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Effect of Secondary Prophylactic G-CSF on the Occurrence of Febrile Neutropenia in Breast Cancer

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Abstract. *Background/Aim: Docetaxel and cyclophosphamide (TC) combination therapy is widely used as adjuvant chemotherapy for early-stage breast cancer and is associated with a high incidence of febrile neutropenia (FN). Granulocyte colony-stimulating factor (G-CSF) is recommended in the primary prevention of febrile neutropenia (FN). This study aimed to evaluate the FN-suppressing effect of G-CSF in patients with breast cancer receiving TC. Patients and Methods: We performed 272 treatment cycles after FN onset in 106 patients with breast cancer receiving TC. We retrospectively evaluated the effect of G-CSF as secondary prophylaxis. The frequency of FN was calculated based on the treatment cycles to adjust for differences in the number of cycles per case and FN occurrence. Results: FN occurred in 58 cycles (21.3%). The incidence of FN with and without secondary prophylactic G-CSF was 10.1% and 25.9%, respectively (p=0.003). Multivariate analysis showed secondary prophylactic G-CSF administration to be an independent predictor of FN incidence [odds ratio (OR)=0.33, 95% confidence interval (CI)=0.14-0.74, p=0.007]. Conclusion: Secondary prophylaxis with G-CSF is recommended for patients with breast cancer undergoing TC chemotherapy to reduce the incidence of FN.*

Febrile neutropenia (FN) is a severe adverse event associated with cancer chemotherapy and is occasionally fatal due to the infection caused. Thus, dose reduction or delay of treatment may take place after the onset of FN. However, maintaining a relative dose intensity (RDI), which is the ratio of the actual dose intensity of chemotherapy delivered to the standard recommended dose intensity, is important to improve the prognosis for breast cancer. For example, adjuvant therapy with cyclophosphamide, methotrexate, and fluorouracil (CMF) with RDI of less than 85% in patients with breast cancer has been associated with a poor prognosis (1).

Pegfilgrastim is a sustained granulocyte-colony stimulating factor (G-CSF) with a longer half-life in peripheral blood than conventional G-CSFs. It has been shown to reduce FN incidence in patients receiving high- or moderate-risk regimens (2, 3), and is recommended for use in the prevention of FN based on patient risk factors. Pegfilgrastim administration, as a primary G-CSF prophylaxis during docetaxel and cyclophosphamide (TC) chemotherapy for breast cancer, has been reported to reduce the incidence of FN from 68.8% to 1.2% (2).

G-CSF is also administrated as a secondary prophylaxis after FN occurrence in the prior cycle. A history of FN is a risk factor for FN (4), and appropriate preventive measures need to be undertaken. However, limited data exist on secondary prophylactic G-CSF administration (5, 6), and it is unclear whether it is as effective even as a primary prophylaxis.

We, herein, evaluated the efficacy of G-CSF administration as secondary prophylaxis in patients with breast cancer receiving TC chemotherapy.

Patients and Methods

Patients. Of the 299 patients receiving TC (docetaxel 75 mg/m^2 + cyclophosphamide 600 mg/m^2, every 3 weeks, 4 cycles) as postoperative treatment for early-stage breast cancer at the Hiroshima University Hospital from April 2009 to March 2020, 106 patients (35.5%) developed FN. Moreover, we administered 419 treatment cycles to them, and evaluated 272 cycles after the onset of FN (Figure 1). The endpoint of this study is the frequency of FN onset cycles based on the use of G-CSF in treatment cycles after FN occurrence. An overview of the eligibility of treatment cycles for analysis is shown in Figure 2. To eliminate the bias that the number of treatment cycles

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Key Words: Breast cancer, chemotherapy, febrile neutropenia, filgrastim, secondary prophylactic G-CSF.

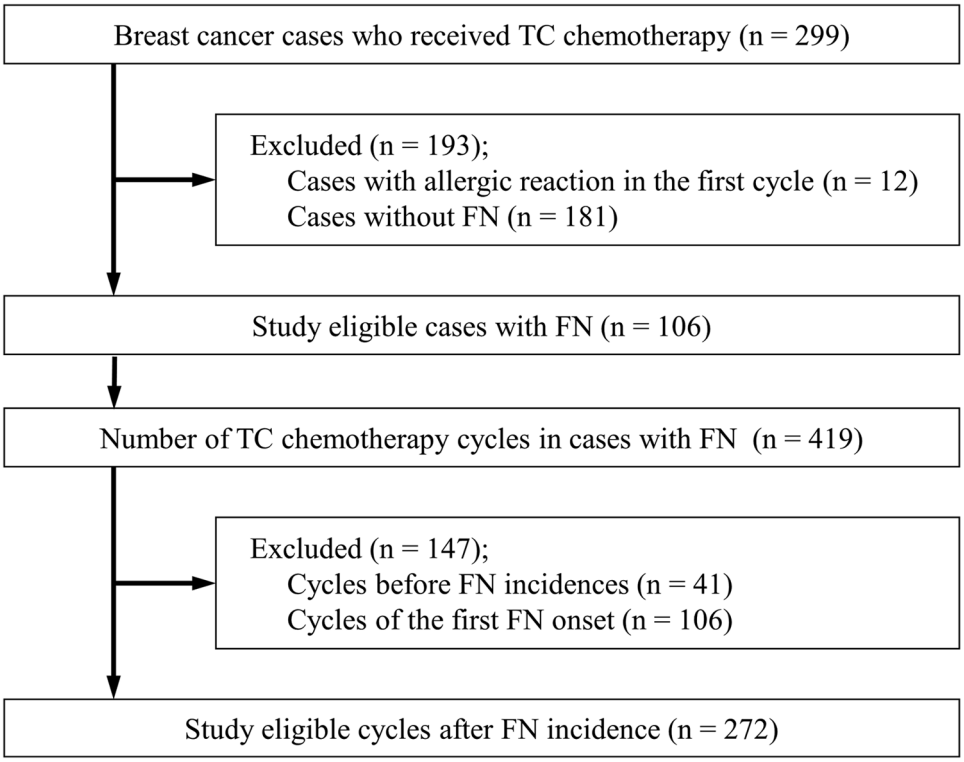

Figure 1. *Procedure of patient selection for study inclusion.*

and FN occurrence differed in each case after FN onset, we evaluated FN onset on a cycle basis. Furthermore, we assessed the association between the use of G-CSF as secondary prophylaxis and the development of FN. All procedures performed in this study involving human participants were conducted in accordance with the ethical standards of the Institutional and/or National Research Committee and with the 1964 Declaration of Helsinki and its later amendments or comparable ethical standards. The Institutional Ethics Committee for Epidemiology (No. E-1157) approved this study.

G-CSF administration. Pegfilgrastim 3.6 mg was administered subcutaneously as a secondary prophylaxis on day 2 or day 3 of chemotherapy. The choice of secondary prophylaxis was made at the discretion of the attending physician. Pegfilgrastim has been available in Japan as from November 2014. Before that date, reduced doses and prophylactic antibiotics were used at the discretion of the attending physician.

Definition of FN. FN was diagnosed when the patient developed fever (>37.5˚C in the axilla) and was grade 3/4 neutropenic ($<1.0\times10^9$/l) or during the neutropenic phase (days 5-14).

Statistics. Variables were presented as numbers and percentages, unless otherwise stated. Logistic regression analysis was performed to identify the predictors of FN. We performed statistical analyses using the EZR software version 1.54 (Saitama Medical Center, Jichi Medical University, Saitama, Japan), a graphical user interface for R versions 4.5. and 4.0.3 (The R Foundation for Statistical Computing, Vienna, Austria). Statistical significance was set at <0.05.

Results

Patient characteristics. Table I illustrates the baseline characteristics of the study participants; their median age was 47 years. There were 50 patients (47.2%) with stage I disease and 49 (46.2%) with stage II disease. Ninety-three patients (87.7%) were estrogen receptor (ER)-positive and 14 (13.2%) were human epidermal growth factor receptor 2 (HER2)-positive. Of the 272 treatment cycles in total, we administered G-CSF in 79 cycles (29.0%), provided antibiotics in 7 cycles (2.6%), and reduced TC dose in 54 cycles (19.9%).

Incidence of FN. FN occurred in 58 cycles of chemotherapy (21.3%). The incidence of FN in cycles with G-CSF was 10.1 %, and that in cycles without G-CSF was 25.9 % (p=0.003) (Table II). FN occurred in 57.1% and 20.4% of cycles with and without prophylactic antibiotics (p=0.039), and 18.5% and 22.0% with and without dose reduction (p=0.711), respectively (Table II).

Predictors for FN. In multivariate analysis, G-CSF administration was an independent inhibitor of FN [odds ratio (OR)=0.33, 95% confidence interval (CI)= 0.14-0.74, p=0.007] (Table III). However, age, dose modification, and antibiotics administration were not associated with the incidence of FN.

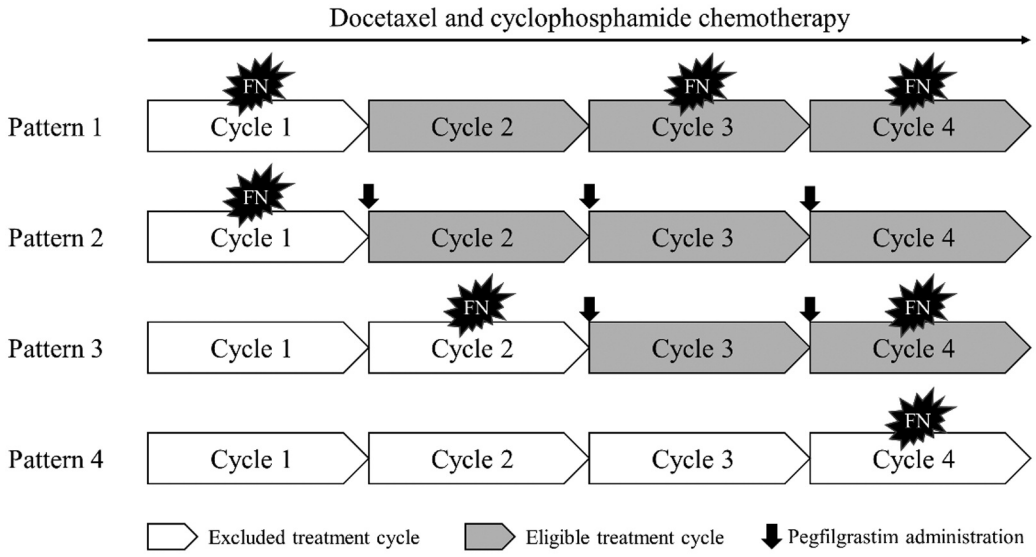

Figure 2. *Overview of eligibility for secondary prophylactic analysis based on treatment cycles. Secondary prophylaxis was provided at the discretion of the attending physician. FN, Febrile neutropenia.*

Table I. *Patient characteristics.*

	Number (%)
Age (y), median (range)	47 (28-84)
Stage	
I	50 (47.2)
II	49 (46.2)
III	6 (5.7)
Locoregional recurrence	1 (0.9)
Histology	
Infiltrating duct carcinoma	95 (89.6)
Invasive lobular carcinoma	6 (5.7)
Others	5 (4.7)
Nuclear grade	
1	3 (2.8)
2	27 (25.5)
3	75 (70.8)
Unknown	1 (0.9
Estrogen receptor positive	93 (87.7)
HER2 positive	14 (13.2)
Ki-67 labeling index (%), median (IQR)	54 (46-62)

HER2, Human epidermal growth factor receptor 2; IQR, interquartile range.

Bacterial infection. Two cases were complicated by bacterial infection; they developed FN in the first cycle. Additionally, chemotherapy was continued without prophylaxis, and in the third cycle they developed urinary tract infection, and subsequently, received antibiotics treatment. In the fourth cycle, they received secondary prophylactic G-CSF and no FN occurred.

Table II. *Relationship between predictors and febrile neutropenia (FN) incidence.*

	No FN (%)	FN (%)	*p*-Value
Total	214 (78.7)	58 (21.3)	
Age			1
<65 years	176 (78.6)	48 (21.4)	
≥65 years	38 (79.2)	10 (20.8)	
Dose reduction			0.711
No	170 (78.0)	48 (22.0)	
Yes	44 (81.5)	10 (18.5)	
Prophylactic G-CSF			0.003
No	143 (74.1)	50 (25.9)	
Yes	71 (89.9)	8 (10.1)	
Prophylactic antibiotics			0.039
No	211 (79.6)	54 (20.4)	
Yes	3 (42.9)	4 (57.1)	

FN: Febrile neutropenia; G-CSF: granulocyte colony-stimulating factor.

Discussion

TC is commonly used as an adjuvant chemotherapy in breast cancer (7). The National Comprehensive Cancer Network (NCCN) guidelines classify TC as a high-risk regimen with FN incidence of 20% or higher (8). A Japanese phase III study on the efficacy of G-CSF prophylaxis in 346 Japanese patients revealed an incidence of 68.8% (2). Asians are presumably more vulnerable to experiencing FN than Caucasians due to differences in their genetic background and the lower

Table III. *Logistic regression analysis for predicting febrile neutropenia (FN) incidence.*

Factors	Univariate analysis		Multivariate analysis	
	OR (95% CI)	*p*-Value	OR (95% CI)	*p*-Value
Age ≥65 years	0.97 (0.45-2.08)	0.927	1.16 (0.53-2.55)	0.717
Dose reduction	0.81 (0.38-1.72)	0.575	0.72 (0.33-1.57)	0.411
Prophylactic G-CSF	0.32 (0.15-0.72)	0.005	0.33 (0.14-0.74)	0.007
Prophylactic antibiotics	5.21 (1.13-24.0)	0.034	4.06 (0.87-19.0)	0.075

CI, Confidence interval; G-CSF, granulocyte colony-stimulating factor; OR, odds ratio.

incidence of obesity (9). Patient-specific risk factors for FN include age (>65 years), previous FN history, low performance status, renal dysfunction, and hepatic dysfunction (8, 10-12). A previous study of perioperative chemotherapy in Japanese patients with breast cancer reported that the TC regimen, age >65 years, and pretreatment absolute neutrophil count (ANC) of <1,000/μl were significant risk factors for the development of FN (13).

The American Society of Clinical Oncology (ASCO), European Organization for Research and Treatment of Cancer (EORTC) and NCCN guidelines recommend primary prophylaxis with G-CSF administration for regimens having >20% risk of developing FN (8, 10, 11). A systematic review demonstrated that primary prophylactic G-CSF administration reduced the risk of developing FN by 45% (14). Severe neutropenia after the first cycle is a significant predictor of a subsequent FN incidence (4) and is associated with low RDI (15). NCCN guidelines recommend secondary prophylactic G-CSF administration if the patient experienced a prior episode of FN, and the same dose is planned for the current cycle (8). Similarly, ASCO and EORTC guidelines recommend secondary prophylaxis with G-CSF in patients with FN history and in whom dose reduction or treatment delay would compromise the main therapeutic effect (10, 11). The goal of secondary prophylaxis is to prevent FN and maintain RDI while safely undergoing chemotherapy. However, only a few studies have assessed the efficacy of secondary prophylactic G-CSF. In a previous report comprising 51 patients who developed FN after intermediate-risk chemotherapy, secondary prophylactic administration of G-CSF with and without dose modification reduced the incidence of FN to 16% and 10%, respectively, in subsequent treatment cycles (5). Additionally, prophylactic administration of G-CSF significantly reduces the use of antimicrobial agents as well as duration of hospitalization (6).

In this study, we showed that secondary prophylactic administration of G-CSF in patients with breast cancer undergoing TC reduced FN incidence. Furthermore, it prevented the incidence of febrile events even in patients who developed bacterial infections in the previous treatment cycle. In the study comprising 45 patients with advanced pancreatic cancer, secondary prophylactic G-CSF significantly prolonged PFS, but not OS (16). Although there are no reports that secondary prophylactic G-CSF prolongs survival in patients with breast cancer, there are reports that secondary prophylactic G-CSF can maintain RDI (17, 18). Therefore, it is expected that secondary prophylactic G-CSF prolongs PFS by preserving RDI.

Our study has certain limitations. First, it was limited by its retrospective study design. Second, FN was clinically determined, and might have been overestimated; most patients with fever did not have neutrophil counts measured and were judged by the timing of the fever. However, our definition of fever is validated by previous studies (13, 19). Although the frequency of FN was calculated based on treatment cycles, we believe that our findings directly demonstrated the preventive effect of G-CSF.

In conclusion, in patients with breast cancer receiving TC, secondary prophylactic administration of G-CSF is recommended to reduce FN incidence in the subsequent cycles.

Conflicts of Interest

The Authors declare no competing interests.

Authors' Contributions

Kanako Suzuki and Shinsuke Sasada contributed to the study conception and design. Clinical data collection was performed by Kanako Suzuki, Shinsuke Sasada, Yuri Kimura, Akiko Emi, and Takayuki Kadoya. Kanako Suzuki and Shinsuke Sasada analyzed the data and wrote the manuscript. All Authors read and approved the final manuscript.

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