Factors Associated with Absolute Neutrophil Count Dynamics and Docetaxel-Adryamicin-Cyclophosphamide (TAC) Chemotherapy Induced Neutropenia During Extended Filgrastim Administration in Breast Cancer Patients

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ABSTRACT

Background: *Myelosuppressive effects of chemotherapy for breast cancer treatment may trigger chemotherapy-induced neutropenia (CIN) and febrile neutropenia (FN). Filgrastim has been widely used as prophylaxis against CIN and FN. However despite filgrastim administration, some study showed FN still occur and cause patient vulnerability to infection. This study aims to evaluate factors associated with Absolute Neutrophil Count (ANC) dynamics and Docetaxel-Adryamicin-Cyclophosphamide (TAC) CIN during extended filgrastim administration in breast cancer patients.* ***Methods:*** *Patients were selected among breast cancer in-patients who fulfilled the eligibility criteria. Patient characteristics data and ANC were collected. The entire patients received 5µg/kg/day filgrastim by subcutaneous injection 24 hours post-chemotherapy. ANC was monitored daily and filgrastim administration was stopped when ANC reached >10000/mm^3 or 14 days of administration. Kruskall-Wallis test and Spearman Correlation test was performed to analyze ANC dynamics and CIN-related factors.* ***Results:*** *This study included 42 breast cancer patients. Patient age median was 52 (31-70) years old. ANC nadir could be observed around 5-7 days after chemotherapy and FN occurred in two out of 38 grade 4 neutropenia patients (4.8%). Critical ANC lasted for 1 day, 2 days, and 3 days respectively in 9 (23.7%), 25 (65.8%) and 4 (10.5%) patients. There was no correlation between neutropenia and age. ANC slope and recovery duration did not show a significant difference. However, depth of nadir is inversely correlated with the duration of ANC recovery (>10000/mm^3) and the duration during the peak on the 2nd day until reaching nadir both with fair strength, $r = -0.489$ and $r = -0.438$ ($p < 0.05$), respectively. No sepsis incidence had manifested.* ***Conclusion:*** *CIN still occurred in breast cancer patient receiving filgrastim primary prophylaxis regardless of age and neutropenia severity. Nadir as the lowest point of ANC should be noted as a pivotal milestone for ANC slope and recovery evaluation.*

Keywords**:** *breast cancer, cancer, TAC chemotherapy, febrile neutropenia, filgrastim.*

INTRODUCTION

Breast cancer is one of the most prevalent cancers in women that have caught the attention of clinicians and researchers worldwide.[1] Chemotherapy remains an important part of the standard cancer treatment, aside from surgery and radiotherapy.[2] Chemotherapy generally acts by inducing the death and mitosis arrest of malignant cells[3]; however, it causes significant adverse effects that continue to be a point of concern in clinical settings. These adverse effects of chemotherapy hinder multiple components of cancer management that include affecting the patients' motivation to undergo chemotherapy. Chemotherapy-induced neutropenia (CIN) is one of the critical hematological adverse effects that contribute greatly to the morbidity and mortality of patients.[4]

CIN is defined as a decline of neutrophils in the blood circulation due to administration of myelosuppressive chemotherapeutic agents.[5] Docetaxel, doxorubicin, and cyclophosphamide (TAC) combination chemotherapy for breast cancer is one such myelosuppressive regimen, which results in 22%–25% CIN occurrence.[4] CIN incidence steadily increases the infection risk and treatment delay in patients with cancer.[6] Granulocyte colony-stimulating factor (G-CSF) or filgrastim is an available growth factor medicament applied to stimulate myeloid granulocyte proliferation.[7] The prophylactic use of filgrastim potentially reduces the risk of CIN, and thus, its complications, including sepsis.[7] However, despite prophylaxis, CIN and febrile neutropenia (FN) still occur,[8–10] leaving patients vulnerable to infections. The degree of infection risk is a considerable matter of concern in patient management, particularly in tropical countries like Indonesia.[11]

Filgrastim administration has been proven to improve neutropenia especially in patients receiving high-risk myelosuppressive chemotherapy. In previous study of patients with breast cancer in Indonesia that received TAC chemotherapy suggested that even with filgrastim administration, FN still occurred in 12 out of 61 patients.[8] Another study of malignant lymphoma patients who received cyclophosphamide, cytarabine, etoposide and dexamethasone ± rituximab (CHASE(R)) also showed 30 out of 54 patients still suffered from FN despite the administration of filgrastim.[12] Various optimization of filgrastim administration could be adjusted in several aspects including dose, administration timing, duration, and absolute neutrophil count (ANC) target for improving CIN and FN outcomes in terms of complication, morbidity, mortality, length of stay, and medical expenses.[4] Extended filgrastim administration combined with a higher ANC target recovery modification could potentially improve the outcome of therapy.

The guidelines of filgrastim administration differ for the administration length and the indication to start its administration.[6,7,13] This study aims to assess ANC dynamics and CIN-related factors during extended filgrastim administration on breast cancer patients receiving the TAC regimen chemotherapy to pinpoint important parameters that correlates with ANC recovery aiming for a better monitoring during patient care.

METHODS

This study was a cross-sectional study of extended filgrastim administration during first cycle of TAC chemotherapy receiving breast cancer patients.

Patients

The study has been approved by the Ethical Committee in Health Research, Dr. Soetomo General Hospital Surabaya, as stated on the ethical clearance document no. 107/Panke. KKE/II/2017. The patients for this study were selected from the inpatients undergoing TAC chemotherapy regimens for breast cancer, admitted from February 2017 to December 2018 in Dr. Soetomo Teaching Hospital, Surabaya, Indonesia. The inclusion criteria of the patients were as follows: female, diagnosed with breast cancer, and older than 18 years. This study did not include patients with any record of previous chemotherapy or patients diagnosed with malignancies other than breast cancer. Patients with neutropenia before chemotherapy administration were also excluded.

Minimum sample count was determined based on sample size formula for correlation test[14] $N = \{(Z_\alpha+Z_\beta)/ 0.5 \times \ln [(1 + r)/(1 – r)]\}2 + 3$, where N is the minimum sample size, Z_α is the standard normal deviate for α (0.05), Z_β is the standard normal deviate for β (0.2), and r is the expected correlation coefficient (0.5). The minimum sample required from the calculation was 29. A total of 42 patients were included in this study. Before enrollment, all the patients had given their informed consent. All the patients were treated in a non-sterile room in Graha Amerta, Dr. Soetomo Teaching Hospital, Surabaya, Jawa Timur, Indonesia. All the patients received the taxane (docetaxel 75 mg/m^2), Adriamycin (doxorubicin 50 mg/m^2 IV), and cyclophosphamide (500 mg/m^2) combination chemotherapy regimen on day zero in the 1st cycle. Filgrastim (5 μg/kg) was administered daily by a single subcutaneous injection, starting from the first 24 hours after chemotherapy (day one) and repeated with intervals of exactly 24 hours until the last dose. During the study, ANC was monitored and recorded each day at exactly 24-hour intervals together with filgrastim administration, patient related data was extracted through anamnesis and medical record, and the patients were monitored daily for incidence of sepsis using the quick sepsis-related organ failure assessment (qSOFA) score as assessment of infections related to depleted ANC condition. Nadir ANC is defined as the lowest ANC value during monitoring, whereas critical ANC is defined as ANC ≤500/mm^3. Filgrastim administration was continued for 14 days or until ANC reached more than 10000/mm^3, and the number of days of filgrastim administration was recorded.

Statistical Analysis

ANC evaluation statistical analysis was performed by assessing total duration of ANC recovery (ANC ≥10000/mm^3) among the entire subject post-TAC chemotherapy and filgrastim administration through Kruskall-Wallis test for analyzing similarity of ANC recovery duration during filgrastim administration. Further correlation analysis among ANC slope (duration from 2nd day ANC peak until reaching nadir), ANC recovery (duration from nadir until reaching ANC ≥10000/mm^3), and depth of nadir was performed through pairwise spearman correlation analysis.

ANC parameter analysis towards age was performed by analyze highest grade of neutropenia, critical ANC duration, and ANC recovery through pairwise spearman correlation analysis.

RESULTS

This study included a population of 42 patients with breast cancer. The age of the patients varies between 31 and 70 years, with a mean age of 50.8 ± 9.8 years. The number of patients with stage II, III, and IV breast cancer included in this study were 15 (35.7%), 24 (57.1%), and 3 (7.1%), respectively. Four (9.5%) geriatric patients were included in this study (**Table 1**). No bone pain complaint was observed during filgrastim administration.

Table 1. Patient baseline characteristic.

	n	%
Age (years)	52 (41.2 – 57.5)	
Geriatric status		
Non-geriatric (<60 years old)	33	78.6
Geriatric (≥60 years old)	9	21.4
Breast cancer staging		
II	15	35.7
III	24	57.1
IV	3	7.1
Grade of Neutropenia		
Grade 0 (no neutropenia)	1	2.4
Grade 1	0	0
Grade 2	0	0
Grade 3	3	7.14
Grade 4 (critical ANC, <500/mm^3)	38	90.5
Incidence of Febrile Neutropenia		
Non febrile neutropenia	40	95.2
Febrile Neutropenia	2	4.8
Duration of ANC reaching >10000/mm^3 from the start of filgrastim administration (days)		
Mean	9.57±0.70	
Median (min-max)	10 (8-11)	
Days		
8	2	4.8
9	17	40.5
10	20	47.6
11	3	7.14%

Slope Duration from Peak (Day 2) Until Nadir		
Mean	4.3±0.5	
Median (min-max)	4 (3-5)	
Days		
3	1	2.4
4	27	64.3
5	14	33.3
Mean	6.3±0.5	
Median (min-max)	6 (5-7)	
Days		
5	1	2.4
6	27	64.3
7	14	33.3
Critical ANC (<500/mm^3) duration (days) (n = 38)		
Mean	1.9±0.6	
Median (min-max)	2 (1-3)	
Days		
1	9	23.7
2	25	65.8
3	4	10.5
Duration from Nadir Until ANC>10000/mm^3 (days) (n=42)		
Mean	3.3±0.8	
Median (min-max)	3 (1-5)	
Days		
1	1	2.4
2	5	11.9
3	19	45.2
4	16	38.1
5	1	2.4

All the participants were patients with stage II (15/42), III (24/42), and IV (3/42) breast cancer under the care of Hematology-Medical Oncology Department of Internal Medicine, Dr. Soetomo General Teaching Hospital, Surabaya, Indonesia who received TAC chemotherapy. The age of the patients varied between 31 and 70 years. The mean age was 50.8 ± 9.8 years, hence the results of this study are limited to middle-aged and geriatric patients without the representation of stage I breast cancer.

Neutropenia Grading and Febrile Neutropenia Incidence

Out of the 42 patients, 41 (97.6%) patients had neutropenia. Two incidences of FN occurred during filgrastim administration in patients with grade IV neutropenia. A difference in the duration of FN between the two patients was observed; the patient with a lower nadir (70/mm^3) experienced two days of FN, whereas the other patient with 150/mm^3 nadir recovered immediately. Both patients with FN eventually stabilized and their ANC recovered to more than 10000/mm^3.

ANC Evaluation

The evaluation of ANC in this study suggested a requirement for a similar duration of filgrastim administration to reach 10000/mm^3 of ANC with a similar response to filgrastim (p = 0.968). The duration of the critical ANC (<500/mm^3) or stage IV neutropenia detected in this study ranged between 1 and 3 days with an average of 1.9 ± 0.6 days and a median of two days. A patient with 2770/mm^3 ANC nadir point was the highest among the participants.

Based on this study, the evaluation of ANC slope and recovery duration did not show a significant difference. However, we discovered that the depth of nadir is inversely correlated with ANC recovery duration and ANC slope duration both with fair strength, r = −0.489 and r = −0.438 (p <0.05), respectively. Based on this result, it is suggested that nadir as the lowest point of ANC should be noted as a pivotal milestone for ANC slope and recovery evaluation as the correlation suggests in patient with lower ANC nadir could prolong both ANC slope and recovery which eventually resulting in longer duration of filgrastim administration.

Assessment of ANC Parameter Correlation to Age

The correlation analysis of highest grade of neutropenia - age (p = 0.274); critical ANC duration - age (p = 0.126), and ANC recovery duration – age (p = 0.608) did not show any significant result. These results suggest that age was not correlated with neutropenia severity and ANC recovery, which implicate that filgrastim administration in breast cancer patient receiving TAC chemotherapy still provide a comparable recovery regardless of age.

DISCUSSION

This study evaluated the implementation of extended filgrastim administration based on a higher target of ANC 10000/mm^3 as compared to recommendations of target ANC that vary between post nadir[13] and 2000–3000/mm^3.[15] The duration of treatment to reach >10000/mm^3 ANC in this study was 8–11 days, with an average of 9.6±0.7 days. The majority of the patients (41/42) in this study suffered from CIN; however,

FN only occurred in two (4.8%) patients with zero incidence of sepsis. A previous study also reported 9.8 ± 0.8 days of administration with a target ANC of 5000/mm^3, that showed a faster ANC recovery in this study population even with higher ANC target compared to previously reported study.[10] This difference might be caused by distinct responses of the population toward the myelosuppressive effect of filgrastim or chemotherapy, which is yet to be explained.[10] Further studies regarding the pharmacogenomics or epigenetics of the involved drugs should also be conducted. Nonetheless, it may be preferable to achieve a higher ANC target in a shorter duration to obtain better protection against infections.[16]

The critical ANC duration in this study lasted for an average of 1.9 ± 0.6 days, with a median of two days. A similar study in Korea within breast cancer patients receiving TAC chemotherapy showed an average critical ANC duration of 2.48 ± 1.03 days in patients receiving TAC and daily filgrastim administration.[10] During the duration of critical ANC, patients are vulnerable to FN and infections,[16] and thus, achieving a shorter duration of critical ANC is favored. A multi-center study in Canada showed that a 5-day filgrastim administration was not inferior to 7 and 10-days administration in terms of preventing FN.[17] Investigation of the correlation between filgrastim administration and critical ANC duration requires further study, especially in similar settings as the dynamics of ANC during chemotherapy and filgrastim administration was not evaluated in prior study and therefore this study could provide a better understanding of ANC slope and recovery to fill the gap of previous study limitation. However, limitation of this study lies in the absence of control group with ANC target of ≥ 5000/mm3 with comparison to previously reported study.

Beside the clinically overt adverse effects, the myelosuppressive effects of chemotherapy could lead to the occurrence of CIN.[18] CIN condition further prompts the occurrence of FN and sepsis. These unfavorable events worsen the overall prognosis of patients with breast cancer. The novel approach of filgrastim administration could potentially minimize the mortality and morbidity caused by the myelosuppressive effects of chemotherapy.[19] The TAC chemotherapy regimen has been classified as high-risk for inducing FN.[20] A study involving 61 patients receiving the TAC chemotherapy regimen along with pegfilgrastim prophylaxis also reported CIN incidence within the participants at least during one cycle.[9] An Indonesian study also reported neutropenia occurring in 98% of patients receiving the TAC chemotherapy along with filgrastim administration.[8] This result confirmed and emphasized that the TAC chemotherapy regimen has a high risk of inducing CIN, even when combined with filgrastim administration.

The nadir was observed 5–7 days post chemotherapy and commonly seen on the 6th day (**Figure 1**), demonstrating an earlier nadir than a previous study, which suggested the 7th day as the most common day for nadir.[9] The nadir ANC median was 155/mm^3 with a similarity across all the patients (p >0.05). On a closer look, the patient with a high outlier nadir ANC (2770/mm^3) presented with asthma as a co-morbidity. The lung tissues of patients with asthma are known to produce a higher level of G-CSF, and thus, they have a higher G-CSF level in their circulation.[21] This effect was shown to be able to ameliorate the myelosuppressive effect of chemotherapy and protect the patient from neutropenia. However, besides its benefits, this observation also suggests that filgrastim administration could trigger asthma exacerbation, which is an important point for clinical practice.

The result of this study revealed a similar change in ANC among patients, commencing with an increasing ANC, which consistently reached its peak after two days following chemotherapy. After reaching its peak on the 2nd day post chemotherapy, ANC then decreased until it reached the lowest point of ANC or the nadir point, which can be observed around 5–7 days post chemotherapy. The nadir point should be the primary focus of the clinician when giving care to patients receiving myelosuppressive chemotherapy, without overlooking the tendency of critical ANC alongside the nadir point as it could lead to FN or dire infection including sepsis. Moreover, this study revealed that the critical ANC duration lasted for 1 day in 9 patients (23.7%), 2 days in 25 patients (65.8%),

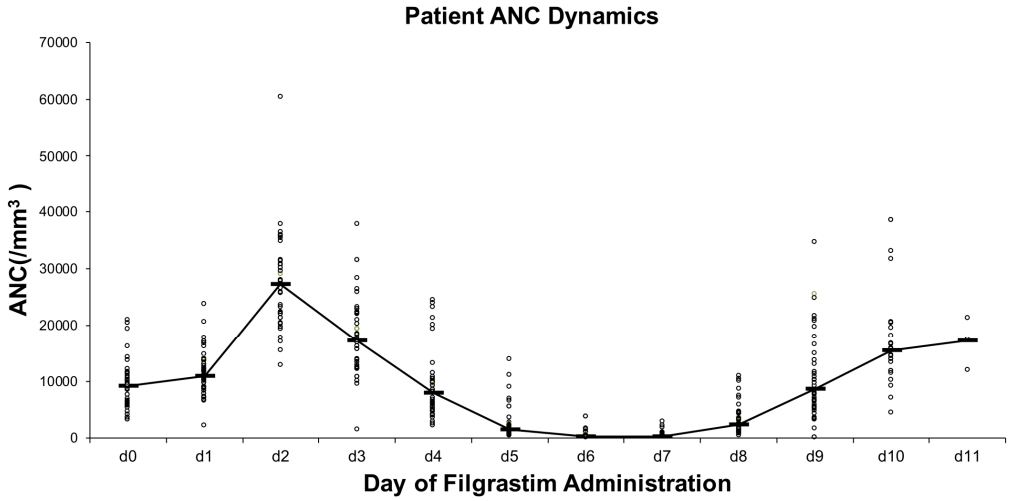

Figure 1. Curve of patients ANC during filgrastim administration. ANC: absolute neutrophil count; d0 = chemotherapy administration; d1: day 1 of filgrastim administration.

and 3 days in 4 patients (10.5%).

All the patients were treated in a non-sterile room and there were zero incidences of sepsis. The maintenance of the immune system, including ANC control, in patients undergoing chemotherapy is critical in preventing infection, especially in a tropical country like Indonesia. The target ANC recommended from various guidelines as an indication to stop filgrastim administration varies between post nadir and 2000–3000/mm^3.[13,15] However, to the best of our knowledge, the available guidelines were not generated based on studies conducted in Indonesia. This study used 10000/mm^3 as ANC for prevention of infections. Further study is required to compare target ANC values for prevention of FN and infections as well as for survival and therapeutic response in the same settings.

The nadir depth (ANC during nadir) was inversely correlated with the duration of ANC recovery to >10000/mm^3 with fair strength (r = −0.489, p <0.05). Also, the duration of ANC slope from the ANC peak in the 2nd day until reaching nadir is inversely correlated with ANC recovery duration with fair strength (r = −0.438, p <0.05). This finding suggested that the depth of nadir and the duration to reaching nadir from the 2nd day can be used to predict ANC recovery and help clinicians monitor patients with a tendency of longer ANC recovery.

Out of the 42 patients, there were two incidences of FN in patients with grade IV neutropenia. FN lasted for 1–2 days and immediately recovered, reaching >10000/mm^3 ANC. Patients with lower ANC exhibited a longer duration of FN (two days), which further emphasized the importance of monitoring patients with low ANC.

Clinical Applicability

Clinical applicability of this study suggests that the time-point of ANC nadir post-chemothrapy during filgrastim administration could be measured during 5-7 days post-chemothrapy that could predict ANC recovery duration. Furthermore, measurement of 2nd day and nadir duration could also predict ANC recovery duration. With a more caution focused on patient with a faster ANC slope and lower nadir.

Extrapolation of the Results to Target Population

This study was performed in Dr. Soetomo Teaching Hospital in Surabaya, Jawa Timur, Indonesia as representation of the ethnicity. Therefore, this study might provide a data from population that could be comparable to Indonesia national settings compared to prior study in different ethnicity background.

Suggestion for Further Research

Based on this study in a limited sampling-frame, it is suggested that multi-center study in Indonesia could be performed to further confirm these findings and additional control group could further explain benefit of proposed extended filgrastim administration together with modified ANC target.

CONCLUSION

Extended filgrastim administration after TAC chemotherapy could ameliorate FN incidence and minimize its duration. However, CIN still occurs in breast cancer patient receiving filgrastim primary prophylaxis regardless of age and neutropenia severity. Nadir as the lowest point of ANC should be noted as a pivotal milestone for ANC slope and recovery evaluation

CONFLICT OF INTEREST

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REFERENCES

1. Bray F, Ferlay J, Soerjomataram I, et al. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin. 2018;68:394–424.
2. Gerber B, Freund M, Reimer T. Recurrent breast cancer: treatment strategies for maintaining and prolonging good quality of life. Deutsches Ärzteblatt International. 2010;107(6):85–91.
3. Abdullah LN, Chow EK-H. Mechanisms of chemoresistance in cancer stem cells. Clin Transl Med. 2013;2(1):3.
4. Aapro M, Crawford J, Kamioner D. Prophylaxis of chemotherapy-induced febrile neutropenia with granulocyte colony-stimulating factors: Where are we now? Support Care Cancer. 2010;18(5):529–41.
5. Trotti A, Colevas A, Setser A, et al. Development of a comprehensive grading system for the adverse effects of cancer treatment. Semin Radiat Oncol. 2003;13(3):176–81.
6. Crawford J, Dale DC, Lyman GH. Chemotherapy-induced neutropenia: Risks, consequences, and new directions for its management. Cancer. 2004;100(2):228–37.
7. Ludwig H, Bokemeyer C, Aapro M, et al. Chemotherapy-induced neutropenia/febrile neutropenia prophylaxis with biosimilar filgrastim in solid tumors versus hematological malignancies: MONITOR-GCSF study. Futur Oncol. 2019;15(8):897–907.
8. Hima NA, Andrajati R, Radji M. Kejadian demam neutropenia pada pasien kanker payudara setelah menerima regimen kemoterapi TAC-G-CSF dan FAC di RSUP Dr. Hasan Sadikin Bandung . Indones J Clin Pharm. 2021;10(1):1.
9. Lee J, Lee JE, Kim Z, et al. Pegfilgrastim for primary prophylaxis of febrile neutropenia in breast cancer patients undergoing TAC chemotherapy. Ann Surg Treat Res. 2018;94(5):223–8.
10. Park KH, Lee S, Park JH, et al. A randomized, multi-center, open-label, phase III study of once-per-cycle DA-3031, a pegylated G-CSF, in comparison with daily filgrastim in patients receiving TAC chemotherapy for breast cancer. Support Care Cancer. 2013;25(2):505–11.
11. Coker RJ, Hunter BM, Rudge JW, et al. Emerging infectious diseases in southeast Asia: regional challenges to control. Lancet. 2011;377(9765):599–609.
12. Kubo K, Miyazaki Y, Murayama T, et al. A randomized, double-blind trial of pegfilgrastim versus filgrastim for the management of neutropenia during CHASE(R) chemotherapy for malignant lymphoma. Br J Haematol. 2016;174:563–70.
13. Klastersky J, de Naurois J, Rolston K, et al. Management of febrile neutropaenia: ESMO clinical practice guidelines. Ann Oncol. 2016;27:v111–v118.
14. Hulley SB, Cummings SR, Browner WS, Grady DG, Newman TB. Designing clinical research. Fourth edition. Philadelphia: Lippincot Williams & Wilkins, a Wolters Kluwer business; 2013. p. 79.
15. Smith TJ, Bohlke K, Lyman GH, et al. Recommendations for the use of WBC growth factors: American society of clinical oncology clinical practice guideline update. J Clin Oncol. 2015;33(28):3199–212.
16. Newburger PE, Dale DC. Evaluation and management of patients with isolated neutropenia. Semin Hematol. 2013;50(3):198–206.
17. Clemons M, Fergusson D, Simos D, et al. A multicentre, randomised trial comparing schedules of G-CSF (filgrastim) administration for primary prophylaxis

of chemotherapy-induced febrile neutropenia in early stage breast cancer. Ann Oncol. 2020;31(7):951–7.
18. Jagarlamudi K, Ahluwalia M, Patel J, et al. A single dose filgastrim in the treatment of chemotherapy induced neutropenia. Blood. 2010;116(21):4774.
19. Heuser M, Ganser A, Bokemeyer C. Use of colony-stimulating factors for chemotherapy-associated neutropenia: Review of current guidelines. Semin Hematol. 2007;44(3):148–56.
20. Cortés de Miguel S, Calleja-Hernández MÁ, Menjón-Beltrán S, et al. Granulocyte colony-stimulating factors as prophylaxis against febrile neutropenia. Support Care Cancer. 2015;23(2):547–59.
21. Kim YM, Kim H, Lee S, et al. Airway G-CSF identifies neutrophilic inflammation and contributes to asthma progression. Eur Respir J. 2020;55(2):1900827.