Journal of Breast Cancer

J Breast Cancer 2016 March; 19(1): 76-82 http://dx.doi.org/10.4048/jbc.2016.19.1.76

ORIGINAL ARTICLE

Incidence of Febrile Neutropenia in Korean Female Breast Cancer Patients Receiving Preoperative or Postoperative Doxorubicin/Cyclophosphamide Followed by Docetaxel Chemotherapy

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Purpose: Doxorubicin/cyclophosphamide followed by docetaxel chemotherapy (AC-D) is an intermediate risk factor (incidence of 10%–20%) for febrile neutropenia (FN) in breast cancer. However, the reported incidence of FN while using this regimen was obtained mostly from Western breast cancer patients, with little data available from Asian patients. This study aimed to assess the incidence of FN in Korean breast cancer patients and to describe clinical variables related to FN. **Methods:** From September 2010 to February 2013, data from the Yonsei Cancer Center registry of breast cancer patients who received neoadjuvant or adjuvant chemotherapy with four cycles of AC-D (60 mg/m^2 doxorubicin, 600 mg/m^2 cyclophosphamide every 3 weeks for four cycles followed by 75 mg/m^2 or 100 mg/m^2 docetaxel every 3 weeks for four cycles) were analyzed. The incidence of FN, FN associated complications, dose reduction/delays, and relative dose intensity (RDI) were investigated. **Results:** Among the 254 patients reported to the registry, the FN incidence after AC-D chemotherapy was 29.5% (75/254), consisting of 25.2% (64/254) events during AC and 4.7% (12/254) during docetaxel chemotherapy. Dose reductions, delays, and RDI less than 85.0% during AC were observed in 16.5% (42/254), 19.5% (47/254), and 11.0% (28/254) of patients, respectively. Patients with FN events frequently experienced dose reduction/delays, which eventually led to a decreased RDI. **Conclusion:** The incidence of FN during AC-D neoadjuvant or adjuvant chemotherapy was higher than expected in Korean breast cancer patients. Whether these patients should be classified as a high-risk group for FN warrants future prospective studies.

Key Words: *Breast neoplasms, Chemotherapy-induced febrile neutropenia, Cyclophosphamide, Docetaxel, Doxorubicin*

INTRODUCTION

The efficacy of myelosuppressive chemotherapy regimens is often restricted by dose-limiting toxicities that can delay subsequent treatment cycles. Febrile neutropenia (FN) is a common adverse effect of chemotherapy, sometimes causing life-threatening complications [1]. Chemotherapy-induced FN may also result in modifications to the chemotherapy dose or schedule, which may compromise treatment efficacy [2]. In breast cancer, there is evidence supporting a close correlation between maintaining the relative dose intensity (RDI) of neoadjuvant or adjuvant chemotherapy and the clinical outcomes of patients [3,4]. Prevention of chemotherapy-induced FN is therefore a medical priority in neoadjuvant or adjuvant settings.

Recombinant granulocyte-colony stimulating factor (G-CSF) products have emerged as effective therapies for reducing the duration and incidence of chemotherapy-induced neutropenia and FN by stimulating neutrophil proliferation and differentiation in cancer patients [5]. Clinical guidelines from the American Society of Clinical Oncology (ASCO) and the National Comprehensive Cancer Network (NCCN) in the United States, and from the European Organization for Research and Treatment of Cancer (EORTC), all recommend that G-CSF should be administered prophylactically if the risk of FN is greater than 20%. In the case of chemotherapeutic regimens with an intermediate risk of FN (10%–20%), the

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Received: October 18, 2015 **Accepted:** March 8, 2016

http://ejbc.kr | pISSN 1738-6756
eISSN 2092-9900

guidelines emphasize the importance of considering several risk factors for evaluating a patient's overall risk for FN [6,7]. These risk factors include old age, previous chemotherapy or radiotherapy, pre-existing neutropenia or infection, poor performance status, and poor renal or hepatic functions. However, ethnic or geographic differences in response to the same chemotherapy regimen have so far been poorly investigated.

Sequential doxorubicin/cyclophosphamide and docetaxel (AC-D) is a widely used neoadjuvant and adjuvant chemotherapy regimen for breast cancer. The incidence of FN ranges widely from 3.1% to 25%, and many guidelines including the NCCN, ASCO, and EORTC have categorized this regimen into the intermediate risk group (e.g., the risk of FN is 10%–20%) [8,9]. However, most of these studies were conducted in Western countries [10,11], and there have been few reports on the incidence of FN in Asian countries.

Several studies showed that the incidence of hematologic toxicity caused by chemotherapy differs between ethnic groups [12-15]. Here we report the incidence of FN with AC-D as neoadjuvant or adjuvant chemotherapy in Korean breast cancer patients.

METHODS

This study was approved by the Institutional Review Board of Yonsei Cancer Center (approval number: 4-2015-1154). Breast cancer patients who received neoadjuvant or adjuvant sequential AC-D from September 2010 to February 2013 were analyzed from the Yonsei Cancer Center registry of breast cancer. Patients with previous exposure to chemotherapeutic agents; inflammatory breast cancer; major cardiovascular, liver, or renal diseases; active infection; inadequate follow-up; or preexisting neutropenia were excluded in order to minimize other confounding factors (Figure 1).

Four cycles of doxorubicin (60 mg/m^2) and cyclophosphamide (600 mg/m^2) followed by four cycles of docetaxel (75 mg/m^2 or 100 mg/m^2) were administered. Blood samples were collected before each cycle for complete blood cell counts with differential and serum samples for chemistry assays. During the first cycle, nadir blood cell counts were measured between days 10 and 14. After the first cycle, nadir blood cell counts were measured selectively (Figure 2).

Data on patient demographics, pretreatment laboratory pa-

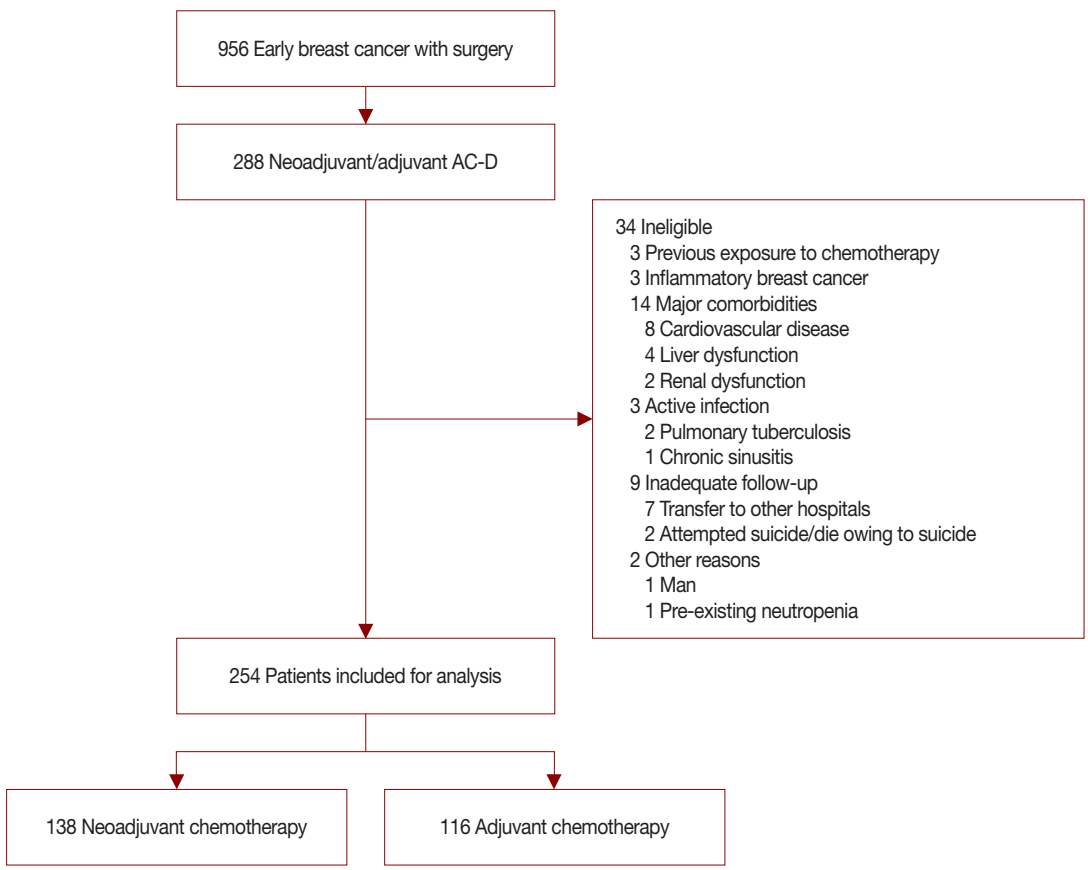

Figure 1. The consort diagram shows the patient inclusion and exclusion criteria.
AC = doxorubicin/cyclophosphamide; D = docetaxel.

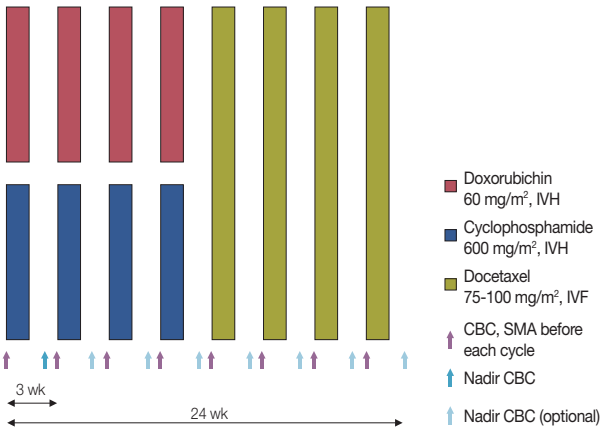

Figure 2. The treatment schema shows the regimen schedule. IVH = intravenous bolus; IVF = intravenous infusion; CBC = complete blood cell count; SMA = serum metabolic analysis.

rameters, and tumor characteristics were collected. Patients were divided into four subtypes in accordance with the St. Gallen 2011 consensus [16]. The incidence of FN, FN-related hospitalization requiring intravenous antibiotics, FN associated with shock or death, subsequent dose reduction/delay, and other hematologic toxicities 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 reductions in the delivered dosages of agents administered relative to the standard values, and dose delay was defined as a chemotherapy interval of more than 28 days (more than 7 days delay) or early cessation of chemotherapy. RDI was calculated by the method described in Supplementary Table 1 (available online) [17].

All patients received neither G-CSF nor antibiotics as primary prophylaxis for FN. Secondary prophylaxis with G-CSF, antibiotics for FN, and dose reduction/delay were administered at the physicians' discretion. Filgrastim was the most commonly used G-CSF analogue, and choice of antibiotics was based on NCCN guidelines.

Statistical analyses were performed using SPSS version 21.0 for Window (IBM Corp., Armonk, USA). Descriptive statistics were used for baseline characteristics. Binomial two-sided 95% confidence intervals (CIs) for the incidence of FN and dose reduction/delays were calculated. The chi-square test was used for comparison between categorical variables, and the two-sample t-test was used for comparison between continuous variables. Two-sided *p*-values less than 0.05 were considered statistically significant.

Table 1. Baseline characteristics

Characteristic	Total (n = 254) No. (%)
Age (yr)*	50 (27–70)
Body weight (kg)†	59.3 ± 8.5
BMI (kg/m²)†	23.7 ± 3.4
BSA (m²)†	1.61 ± 0.11
ECOG	
0	174 (68.5)
1 or 2	80 (31.5)
Stage	
IA	17 (6.7)
IB	11 (4.3)
IIA	78 (30.7)
IIB	70 (27.6)
IIIA	63 (24.8)
IIIB	2 (0.8)
IIIC	13 (5.1)
ER status	
Positive	191 (75.2)
Negative	63 (24.8)
PR status	
Positive	117 (46.1)
Negative	137 (53.9)
HER2 status	
Positive	67 (26.4)
Negative	187 (73.6)
Subtype	
Luminal A-like	120 (47.2)
Luminal B-like	71 (28.0)
Basal-like	34 (13.4)
HER2-enriched	29 (11.4)
Histology	
Ductal	237 (93.3)
Lobular	5 (2.0)
Mixed	12 (4.7)

BMI = body mass index; BSA = body surface area; ECOG = Eastern Cooperative Oncology Group; ER = estrogen receptor; PR = progesterone receptor; HER2 = human epidermal growth factor receptor 2.
*Expressed as median (range); †Expressed as mean ± SD.

RESULTS

Between September 2010 and February 2013, 254 Korean breast cancer patients receiving AC-D were recruited for the analysis (Table 1). The median patient age was 50 years (range, 27–70 years) and 5.9% (15/254) of patients were more than 65 years old. The mean body weight, body mass index, and body surface area were 59.3 ± 8.5 kg, 23.7 ± 3.4 kg/m², and 1.61 ± 0.11 m², respectively. The number of patients with Eastern Cooperative Oncology Group performance status 1 or 2 was 31.5% (80/254). There were 13.4% (34/254) cases of basal-like subtype tumors and 11.4% (29/254) cases of human epidermal growth factor receptor 2 (HER2) enriched subtype tu-

http://dx.doi.org/10.4048/jbc.2016.19.1.76

Table 2. Incidence of febrile neutropenia, dose reduction, dose delay, and relative dose intensity <85.0% during doxorubicin/cyclophosphamide

Variable	No. of patients experienced	Incidence (%)	95% CI
FN during AC+D	75	29.5	23.9–35.2
FN during AC	64	25.2	19.8–30.6
FN during D	12	4.7	2.1–7.4
Dose reduction during AC	42	16.5	11.9–21.1
Dose delay during AC	47	19.5	13.7–23.3
RDI <85.0% during AC	28	11.0	7.1–14.9

CI = confidence interval; FN = febrile neutropenia; AC = doxorubicin/cyclophosphamide; D = docetaxel; RDI = relative dose intensity.

mors. A total of 138 patients received neoadjuvant chemotherapy and 116 patients received adjuvant chemotherapy.

During the AC and D stages of chemotherapy 25.2% (64/254) and 4.7% (12/254) patients experienced FN, respectively (Table 2). Overall, 29.5% of patients experienced FN during chemotherapy (95% CI, 23.9%–35.2%, 75/254). Dose reduction, delays, and RDI less than 85.0% during AC were observed in 16.5% (42/254), 19.5% (47/254), and 11.0% (28/254) of patients, respectively.

The total number of FN events during chemotherapy was 95, including 83 events (87.4%) during AC and 12 events (12.6%) during D (Table 3). Of the 64 patients who experienced FN during AC, 41 patients (64.1%) experienced FN in the first cycle. Of 95 events of FN, 66 events (69.5%) were accompanied by administration of intravenous antibiotics and five (5.3%) were accompanied by septic shock. No chemotherapy-related death was observed. The median duration of admission was 5 days, ranging from 2 to 20 days. β-Lactam/β-lactamase inhibitors were the most frequently used intravenous antibiotics (69.7%) and glycopeptides were used in six events (9.1%). Secondary G-CSF prophylaxis for the next cycle was administered in 58 cases (61.1%). Dose reduction and dose delays were performed in 26.3% and 15.8% of patients, respectively. Fifteen patients experienced more than two events of FN, even with prophylactic G CSF administration, and dose reduction/delays were performed for these patients.

Baseline and treatment characteristics were compared between patients who experienced FN during AC and patients who did not (Table 4). Dose reduction and delay during AC chemotherapy were more frequently observed in patients who experienced FN (39.1% vs. 8.9%, $p<0.001$; 35.9% vs. 12.6%, $p<0.001$, respectively). The dose interval during AC was longer in patients who experienced FN (22.3 vs. 21.6 days, $p=0.002$) and the RDI during AC was lower in patients who experienced FN (90.5% vs. 96.7%, $p<0.001$). Patients who experienced FN during AC were more likely to have an RDI less than 85.0% (25.0% vs. 6.3%, $p<0.001$).

Table 3. Description of febrile neutropenia* (total no. of events = 95, total no. of patients = 75)

Variable	Observed events or patients No. (%)
FN during AC	83/95 (87.4)
FN during D	12/95 (12.6)
Patients experienced FN during AC	64/75
1st cycle	41/64 (64.1)
2nd cycle	7/64 (10.9)
3rd cycle	9/64 (14.1)
4th cycle	7/64 (10.9)
Patients experienced FN during D	12/75
5th cycle	5/12 (41.7)
6th cycle	4/12 (33.3)
7th cycle	3/12 (25.0)
8th cycle	0/12 (0.0)
FN associated complications	
Admission for intravenous antibiotics	66/95 (69.5)
Shock	5/95 (5.3)
Death	0/95 (0.0)
Intravenous antibiotics	
β-Lactam/β-lactamase inhibitor	46/66 (69.7)
Cephalosporin	20/66 (30.3)
Fluoroquinolone	3/66 (4.5)
Glycopeptide	6/66 (9.1)
Oral antibiotics	
β-Lactam/β-lactamase inhibitor	16/29 (55.2)
Cephalosporin	9/29 (31.0)
Fluoroquinolone	20/29 (69.0)
Secondary G-CSF prophylaxis	58/95 (61.1)
Dose reduction	25/95 (26.3)
Dose delay	15/95 (15.8)
Patients experienced FN more than twice	15/75 (20.0)

FN = febrile neutropenia; AC = doxorubicin/cyclophosphamide; D = docetaxel; G-CSF = granulocyte colony stimulating factor.
*Expressed as "actual number of events or patients/total number of events or patients" in proper circumstances.

We investigated other hematologic toxicities by using the CTCAE grading system (Supplementary Table 2, available online). Patients with FN during AC cycles were more likely to experience grade 3/4 lymphopenia, anemia, and thrombocytopenia (Supplementary Table 3, available online).

DISCUSSION

This study showed that the incidence of FN during AC-D chemotherapy was 29.5% in breast cancer patients in Korea. FN events occurred frequently during AC chemotherapy (25.2%) and more than half of the FN events (64.1%) occurred in the first cycle. Patients who experienced FN were more likely to have poor performance status and low pretreatment albumin levels, similar to the results of a previous study

Table 4. Comparison of patient and treatment characteristics by experience of febrile neutropenia during doxorubicin/cyclophosphamide (experience of febrile neutropenia versus no experience of febrile neutropenia during doxorubicin/cyclophosphamide)

Characteristic	FN during AC (n=64) No. (%)	No FN during AC (n=190) No. (%)	*p*-value*
Age (yr)†	52 (31–68)	50 (27–70)	0.081
Body weight (kg)‡	60.0±9.9	59.0±8.0	0.431
BMI (kg/m^2)‡	24.3±3.6	23.6±3.3	0.162
BSA (m^2)‡	1.61±0.12	1.60±0.11	0.704
ECOG			0.002
0	34 (53.1)	140 (73.7)	
1 or 2	30 (46.9)	50 (26.3)	
Baseline CBC‡			
WBC (cells/μL)	5,911±1,546	6,230±1,793	0.204
ANC (cells/μL)	3,534±1,237	3,820±1,548	0.181
Lymphocyte (cells/μL)	1,740±663	1,794±612	0.552
Hgb (g/dL)	12.5±1.4	12.7±1.2	0.460
PLT (10^3 cells/μL)	255±78	279±73	0.025
Baseline albumin (mg/dL)	4.16±0.42	4.28±0.34	0.016
Stage			0.809
IA	3 (4.7)	14 (7.4)	
IB	2 (3.1)	9 (4.7)	
IIA	22 (34.4)	56 (29.5)	
IIB	20 (31.2)	50 (26.3)	
IIIA	15 (23.4)	48 (25.3)	
IIIB	0	2 (1.1)	
IIIC	2 (3.1)	11 (5.8)	
ER status			0.477
Positive	46 (71.9)	145 (76.3)	
Negative	18 (28.1)	45 (23.7)	
PR status			0.313
Positive	26 (40.6)	91 (47.9)	
Negative	38 (59.4)	99 (52.1)	
HER2 status			0.306
Positive	20 (31.2)	47 (24.7)	
Negative	44 (68.8)	143 (75.3)	
Subtype			0.878
Luminal A-like	30 (46.9)	90 (47.4)	
Luminal B-like	16 (25.0)	55 (28.9)	
Basal-like	10 (15.6)	24 (12.6)	
HER2-enriched	8 (12.5)	21 (11.1)	
Histology			0.743
Ductal	59 (92.2)	178 (93.7)	
Mixed	3 (4.7)	9 (4.7)	
Lobular	2 (3.1)	3 (1.6)	
Dose reduction during AC	25 (39.1)	17 (8.9)	<0.001
Dose delay during AC	23 (35.9)	24 (12.6)	<0.001
Dose interval during AC (day)‡	22.3±1.8	21.6±1.4	0.002
RDI during AC (%)‡	90.5±10.8	96.7±6.4	<0.001
RDI <85.0% during AC	16 (25.0)	12 (6.3)	<0.001

FN=febrile neutropenia; AC=doxorubicin/cyclophosphamide; BMI=body mass index; BSA=body surface area; ECOG=Eastern Cooperative Oncology Group; CBC=complete blood cell count; WBC=white blood cell count; ANC=absolute neutrophil count; Hgb=hemoglobin; PLT=platelet; ER=estrogen receptor; PR=progesterone receptor; HER2=human epidermal growth factor receptor 2; RDI=relative dose intensity.
*Comparison between patients who experienced febrile neutropenia and those who did not; †Expressed as median (range); ‡Expressed as mean±SD.

[18]. Patients with FN events frequently experienced dose reduction/delays, which eventually led to a decreased RDI. Furthermore, we observed frequent hospitalization and use of intravenous antibiotics for the management of FN.

Previous studies reported a diverse range of FN incidence during AC or AC-D chemotherapy. The ECOG 1199 and CALBG 40101 trials reported an incidence of FN of 6.5% and 6.0%, respectively, during adjuvant AC chemotherapy [19,20]. The CALGB 9741 and BCIRG-005 trials reported an incidence of 6.0% and 7.7%, respectively, during adjuvant AC-D chemotherapy [11,21]. The GEPARDUO study documented an incidence of 3.7% during neoadjuvant AC-D chemotherapy [8]. In contrast to early breast cancer patients, the FN incidence was higher in patients with metastatic breast cancer during AC-D chemotherapy, up to 25% of those without prophylactic G-CSF support [22]. Chan et al. [23] investigated the incidence of FN following AC chemotherapy in Asian countries. After the first cycle, 9.1% (17/189) of patients developed FN and after all cycles this rose to 13.8%. The authors pointed out that the relatively lower incidence of FN in previous randomized control trials could be attributed to patient selection before inclusion into the trial.

Ethnic differences in hematologic toxicity from chemotherapeutic agents or monoclonal antibodies have been described in lung cancer [12,13,24] and renal cell carcinoma patients [14]. In breast cancer, the pharmacokinetics and pharmacodynamics of doxorubicin and docetaxel are different in terms of nadir white blood cell count and neutrophil count between ethnicities [25]. Genetic polymorphisms also influence nadir white blood cell and neutrophil counts in patients receiving cyclophosphamide-based combination chemotherapy [26]. In these previous studies, severe hematologic toxicities were more frequently observed in Asian patients than in Western patients. These findings provide indirect evidence that Asian patients are more likely to experience FN during chemotherapy. Consistent with the findings above, although the patients in our study did not have any of the baseline characteristics that elevate the risk of FN, including other comorbidities, they had FN events more frequently and lower RDIs during AC-D chemotherapy compared to study populations in previous studies that were mostly conducted in Western countries.

Our study has several limitations, including its relatively small sample size, being conducted in a single institution, and its retrospective nature. Indications for admission, selection of antibiotics, secondary G CSF prophylaxis, and dose reduction/delay were according to the individual physicians' judgment rather than protocol-defined management. Additionally, only FN reported officially was counted, and patients' or caregivers' self-documentation of febrile events were excluded,

http://dx.doi.org/10.4048/jbc.2016.19.1.76

which could imply under-estimation of the incidence of FN. When we included possible cases of FN in the analysis, 32.7% (95% CI, 26.9%–38.5%) and 28.3% (95% CI, 22.8%–33.9%) patients experienced FN during any cycle and during AC cycles, respectively.

In conclusion, the incidence of FN during AC-D in breast cancer patients was 29.5%, 25.2% during AC and 4.7% during D chemotherapy. Patients who experienced FN had more occurrences of hospitalization and dose reduction/delays, which may compromise treatment efficacy and quality of life. Further large prospective studies are required to define the exact incidence of FN in Asian patients with this regimen. In addition, whether to consider the use of prophylactic G-CSF in Korean breast cancer patients treated with this regimen needs to be validated in future prospective clinical trials.

CONFLICT OF INTEREST

The authors declare that they have no competing interests.

ACKNOWLEDGMENTS

The authors would like to thank Dong-Su Jang, a medical illustrator in the Medical Research Support section of Yonsei University College of Medicine, Seoul, Korea, for assistance with the illustrations, and Su Kyoung Park, a medical record administrator in the Analysis Division of Medical Record Team at this institution, for assistance with data management.

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