

5 | Conclusion

In conclusion, daily administration of G-CSF starting from the second day of the chemotherapy cycle and continuing for at least 7 days is highly effective in preventing FN during adjuvant TAC chemotherapy in breast cancer patients. These findings could inform the optimization of daily G-CSF administration protocols for adjuvant TAC chemotherapy in clinical practice.

Acknowledgments

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Conflicts of Interest

The authors declare no conflicts of Interest.

Data Availability Statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

References

1. “GLOBOCAN 2022: Global Cancer Statistics 2022,” International Agency for Research on Cancer, World Health Organization, accessed April 26, 2024. <https://gco.iarc.fr/today>.

2. J. E. Choi, Z. Kim, C. S. Park, et al., "Breast Cancer Statistics in Korea, 2019," *Journal of Breast Cancer* 26, no. 3 (2023): 207–220.
3. M. Martin, T. Pienkowski, J. Mackey, et al., "Adjuvant Docetaxel for Node-Positive Breast Cancer," *New England Journal of Medicine* 352, no. 22 (2005): 2302–2313.
4. M. Martín, M. A. Seguí, A. Antón, et al., "Adjuvant Docetaxel for High-Risk, Node-Negative Breast Cancer," *New England Journal of Medicine* 363, no. 23 (2010): 2200–2210.
5. J. R. Mackey, M. Martin, T. Pienkowski, 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 Oncology* 14, no. 1 (2013): 72–80.
6. G. H. Lyman, D. C. Dale, and J. Crawford, "Incidence and Predictors of Low Dose-Intensity in Adjuvant Breast Cancer Chemotherapy: A Nationwide Study of Community Practices," *Journal of Clinical Oncology* 21, no. 24 (2003): 4524–4531.
7. H. Wildiers and M. Reiser, "Relative Dose Intensity of Chemotherapy and Its Impact on Outcomes in Patients With Early Breast Cancer or Aggressive Lymphoma," *Critical Reviews in Oncology/Hematology* 77, no. 3 (2011): 221–240.
8. C. Gómez Raposo, A. Pinto Marín, and M. González Barón, "Colony-Stimulating Factors: Clinical Evidence for Treatment and Prophylaxis of Chemotherapy-Induced Febrile Neutropenia," *Clinical & Translational Oncology* 8, no. 10 (2006): 729–734.
9. N. M. Kuderer, D. C. Dale, J. Crawford, and G. H. Lyman, "Impact of Primary Prophylaxis With Granulocyte Colony-Stimulating Factor on Febrile Neutropenia and Mortality in Adult Cancer Patients Receiving Chemotherapy: A Systematic Review," *Journal of Clinical Oncology* 25, no. 21 (2007): 3158–3167.
10. L. Sung, P. C. Nathan, S. M. Alibhai, G. A. Tomlinson, and J. Beyene, "Meta-Analysis: Effect of Prophylactic Hematopoietic Colony Stimulating Factors on Mortality and Outcomes of Infection," *Annals of Internal Medicine* 147, no. 6 (2007): 400–411.
11. G. H. Lyman, N. M. Kuderer, and B. Djulbegovic, "Prophylactic Granulocyte Colony-Stimulating Factor in Patients Receiving Dose Intensive Cancer Chemotherapy: A Meta-Analysis," *American Journal of Medicine* 112, no. 5 (2002): 406–411.
12. J. Muñoz Langa, P. Gascón, and J. de Castro, "SEOM Clinical Guidelines for Myeloid Growth Factors," *Clinical & Translational Oncology* 14, no. 7 (2012): 491–498.
13. T. J. Smith, K. Bohlke, G. H. Lyman, et al., "Recommendations for the Use of WBC Growth Factors: American Society of Clinical Oncology Clinical Practice Guideline Update," *Journal of Clinical Oncology* 33, no. 28 (2015): 3199–3212.
14. "Clinical Practice Guidelines in Oncology: Hematopoietic Growth Factors, Version 3," National Comprehensive Cancer Network (NCCN), accessed April 26, 2024. https://www.nccn.org/professionals/physician_gls/pdf/growthfactors.pdf.
15. J. Klastersky, J. de Naurois, K. Rolston, et al., "Management of Febrile Neutropenia: ESMO Clinical Practice Guidelines," *Annals of Oncology* 27, no. 5 (2016): v111–v118.
16. M. Martín, A. Lluch, M. A. Seguí, et al., "Toxicity and Health-Related Quality of Life in Breast Cancer Patients Receiving Adjuvant Docetaxel, Doxorubicin, Cyclophosphamide (TAC) or 5-Fluorouracil, Doxorubicin and Cyclophosphamide (FAC): Impact of Adding Primary Prophylactic Granulocyte-Colony Stimulating Factor to the TAC Regimen," *Annals of Oncology* 17, no. 8 (2006): 1205–1212.
17. M. D. Green, H. Koelbl, J. Baselga, et al., "International Pegfilgrastim 749 Study Group. A Randomized Double-Blind Multicenter Phase III Study of Fixed-Dose Single-Administration Pegfilgrastim Versus Daily Filgrastim in Patients Receiving Myelosuppressive Chemotherapy," *Annals of Oncology* 14, no. 1 (2003): 29–35.
18. W. Zhang, Z. Jiang, L. Wang, C. Li, and J. Xia, "An Open-Label, Randomized, Multicenter Dose-Finding Study of Once-per-Cycle Pegfilgrastim Versus Daily Filgrastim in Chinese Breast Cancer Patients Receiving TAC Chemotherapy," *Medical Oncology* 32, no. 5 (2015): 147.
19. "Neupogen® (Filgrastim)," accessed February 15, 2023. <https://www.accessdata.fda.gov/scripts/cder/daf/index.cfm?event=overview.process&ApplNo=103353>.
20. G. von Minckwitz, S. Kümmel, A. du Bois, et al., "Pegfilgrastim ± Ciprofloxacin for Primary Prophylaxis With TAC (Docetaxel/Doxorubicin/Cyclophosphamide) Chemotherapy for Breast Cancer. Results From the GEPARTRIO Study," *Annals of Oncology* 19, no. 2 (2008): 292–298.
21. D. Weycker, X. Li, S. Tziveleki, et al., "Burden of Chemotherapy-Induced Febrile Neutropenia Hospitalizations in US Clinical Practice, by Use and Patterns of Prophylaxis With Colony-Stimulating Factor," *Supportive Care in Cancer* 25, no. 2 (2017): 439–447.
22. "Common Terminology Criteria for Adverse Events (CTCAE), Version 5.0," National Institutes of Health, National Cancer Institute, published November 27, 2017. https://ctep.cancer.gov/protocoldevelopment/electronic_applications/docs/CTCAE_v5_Quick_Reference_8.5x11.pdf.
23. J. R. Mackey, T. Pienkowski, J. Crown, et al., "Long-Term Outcomes After Adjuvant Treatment of Sequential Versus Combination Docetaxel With Doxorubicin and Cyclophosphamide in Node-Positive Breast Cancer: BCIRG-005 Randomized Trial," *Annals of Oncology* 27, no. 6 (2016): 1041–1047.
24. J. Hilton, L. Vandermeer, M. Sienkiewicz, et al., "Filgrastim Use in Patients Receiving Chemotherapy for Early-Stage Breast Cancer—A Survey of Physicians and Patients," *Supportive Care in Cancer* 26, no. 7 (2018): 2323–2331.
25. C. N. Abboud, N. Lang, H. Fung, et al., "Real-World Safety Experience of Tenvagrastim/Ratiograstim/Biograstim and Tbo-Filgrastim, Short-Acting Recombinant Human Granulocyte Colony-Stimulating Factors," *Supportive Care in Cancer* 27, no. 7 (2019): 2569–2577.
26. D. C. Dale, J. Crawford, Z. Klippel, et al., "A Systematic Literature Review of the Efficacy, Effectiveness, and Safety of Filgrastim," *Supportive Care in Cancer* 26, no. 1 (2018): 7–20.
27. D. Weycker, R. Barron, J. Edelsberg, A. Kartashov, J. Legg, and A. G. Glass, "Risk and Consequences of Chemotherapy-Induced Neutropenic Complications in Patients Receiving Daily Filgrastim: The Importance of Duration of Prophylaxis," *BMC Health Services Research* 14 (2014): 189.
28. P. Cornes, P. Gascon, S. Chan, et al., "Systematic Review and Meta-Analysis of Short- Versus Long-Acting Granulocyte Colony-Stimulating Factors for Reduction of Chemotherapy-Induced Febrile Neutropenia," *Advances in Therapy* 35, no. 11 (2018): 1816–1829.
29. J. Lee, M. H. Ahn, Y. H. Jang, et al., "Toxicity and Quality of Life of Korean Breast Cancer Patients Treated With Docetaxel-Containing Chemotherapy Without Primary G-CSF Prophylaxis," *Breast Cancer* 21, no. 6 (2014): 670–676.