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Risk Factors of Febrile Neutropenia in Early Breast Cancer Patients Receiving Anthracycline-based Chemotherapy

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Abstract

Background: Chemotherapy-induced Febrile Neutropenia (FN) is a major risk factor for infection-related morbidity and mortality during chemotherapy. We aimed to investigate the incidence of FN and its risk factors in breast cancer patients with (neo-) adjuvant anthracycline based chemotherapy.

Methods: Clinical, oncologic, and FN information of 125 women with early or locally advanced breast cancer receiving anthracycline-based chemotherapy as (neo-) adjuvant chemotherapy were retrospectively collected and analyzed in a single center.

Results: Thirty-four (27.2%) of 125 patients, with mean age 51.6 (Range: 35 to 77) years, suffered from FN. In univariate analysis, patients ≥ 65 years old [Odd Ratio (OR): 6.43, 95% confidence interval (95% CI): 2.16-19.16] and those 55 to 65 years old (OR: 4.68, 95% CI: 1.67-13.10) had a higher risk of FN. Patients with Body Surface Area (BSA) ≤ 1.45 m2 (OR: 6.78, 95% CI: 2.26-20.28) and those with Hypertension (HTN) (OR: 2.56, 95% CI: 1.05-6.21) had a higher risk of FN. In multivariate analysis, patients ≥ 65 years old (OR: 5.47, 95% CI: 1.52-19.69), those 55 to 65 years old (OR: 6.01, 95% CI: 1.81-19.93), and those with BSA ≤ 1.45 m2 (OR: 9.19, 95% CI: 2.68-31.48) had a higher risk of FN.

Conclusion: Besides age ≥ 65 years, age 55 to 65 years and low BSA ≤ 1.45 m2 were additional risk factors for FN. Therefore, prophylactic G-CSF support should be considered for breast cancer patients who would receive (neo-) adjuvant anthracycline based chemotherapy and have these risk factors to prevent chemotherapy-induced FN.

Keywords: Adjuvant chemotherapy; Anthracycline; Breast cancer; Febrile neutropenia

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Introduction

Breast cancer is the most common cancer among women and its incidence rate has been constantly increasing from 1983 to 2017 in Korea [1]. Adjuvant chemotherapy has reduced the rate of recurrence and improved breast cancer survival [2]. Historically, anthracyclines have been the backbone of many cytotoxic agents for breast cancer treatment. Adriamycin/Cyclophosphamide (AC) is a frequently administered regimen for breast cancer for adjuvant or neoadjuvant therapy [3]. Cytotoxic agents inhibit the proliferation of or kill tumor cells as well as a number of normal host cells. Cytotoxic chemotherapy predictably suppresses the hematopoietic system, impairing the host's protective mechanism. Neutropenia is a serious chemotherapy-induced hematologic toxicity and the degree and duration of neutropenia are related with the risk of infection [4]. Neutropenia may be complicated by fever, or Febrile Neutropenia (FN). FN is associated with a high morbidity and mortality and thus, hospitalization and administration of empirical broad-spectrum antibiotics is frequent in these patients [5,6].

FN is a significant dose-limiting toxicity induced by chemotherapy and can become a potentially fatal complication of cancer treatment if infection or sepsis develops. Patients developing severe (grade 3/4) FN during chemotherapy frequently receive dose reductions and/or delays to their chemotherapy. Because the dose-response effect is a crucial factor in the administration of anthracycline-based non-taxane schedules for adjuvant treatment of early breast cancer [7], decisions regarding dose reduction should be considered carefully.

Chemotherapy regimens have been classified as having a high, intermediate, or low risk according to developing FN [8]. AC regimen is categorized as intermediate risk as the probability of developing FN is 10% to 20% [9,10]. Clinical practice guidelines recognize that patient risk

Table 1: Patient's baseline characteristics (n=125).

Variables	Subjects without FN (n=91)	Subjects with FN (n=34)	*p*
Age (years), mean ± SD	**49.9 ± 9.0**	**57.1 ± 10.1**	**<0.001**
BSA (m^2), median [IQR]	**1.60 [1.54; 1.70]**	**1.56 [1.44; 1.67]**	**0.037**
Operation type, n (%)			0.462
Mastectomy	19(21.1%)	10(29.4%)	
Breast conserving surgery	71(78.9%)	24(70.6%)	
TNM stage, n (%)			0.546
I	32 (35.2%)	11 (32.4%)	
II	44 (48.4%)	19 (48.4%)	
III	7 (7.7%)	1 (2.9%)	
Invasive ductal cancer, n (%)	73 (80.2%)	26 (76.5%)	0.614
ER positive, n (%)	59 (64.8%)	24 (70.6%)	0.691
PR positive, n (%)	56 (61.5%)	24 (70.6%)	0.466
HER2 positive, n (%)	31 (34.1%)	9 (26.5%)	0.242
Chemotherapy type, n (%)			>0.999
Adjuvant chemotherapy	83 (91.2%)	31 (91.2%)	
Neoadjuvant chemotherapy	8 (8.8%)	3 (8.8%)	
Regimen, n (%)			0.659
AC	82 (90.1%)	29 (85.3%)	
FAC	9 (9.9%)	5 (14.7%)	
Dosage reduction, n (%)	6 (6.6%)	4 (11.8%)	>0.999
Laboratory findings			
Hemoglobin, median [IQR]	12.8 [12.1;13.3]	12.7 [11.7;13.3]	0.521
Albumin, median [IQR]	4.2 [4.1;4.4]	4.2 [4.2;4.3]	0.98
Comorbidity, n (%)			
DM	3 (3.3%)	4 (11.8%)	0.163
HTN	16 (17.6%)	12 (35.3%)	0.061
Hepatitis	1 (1.1%)	2 (5.9%)	0.369
TB	3 (3.3%)	0 (0.0%)	0.678

AC: Adriamycin/Cyclophosphamide; BSA: Body Surface Area; DM: Diabetes Mellitus; ER: Estrogen Receptor; FAC, 5-FU: Adriamycin and Cyclophosphamide; FN: Febrile Neutropenia; HTN: Hypertension; IQR: Interquartile Range; PR: Progesterone Receptor; SD: Standard Deviation; TB: Tuberculosis; Bold: Face values are statistically significant

factors may elevate the risk of FN and recommend the assessment of risk factors to estimate the overall risk of FN [11,12]. There are various risk factors for developing FN such as older age (particularly aged ≥ 65 years old), previous chemotherapy or radiotherapy, pre-existing neutropenia or tumor involvement in the bone marrow, comorbidities (e.g., renal or liver dysfunction), and pre-existing conditions (e.g., recent surgery and/or open wounds). Among these various risk factors, age ≥ 65 years old is the main risk factor for early breast cancer patients receiving adjuvant chemotherapy because they mostly have a low incidence of morbidity. Recently, prophylactic Granulocyte Colony-Stimulating Factor (G-CSF) treatment in breast cancer patients aged ≥ 65 years and treated with AC regimen was included under the national medical insurance coverage in Korea.

There was big difference among a few studies conducted on similar population in the incidence of FN during AC chemotherapy. Similar results were observed in Korean studies [13,14]. Thus, in this study we explored the incidence of FN during AC chemotherapy and investigated its risk factors with the aim of prescribing prophylactic hematologic stimulator factor in Korean breast cancer patients who would receive anthracycline-based chemotherapy. Furthermore, in order to assist in the interpretation of the difference, we also investigated the reasons of big difference of FN incidence between studies.

Methods

Study population and methods

This study was a retrospective study based on medical records. Women who were diagnosed with early or advanced breast cancer (stage I-IIIC) and received more 4 cycles of Adriamycin and cyclophosphamide combination chemotherapy at Kyung Hee University Medical Center from January 2011 to December 2014 were included in this study. Chemotherapies included Adriamycin and cyclophosphamide (AC, doxorubicin, 60 mg/m^2 and cyclophosphamide, 600 mg/m^2 every 21 days) or 5-FU, Adriamycin and cyclophosphamide (FAC, 5-FU, 50 mg/m^2, doxorubicin, 50 mg/m^2 and cyclophosphamide, 500 mg/m^2 every 21 days) as neoadjuvant or adjuvant chemotherapy. This retrospective study was approved by the Institutional Review Board and an independent ethic committee at Kyung Hee University Medical Center (2019-07-006) and meets the standards of the Declaration of Helsinki. The confidentiality of the

patients' data was maintained throughout the study.

We collected patients' demographic and clinical characteristics including age at diagnosis, Body Surface Area (BSA), operation type, stage of disease, histology, Estrogen Receptor (ER) status, Progesterone Receptor (PR) status, HER2 status, setting, type, and dosage of chemotherapy regimen, comorbidities [Diabetes Mellitus (DM), Hypertension (HTN), Hepatitis, Tuberculosis (TB)], and nadir blood count. We also collected information on the first onset cycle and the number of neutropenia and FN events by nadir neutrophil counts. Blood samples were collected before each cycle for complete blood cell counts with differentials and serum samples for chemistry assays. Nadir blood cell counts were measured between days 10 and 14 on every cycle. Neutropenia was defined as less than 500 neutrophils/μl and FN was defined as neutropenia with febrile event (axillary temperature ≥ 38°C) as observed by medical staff. When chemotherapy dose reduction was greater than 15%, it was considered clinically significant. Patients did not receive Granulocyte-Colony Stimulating Factor (G-CSF) or antibiotics as primary or secondary prophylaxis for FN. G-CSF support was administered only for therapeutic purposes. Antibiotics for FN, and dose reduction/delay were administered at the physicians' discretion.

Statistical analysis

Data are presented as mean ± Standard Deviation (SD), median and Interquartile Range (IQR), or number (percentage), unless otherwise specified. Baseline characteristics of the subjects without and with FN were compared using Student's t-tests for continuous variables and χ^2 tests for categorical variables. Receiver-Operating Characteristic (ROC) analysis was performed, comparing areas under the ROC curves (AUCs) to evaluate the ability of age and BSA to predict the likelihood of NF. The cut-off for age and BSA to predict NF was calculated using Youden's index [15]. Logistic regression analyses were performed to generate Odds Ratios (ORs) with a 95% Confidence Interval (95% CI) according to the risk factor. All statistical analyses were performed with SPSS statistical software (version 18.0, SPSS Inc., Chicago, IL) and the open source programming language R, with P<0.05 considered statistically significant.

Results

Patient's characteristics are shown in Table 1 of the 125 patients, 34 (27.2%) suffered from FN. Patients with FN (57.1 ± 10.1 years) were older than those without FN (49.9 ± 9.0 years, p<0.001) and had lower BSA (median: 1.56, IQR: 1.44; 1.67 m^2) than those without FN (median: 1.60, IQR: 1.54; 1.70 m^2, p=0.037). Patients with FN had higher frequency of HTN (n=12 of 34, 35.3%) than those without FN [n=3 of 91 (3.3%), p=0.061]. No significant differences were observed regarding operation type, TNM stage, invasive ductal cancer, hormone receptor status, HER2 status, chemotherapy type, regimen and dosage of chemotherapy, laboratory findings, and history of DM, hepatitis, and TB.

Table 2: Univariate logistic regression analysis for of FN.

	ORs	95% CI	*p*
Age			
Age <55 years	Ref		
Age: 55~64 years	**4.7**	**1.67–13.10**	**0**
Age ≥ 65 years	**6.4**	**2.16–19.16**	**0**
BSA			
BSA > 1.45 m^2	Ref		
BSA ≤ 1.45 m^2	**6.8**	**2.26–20.28**	**0**
HTN			
No HTN	Ref		
HTN	**2.6**	**1.05–6.21**	**0.04**

BSA: Body Surface Area; FN: Febrile Neutropenia; HTN: Hypertension; OR: Odd Ratio; 95% CI: 95% Confidence Interval; Bold: Face values are statistically significant

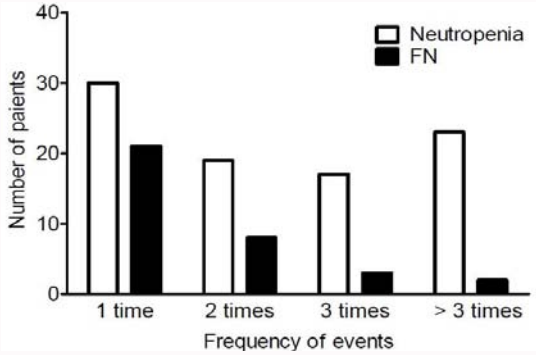

Figure 1: Frequency of neutropenia and Febrile Neutropenia (FN) according to the cycles of chemotherapy.

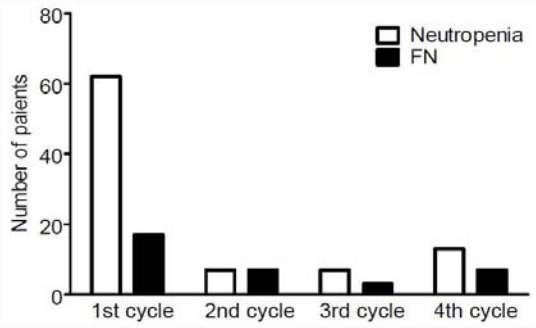

Figure 2: Occurrence of neutropenia and Febrile Neutropenia (FN) according to frequency.

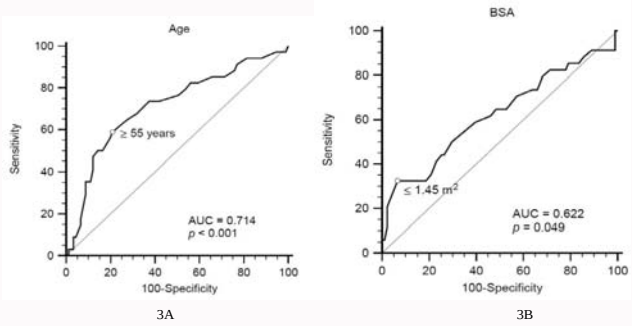

Figure 3: Receiver operating characteristic curve for the prediction of febrile neutropenia, based on age (3A) and BSA (3B). AUC: Area under receiver operating characteristic Curve; BSA: Body Surface Area

Among the total of 125 patients, 89 (71.2%) and 34 (27.2%) suffered from neutropenia and FN, respectively. Of 89 patients with neutropenia, 30 (33.7%) patients experienced neutropenia once, 19 (21.3%) patients experienced it twice, 17 (19.1%) patients three times, and 23 (25.8%) patients four times. Among the 34 patients with FN, 21 (61.8%) patients suffered from it once, 8 (23.5%) patients twice, 3 (8.8%) patients three times, and 2 (5.9%) patients four times (Figure 1). Regarding the timing of neutropenia or FN during chemotherapy,

Table 3: Multivariate logistic regression analysis for of FN.

	ORs	95% CI	*p*
Age			
Age <55 years	Ref		
Age: 55~64 years	**6.01**	**1.81–19.93**	**0.003**
Age ≥ 65 years	**5.47**	**1.52–19.69**	**0.009**
BSA			
BSA >1.45 m^2	Ref		
BSA ≤ 1.45 m^2	**9.19**	**2.68–31.48**	**<0.001**
HTN			
No HTN	Ref		
HTN	1.36	0.44–4.19	0.598

BSA: Body Surface Area; FN: Febrile Neutropenia; HTN: Hypertension; OR: Odd Ratio; 95% CI: 95% Confidence Interval; Bold: Face values are statistically significant

62 (69.7%) and 17 (50%) patients developed neutropenia and FN during the first cycle, respectively, 7 (7.9%) and 7 (20.6%) patients during the second cycle, 7 (7.9%) and 3 (8.8%) patients during the third cycle, and 13 (14.6%) and 7 (20.6%) patients during the fourth cycle, respectively (Figure 2).

In the ROC analysis, the cut-off values, corresponding to Youden's indexes, for age and BSA capable of predicting FN were age ≥ 55 years old and BSA ≤ 1.45 m^2, respectively (Figure 3A and 3B). Age ≥ 65 years old was suggested as a risk factor for FN [11]. Thus, we divided patients into three groups by age (≥ 65 years, 55~64 years, and <55 years) and into two groups by BSA (BSA ≤ 1.45 m^2 and BSA >1.45 m^2). In the multivariate regression analysis (Table 2 and 3), patients ≥ 65 years (OR: 5.47, 95% CI: 1.52-19.69), those 55-65 years (OR: 6.01, 95% CI: 1.81-19.93), and those with BSA ≤ 1.45 m^2 (OR: 9.19, 95% CI: 2.68-31.48) were at higher risk for FN. However, HTN status no longer reached statistical significance.

Discussion

In this study, the incidence of FN during anthracycline based chemotherapy in the curative setting was 27.2%. Besides age ≥ 65 years old which was suggested as a known risk factor, age 55 to 65 years and a low BSA ≤ 1.45 m^2 were identified as additional risk factors for FN. To the best of our knowledge, these findings provide the first suggestion that prophylactic G-CSF support might be considered for patients aged 55 to 65 years and with a low BSA ≤ 1.45 m^2.

In this study, the novel risk factor for FN in breast cancer patients was age 55 to 65 years. Old age has is a well-known risk factor for FN. The NCCN guidelines recommend that age ≥ 65 years old is indicated as a risk factor among patients receiving intermediate risk chemotherapy regardless of gender [11]. The risk score for FN determined by the Multinational Association for Supportive Care of Cancer (MASCC) is based on 60 years of age [16]. Recently, prophylactic G-CSF treatment for breast cancer patients aged ≥ 65 years, treated with AC regimen, was included under the national medical insurance coverage in Korea. In this study, age 55 to 65 years old was identified as an additional risk factor for FN. Twenty-one of 125 (16.8%) patients included in this study were aged 55 to 65 years old. Of the 21 patients, 10 (47.6%) suffered from FN. Patients aged 55 to 65 years old had higher risk for FN in both univariate and multivariate logistic regression analysis. Compared with patients aged <55 years, patients aged 55 to 65 years old had similar OR to those aged ≥ 65 years old. We could not determine the exact reason for the higher risk for FN in patients aged 55 to 65 years old. According to a systematic review, patient-related risk factors for FN were older age, poor performance status, female gender, comorbidities, laboratory abnormalities, BMI, and BSA [17]. Thus, there is the possibility of lowering the age with risk for FN due to breast cancer which predominantly occurred in women with lower BMI or BSA.

In this study, another novel risk factor for FN in breast cancer

Table 4: Comparison of three retrospective studies of FN incidence in patients receiving AC combination chemotherapy.

	Kim et al. [13]	Kim et al. [14]	Present study
Duration	2010.9–2013.2	2005.9–2013.3	2011.1–2014.12
Number	254	610	125
Age, years, mean ± SD	50 (27-70)[a]	49.5 ± 9.4	51.6 ± 10.0
Aged ≥ 65 years, %	5.90%	6.40%	14.40%
Incidence of G4 neutropenia	NA	44.60%	71.00%
Incidence of FN	25.20%	8.50%	27.20%
Predictive factors	NA	G4 neutropenia,	Age ≥ 55 years
		eGFR <60 ml/min,	BSA ≤ 1.45 m^2
		Prophylactic G-CSF use	
Prophylactic G-CSF	2nd prophylaxis	1st or 2nd prophylaxis	No prophylaxis
	by clinician discretion	by clinician discretion.	
Measurement of nadir blood cell counts	Day 10-14[b]	No mention	Day 10-14[c]
How many cycles did patients receive	4	≥ 2	≥ 4
Definition of fever	≥ 38.3°C, or ≥ 38.0°C for over 1 hour	≥ 38.3°C, or ≥ 38.0°C for over 1 hour	≥ 38.0°C
Institution	Yonsei Cancer Center	Korea University Anam Hospital,	Kyung Hee University hospital
		Korea University Guro Hospital,	
		National Cancer Center of Korea	

[a]median (range)
[b]During the first cycle, nadir blood cell counts were measured between days 10 and 14 and After the first cycle, nadir blood cell counts were measured selectively
[c]every cycle
G4: Grade 4; FN: Febrile Neutropenia; e-GFR: estimated Glomerular Filtration Rate; G-CSF: Granulocyte-Colony stimulating Factor; NA: Not Applicable

patients was a low BSA (≤ 1.45 m^2). A few studies conducted on patients with lymphoma or hematologic malignancies have shown that a low BSA is a risk factor for FN. However, cytotoxic agents used for patients with lymphoma or hematologic malignancies are mainly high-risk drugs and thus the cutoff for BSA was also higher (1.9 to 2.0) than the cutoff for BSA in this study [18,19]. There have also been studies indicating that BSA is not associated with the occurrence of FN [14,20]. In this study, low BSA ≤ 1.45 m^2 had higher OR than age 55 to 65 years old and ≥ 65 years old.

Some studies have reported that hematologic toxicity profiles during adjuvant chemotherapy differ between Asian and Caucasian patients [21,22]. Asians had a higher rate of grade 3 hematologic toxicity. Chan et al. [20] reported that the incidence of FN following AC chemotherapy in Asian patients is 13.8%. Previous retrospective studies investigating the incidence of FN during AC chemotherapy have been published [13,14]. The incidence of FN (27.2%) in this study was similar to that reported by Kim CG, et al (25.2%, p=0.676) [13] and higher than that reported by Kim HS, et al (8.5%, p<0.001) [14]. We could not determine the exact reason for the difference in the incidence of FN. There are some differences in the characteristics of the patient population among studies. First, in this study we enrolled a higher proportion of patients aged ≥ 65 years old (14.4%) compared to the study by Kim et al. [13] (5.9%, p=0.006) and Kim et al. [14] (6.4%, p=0.002). Second, we did not use the 1st and 2nd prophylactic G-CSF. Third, we enrolled patients receiving ≥ 4 cycles of chemotherapy. Indeed, about 30% of patients with FN developed FN after the 2nd cycle. Finally, there were some differences in the time points for monitoring nadir blood cell counts and in the definition of fever and institution (Table 4).

Our study has several limitations which include its retrospective design, relatively small sample size, and being conducted in a single institution. Thus, additional studies are needed to extend our findings to populations with large numbers of patients and other ethnicities. However, we obtained results from patients who were monitored with a homogenous policy, such as the measurement of nadir blood cell counts, management of FN, and use of prophylactic or therapeutic G-CSF. In this study, the incidence of FN was relatively high, which is related with active monitoring of nadir blood cell counts and treatment of neutropenic fever.

In conclusion, besides age ≥ 65 years, age 55 to 65 years and a low BSA ≤ 1.45 m^2 were additional risk factors for FN in early breast cancer patients receiving anthracycline-based chemotherapy. Therefore, prophylactic G-CSF support might be considered for patients with risk factors.

References

1. Hong S, Won YJ, Park YR, Jung KW, Kong HJ, Lee ES, et al. Cancer statistics in Korea: Incidence, mortality, survival, and prevalence in 2017. Cancer Res Treat. 2020;52(2):335-50.
2. Berry DA, Cronin KA, Plevritis SK, Fryback DG, Clarke L, Zelen M, et al. Effect of screening and adjuvant therapy on mortality from breast cancer. N Eng J Med. 2005;353(17):1784-92.
3. Fisher B, Brown AM, Dimitrov NV, Poisson R, Redmond C, Margolese RG, et al. Two months of doxorubicin-cyclophosphamide with and without interval reinduction therapy compared with 6 months of cyclophosphamide, methotrexate, and fluorouracil in positive-node breast cancer patients with tamoxifen-nonresponsive tumors: Results from the National Surgical Adjuvant Breast and Bowel Project B-15. J Clin Oncol. 1990;8(9):1483-96.
4. Crawford J, Dale DC, Lyman GH. Chemotherapy-induced neutropenia: Risks, consequences, and new directions for its management. Cancer. 2004;100(2):228-37.
5. 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(10):2258-66.
6. Lyman GH, Michels SL, Reynolds MW, Barron R, Tomic KS, Yu J. Risk of mortality in patients with cancer who experience febrile neutropenia. Cancer. 2010;116(23):5555-63.
7. Chirivella I, Bermejo B, Insa A, Perez-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(3):479-84.
8. Dale DC, McCarter GC, Crawford J, Lyman GH. Myelotoxicity and dose intensity of chemotherapy: Reporting practices from randomized clinical trials. J Natl Compr Canc Netw. 2003;1(3):440-54.
9. Network NCC.
10. Schwartz J, Domchek SM, Hwang WT, Fox K. Evaluation of anemia, neutropenia and skin toxicities in standard or dose-dense doxorubicin/cyclophosphamide (AC) - paclitaxel or docetaxel adjuvant chemotherapy in breast cancer. Ann Oncol. 2005;16(2):247-52.
11. (NCCN) NCCN. NCCN clinical practice Guidelines in Oncology 2019 (Hematopoietic Growth Factors).
12. 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(19):3187-205.
13. Kim CG, Sohn J, Chon H, Kim JH, Heo SJ, Cho H, et al. Incidence of Febrile neutropenia in Korean female breast cancer patients receiving preoperative or postoperative doxorubicin/cyclophosphamide followed by docetaxel chemotherapy. J Breast Cancer. 2016;19(1):76-82.
14. Kim HS, Lee SY, Kim JW, Choi YJ, Park IH, Lee KS, et al. Incidence and predictors of febrile neutropenia among early-stage breast cancer patients receiving anthracycline-based chemotherapy in Korea. Oncology. 2016;91(5):274-82.
15. Perkins NJ, Schisterman EF. The Youden Index and the optimal cut-point corrected for measurement error. Biom J. 2005;47(4):428-41.
16. Klastersky J, Paesmans M, Rubenstein EB, Boyer M, Elting L, Feld R, et al. The multinational association for supportive care in cancer risk index: A multinational scoring system for identifying low-risk febrile neutropenic cancer patients. J Clin Oncol. 2000;18(16):3038-51.
17. Lyman GH, Abella E, Pettengell R. Risk factors for febrile neutropenia among patients with cancer receiving chemotherapy: A systematic review. Crit Rev Oncol Hematol. 2014;90(3):190-9.
18. Moreau M, Klastersky J, Schwarzbold A, Muanza F, Georgala A, Aoun M, et al. A general chemotherapy myelotoxicity score to predict febrile neutropenia in hematological malignancies. Ann Oncol. 2009;20(3):513-9.
19. Scott SD, Chrischilles EA, Link BK, Delgado DJ, Fridman M, Stolshek BS. Days of prophylactic filgrastim use to reduce febrile neutropenia in patients with non-Hodgkin's lymphoma treated with chemotherapy. J Manag Care Pharm. 2003;9(2 Suppl):15-21.
20. Chan A, Chen C, Chiang J, Tan SH, Ng R. Incidence of febrile neutropenia among early-stage breast cancer patients receiving anthracycline-based chemotherapy. Supportive Care Cancer. 2012;20(7):1525-32.
21. Chow LWC, Biganzoli L, Leo AD, Kuroi K, Han HS, Patel J, et al. Toxicity profile differences of adjuvant docetaxel/cyclophosphamide (TC) between Asian and Caucasian breast cancer patients. Asia Pac J Clin Oncol. 2017;13(6):372-8.

22. Han HS, Reis IM, Zhao W, Kuroi K, Toi M, Suzuki E, et al. Racial differences in acute toxicities of neoadjuvant or adjuvant chemotherapy in patients with early-stage breast cancer. Eur J Cancer. 2011;47(17):2537-45.