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Maximum daily dose of G-CSF is critical for preventing recurrence of febrile neutropenia in patients with gynecologic cancer

A case–control study

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Abstract

No study has evaluated the effect of therapeutic granulocyte colony-stimulating factor (G-CSF) in preventing recurrence of febrile neutropenia (FN) and survival outcomes in gynecologic cancer patients. Objective of this study is to optimize and to identify the use of G-CSF and identify the critical factors for preventing the recurrence of FN in women undergoing chemotherapy for the treatment of gynecologic cancer.

The medical records of consecutive patients who underwent chemotherapy for the treatment of gynecologic cancer and experienced FN at least once were retrospectively reviewed. Clinico-laboratory variables were compared between those with and without recurrence of FN to identify risk factors for the recurrence and the most optimal usage of G-CSF that can prevent FN. Student *t* test, χ^2 test, and multivariate Cox regression analysis were used.

A total of 157 patients who met the inclusion criteria were included. Of 157, 49 (31.2%) experienced recurrence of FN. Age ≥55 years (P = .043), previous lines of chemotherapy ≤1 (P = .002), thrombocytopenia (P = .025), total dose (P = .003), and maximum daily dose (P = .009) of G-CSF were significantly associated with recurrence of FN. Multiple regression analysis showed that age ≥55 years (HR, 2.42; 95% CI, 1.14–5.14; P = .022), previous chemotherapy ≤1 (HR, 4.01; 95% CI, 1.40–11.55; P = .010), and maximum daily dose of G-CSF ≤600 μg (HR, 5.18; 95% CI, 1.12–24.02; P = .036) were independent risk factors for recurrent FN. Multivariate Cox regression analysis showed that a maximum daily dose of G-CSF ≤600 μg was the only independent risk factor for short recurrence-free survival of FN (HR, 4.75; 95% CI, 1.15–19.56; P = .031).

Dose-dense administration of G-CSF >600 μg/day could prevent recurrence of FN in women who undergo chemotherapy for the treatment of gynecologic cancer and FN. Old age and FN at early lines of chemotherapy seem to be associated with FN recurrence.

Abbreviations: ANC = absolute neutrophil count, FN = febrile neutropenia, G-CSF = granulocyte colony-stimulating factor, GM-CSF = granulocyte-macrophage colony-stimulating factor, MGF = myeloid growth factor.

Keywords: chemotherapy, febrile neutropenia, granulocyte colony-stimulating factor, gynecologic cancer

1. Introduction

Febrile neutropenia (FN) is one of the potentially life-threatening complications of chemotherapy in cancer treatment. FN is defined as fever with a single temperature >38.3°C orally or a temperature >38.0°C over 1 hour, accompanied by neutropenia with an absolute neutrophil count (ANC) of <500/μL or a predicted decline to <500/μL within the next 48 hours.[1] The incidence of chemotherapy-induced FN varies from 2% to 50% in solid tumors depending on patient-related risk factors, type of neoplasm, chemotherapy regimen, and genetic susceptibility. The frequency of FN is approximately 7% to 12% in patients with gynecologic cancer.[2,3] The incidence of septic shock in patients with chemotherapy-induced FN is 25% to 30%, and the mortality rate associated with FN is reported to be 10% to 21%.[4] FN may affect subsequent chemotherapy by delay or dose reduction, leading to a potentially compromised survival.[5]

Myeloid growth factors (MGFs), which promote neutrophil proliferation and maturation, are used for the prophylactic or therapeutic purposes of myelosuppressive chemotherapy-induced FN. MGFs are divided into granulocyte colony-stimulating factor (G-CSF) and granulocyte-macrophage colony-stimulating factor (GM-CSF) according to the promotion of blood cells.[6]

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The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

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Most previous studies on MGFs have focused on FN prophylaxis. Studies have demonstrated that the use of prophylactic MGF is effective in preventing FN, reducing infection-related mortality, and enabling full dose-intensity chemotherapy without dose reduction.[7,8]

There are relatively few studies on therapeutic G-CSF in patients with chemotherapy-induced FN. Most clinical studies on therapeutic G-CSF were conducted between the 1990s and the early 2000s, and the studies had a small study population and a low rate of clinical events such as death. In addition, studies have shown conflicting results regarding mortality or recovery outcomes from FN.[9–12] These findings may be underpowered to determine the routine use of G-CSF in patients with chemotherapy-induced FN. Despite the low level of evidence, systematic review or meta-analysis studies of small-sized randomized controlled trials showed that therapeutic use of G-CSF in FN patients did not significantly change mortality but reduced the duration of hospital stay and recovery time from neutropenia or fever.[13–15] Based on the study results, the National Comprehensive Cancer Network (NCCN) does not recommend the routine use of therapeutic G-CSF for patients with FN. Therapeutic use of G-CSF is recommended only in patients who have not received prophylactic G-CSF and are at a high risk of infection. However, the optimal usage of therapeutic G-CSF, including dosage, duration, and ANC target, is not specified in the guideline.[1] No study has evaluated the effect of therapeutic G-CSF in preventing recurrence of FN and survival outcomes in gynecologic cancer patients.

We aimed to identify the optimal usage of therapeutic G-CSF and to identify critical factors associated with the recurrence of FN in women undergoing chemotherapy for the treatment of gynecologic cancer.

2. Methods

Consecutive patients who underwent chemotherapy for the treatment of gynecologic cancer and experienced FN at least once at the Seoul National University Bundang Hospital (SNUBH) between April 2003 and March 2021 were gathered. Medical records were retrospectively reviewed. The inclusion criteria were as follows:

1. Patients diagnosed with cervical, uterine corpus, and ovarian cancer (including tubal cancer and primary peritoneal cancer);
2. Patients receiving chemotherapy including concurrent chemoradiation therapy (CCRT) for the treatment of gynecologic cancer.

Patients who experienced the first episode of FN after chemotherapy at the other hospitals were excluded from the study population. FN was defined as a fever >38.0°C and grade 4 neutropenia with ANC <500/μL. Patients with a history of cancer diagnosis other than gynecologic cancer or chemotherapy at other hospitals were excluded. The Institutional Review Board of SNUBH approved this study (B-2111-721-104). Informed consent from the patients was waived as this was a study based on retrospective medical chart review.

Clinical characteristics including age at initial FN, cancer type, number of previous chemotherapy lines, regimen of chemotherapy, use of prophylactic G-CSF before initial FN, septic shock, and bacteremia at initial FN were collected. Additionally, laboratory data on ANC at diagnosis of FN and after recovery from FN, hemoglobin, and platelet level at initial FN were collected. Data on the use of G-CSF, including dose and duration during initial FN and subsequent recurrence of FN in all patients, were retrospectively reviewed. Recurrence-free survival (RFS) was defined as the period between the initial FN and the first recurrence of FN. Progression-free survival (PFS) was defined as the time from initial FN to disease progression based on the Response Evaluation Criteria in Solid Tumors criteria for imaging evaluation or death of any cause. Overall survival (OS) was defined as the period between initial FN and death.

Student t test, χ^2 test, and regression analyses were used to compare clinicopathologic characteristics between groups of recurrence of FN (+) and (–). Cox regression analysis was used to determine the association of the clinico-laboratory characteristics, including various usages of G-CSF with RFS of FN. Statistical analysis was performed using IBM SPSS Statistics for Windows (version 25.0; IBM Corp., Armonk, NY). Statistical significance was set at a P value of $< .05$.

3. Results

A total of 157 patients who met the inclusion criteria were enrolled in the study. Forty-nine patients (31.2%) experienced FN recurrence. Baseline characteristics of the study population are shown in Table 1.

The mean age at the time of initial FN was 54.9 ± 14.1 years. In terms of cancer types of the patients, the most common cancer was ovary, tubal, and primary peritoneal cancer (n = 77, 49.0%), followed by corpus (n = 44, 28.0%) and cervix (n = 34, 21.7%). Sixty-four patients (40.8%) experienced grade 4 neutropenia without fever before the initial FN event. Eighty-three patients (52.9%) had the first episode of FN during first-line chemotherapy without a previous history of chemotherapy. Thirty-two (20.4%) patients had a previous history of chemotherapy with 1 line, and 42 (26.8%) had 2 or more lines of chemotherapy. Regarding the chemotherapy regimen used at the time of initial FN, 118 (75.2%) and 26 (16.6%) received combination and single-regimen chemotherapy, respectively.

Table 1

Baseline characteristics of the patients (n = 157).

	N (%)
Age at initial FN	54.9 ± 14.1
Cancer types	
Cervix	34 (21.7)
Ovary, tube, and primary peritoneum	77 (49.0)
Corpus	44 (28.0)
Unknown	1 (0.6)
Double primary (corpus and ovary)	1 (0.6)
Grade 4 neutropenia event before initial FN	64 (40.8)
Previous lines of chemotherapy	
0	83 (52.9)
1	32 (20.4)
≥2	42 (26.8)
Chemotherapy regimen	
Combination	118 (75.2)
Single	26 (16.6)
Combination + radiation	13 (8.3)
ANC at initial FN	174.6 ± 144.8
Grade 3 or 4 anemia at initial FN	38 (24.2)
Grade 3 or 4 thrombocytopenia at initial FN	48 (30.6)
Bacteremia at initial FN	27/143 (18.9)
Septic shock at initial FN	12 (7.6)
G-CSF usage at initial FN	
Total dose (μg)	1538.9 ± 1226.8
Max. daily dose (μg)	482.5 ± 258.3
Duration (d)	3.8 ± 2.4
Type of G-CSF*	
Filgrastim	138 (87.9)
Lenograstim	16 (10.2)
Both (filgrastim, lenograstim)	2 (1.3)
Recurrence of FN	49 (31.2)

Values are presented as mean ± standard deviation or number (%).

ANC = absolute neutrophil count, FN = febrile neutropenia, G-CSF = granulocyte colony-stimulating factor.

*One patient who did not receive G-CSF was excluded in the category of type of G-CSF.

Table 2

Clinical and laboratory factors according to recurrence of febrile neutropenia.

	Recurrence of FN (–) (n = 108)	Recurrence of FN (+) (n = 49)	*P*
Age at initial FN ≥55 (yr)	54 (50.0)	33 (67.3)	.043*
Previous line of chemotherapy			.002*
≤1	71 (65.7)	44 (89.8)	
≥2	37 (34.3)	5 (10.2)	
Concurrent chemoradiation	8 (7.4)	5 (10.2)	.556
Prophylactic G-CSF before initial FN	35 (32.4)	12 (24.5)	.316
Blood count at initial FN			
ANC (per μL)	177.5 ± 145.9	168.3 ± 143.5	.713
Anemia ≥ Grade 3	24 (22.2)	14 (28.6)	.389
Thrombocytopenia ≥ Grade 3	39 (36.1)	9 (18.4)	.025*
Complication at initial FN			
Septic shock	9 (8.3)	3 (6.1)	.755
Bacteremia	21/98 (21.4)	6/45 (13.3)	.251
G-CSF usage at initial FN			
Total dose (μg)	1715.7 ± 1290.0	1149.0 ± 997.6	.003*
Duration (day)	4.0 ± 2.4	3.2 ± 2.3	.057
Maximum daily dose (μg)	515.7 ± 271.6	409.2 ± 210.8	.009*
≤600	87 (80.6)	47 (95.9)	.013*
>600	21 (19.4)	2 (4.1)	
Target ANC at (per μL)			
Day of last G-CSF dose	2756.7 ± 4012.6	3572.9 ± 5616.5	.373
Next day of last G-CSF dose	6749.1 ± 5826.5	7217.9 ± 8794.1	.720

Values are presented as mean ± standard deviation or number (%).
ANC = absolute neutrophile count, FN = febrile neutropenia, G-CSF = granulocyte colony-stimulating factor.
*Statistically significant.

Thirteen patients (8.3%) received radiotherapy with combination chemotherapy. The mean ANC level at diagnosis of initial FN was 174.6 ± 144.8/μL. Grade 3 or more anemia and thrombocytopenia at the initial FN event occurred in 38 (24.2%) and 48 women (30.6%), respectively. During the initial FN event, 27 (18.9%) patients had bacteremia and 12 (7.6%) had septic shock. Regarding the G-CSF type, most of the patients (n = 138, 87.9%) used filgrastim.

Clinical and laboratory characteristics were compared between the recurrence of FN (+) and (–) (Table 2). Age ≥55 years (P = .043), previous lines of chemotherapy ≤1 (P = .002), total dose (P = .003), and maximum daily dose (P = .009) of G-CSF were significantly associated with recurrence of FN. The frequency of grade 3 or 4 thrombocytopenia was significantly lower in the group with recurrence of FN. However, the use of prophylactic G-CSF prior to initial FN, ANC level at the time of initial FN, grade 3 or 4 anemia, septic shock during initial FN event, CCRT, ANC after administration of G-CSF, and total duration of G-CSF usage did not differ between the 2 groups.

The results of univariate and multivariate Cox regression analyses of risk factors for recurrence of FN are shown in Table 3. The cutoff values of total dose and maximum daily dose of G-CSF used during the initial FN period were 2000 and 600 μg, respectively. In the univariate analysis, age ≥55 years (HR, 2.03; 95% CI, 1.02–4.18; P = .045), previous lines of chemotherapy ≤1 (HR, 4.59; 1.68–12.55; P = .003), total dose of G-CSF <2000 μg (HR, 3.29; 95% CI, 1.28–8.48; P = .014), and maximum daily dose of G-CSF ≤600 μg (HR, 5.67; 95% CI 1.27–25.25; P = .023) were associated with recurrent FN. However, grade 3 or 4 thrombocytopenia was associated with a decreased risk of FN recurrence (HR, 0.40; 95% CI, 0.18–0.91; P = .028). Multivariate regression analysis showed that age ≥55 years (HR, 2.42; 95% CI, 1.14–5.14; P = .022), previous lines of chemotherapy ≤1 (HR, 4.01; 95% CI, 1.40–11.55; P = .010), and maximum daily dose of G-CSF ≤600 μg (HR, 5.18; 95% CI, 1.12–24.02; P = .036) were independent risk factors for recurrent FN.

In the multivariate Cox regression analysis, the maximum daily dose of G-CSF was the only independent risk factor for RFS after adjusting for other relevant factors in the univariate analysis (Table 4). A maximum daily dose of G-CSF ≤600 μg was significantly associated with the short RFS of FN, with an HR of 4.67 (95% CI, 1.13–19.26; P = .033). However, there were no significant differences in both PFS (P = .807) and OS (P = .699) between the maximum daily dose of G-CSF ≤600 and >600 μg, as shown in Figure 1.

Additional analysis was performed to investigate the association between the maximal target level of ANC and RFS of FN. There were no significant differences in the RFS of FN according to any cutoff levels (3000, 5000, and 10,000/μL) of the target ANC level of therapeutic G-CSF administration, as shown in Figure 2.

Table 5 shows that the side effects of G-CSF, such as bone pain, diarrhea, and thrombosis, were not different between the maximum daily dose of G-CSF ≤600 and >600 μg. For patients who had a first recurrence of FN, the recovery time from the first recurrence of FN, which was defined as the days from diagnosis of FN to ANC ≥1500/μL, was not different between the 2 groups (4.12 ± 2.26 vs 3.00 ± 2.83; P = .500). Serious complications, such as splenic rupture or acute myeloid leukemia (AML)/myelodysplastic syndrome (MDS), were not observed during the study period.

4. Discussion

The principal findings of this study were as follows:

1. Age >55 years and the number of previous chemotherapy lines <1 were significantly associated with the recurrence of FN;
2. A maximum daily G-CSF dose of 600 μg or less was an independent risk factor for FN recurrence and short RFS; and
3. There were no differences in the adverse effects such as bone pain, diarrhea, and deep vein thrombosis between patients receiving a maximum daily dose of G-CSF ≤600 and >600 μg.

The study population in the present study included patients who discontinued chemotherapy after initial FN either because they died after initial FN or FN occurred during the last chemotherapy schedule, and the cancer did not recur thereafter. Further analysis was performed on 129 patients who continued chemotherapy after the initial FN event. The maximum daily dose of G-CSF ≤600 μg was the only independent risk factor for recurrent FN and RFS of FN (HR, 5.88; 95% CI, 1.29–26.79; P = .022; HR, 4.95; 95% CI, 1.20–20.41; P = .027, respectively). These results were in agreement with those of the whole study population.

Old age; female sex; low BMI or BSA; preexisting active cardiovascular, renal, endocrine, or pulmonary comorbidities; low pretreatment lymphocyte or neutrophil count; and poor nutritional status have been demonstrated as patient-related risk factors for chemotherapy-induced FN.[16] In accordance with previous studies, age of 55 years or older increased the risk of recurrent FN in the current study. The results can be explained by a hypothesis that chemotherapy-induced adverse effects are mediated by mitochondrial damage and older patients are more susceptible to the cytotoxic chemotherapy due to aging-related mitochondrial dysfunction and oxidative stress.[17,18] Several researchers have reported that a history of previous chemotherapy was associated with a higher risk of FN. However, these studies only considered the presence or absence of previous chemotherapy and not the number of previous chemotherapy lines.[19,20] In our study, the number of previous chemotherapy lines was considered, and the results showed that the number of previous chemotherapy lines <1 was significantly associated with recurrence of FN compared with that of ≥2. It is suggested that the first experience of FN at

Table 3

Univariate and multivariate logistic regression analysis of risk factors for recurrence of febrile neutropenia.

		Univariate			Multivariate		
	N (%)	HR	95% CI	*P*	HR	95% CI	*P*
Age at initial FN (yr)							
<55	70 (44.6)	1			1		
≥55	87 (55.4)	2.03	1.02–4.18	.045*	2.42	1.14–5.14	.022*
Previous lines of chemotherapy							
>1	42 (26.8)	1			1		
≤1	115 (73.2)	4.59	1.68–12.55	.003*	4.01	1.40–11.55	.010*
Grade 3 or 4 thrombocytopenia							
No	109 (69.4)	1			1		
Yes	48 (30.6)	0.40	0.18–0.91	.028*	0.50	0.21–1.21	.126
Total dose of G-CSF (μg)							
≥2000	40 (25.5)	1			1		
<2000	117 (74.5)	3.29	1.28–8.48	.014*	2.20	0.81–6.00	.123
Max. daily dose of G-CSF (μg)							
>600	23 (14.6)	1			1		
≤600	134 (85.4)	5.67	1.27–25.25	.023*	5.18	1.12–24.02	.036*

CI = confidence interval, FN = febrile neutropenia, G-CSF = granulocyte colony-stimulating factor, HR = hazard ratio.
*Statistically significant.

Table 4

Univariate and multivariate Cox regression analysis of risk factors for recurrence-free survival of febrile neutropenia.

		Univariate			Multivariate		
	N (%)	HR	95% CI	*P*	HR	95% CI	*P*
Age at initial FN (yr)							
<55	70 (44.6)	1					
≥55	87 (55.4)	1.73	0.95–3.15	.073			
Previous lines of chemotherapy							
>1	42 (26.8)	1			1		
≤1	115 (73.2)	2.56	1.01–6.54	.049*	2.30	0.90–5.87	.082
Grade 3 or 4 thrombocytopenia							
No	109 (69.4)	1					
Yes	48 (30.6)	0.60	0.29–1.25	.171			
Total dose of G-CSF (μg)							
≥2000	40 (25.5)	1			1		
<2000	117 (74.5)	2.46	1.05–5.78	.039*	1.19	0.45–3.14	.721
Max. daily dose of G-CSF (μg)							
>600	23 (14.6)	1			1		
≤600	134 (85.4)	5.10	0.24–20.99	.024*	4.67	1.13–19.26	.033*

CI = confidence interval, FN = febrile neutropenia, G-CSF = granulocyte colony-stimulating factor, HR = hazard ratio.
*Statistically significant.

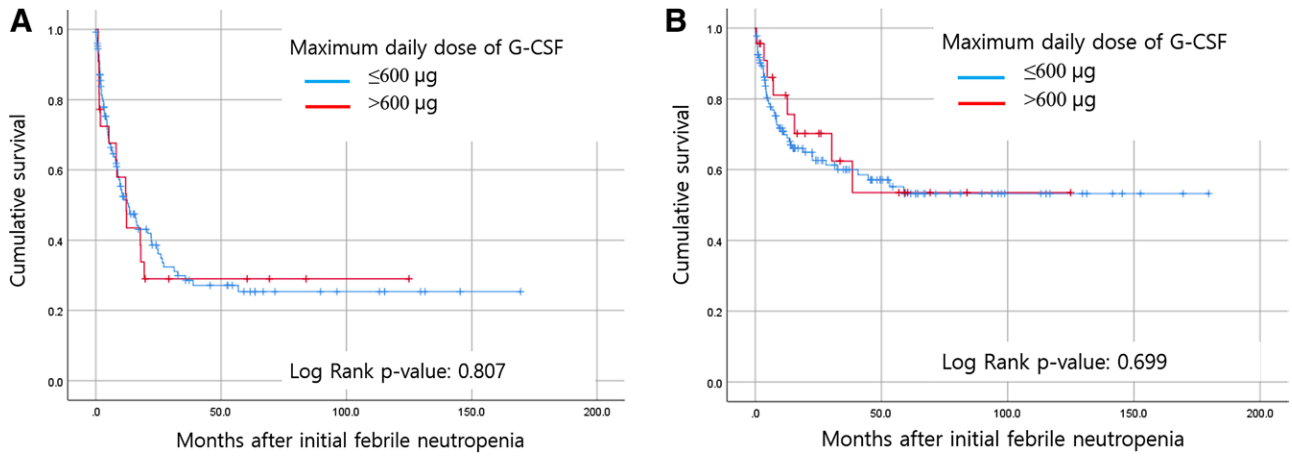

Figure 1. Kaplan–Meier curves of (A) progression-free survival and (B) overall survival after initial febrile neutropenia according to maximum daily dose of G-CSF 600 μg. G-CSF = granulocyte colony-stimulating factor.

early lines of chemotherapy with previous chemotherapy history seems to be associated with recurrent FN. This finding is probably related to the underlying bone marrow status of the individual patients. In other words, it can be presumed that patients with poor bone marrow status develop FN in early lines of chemotherapy and have a higher risk of FN recurrence.

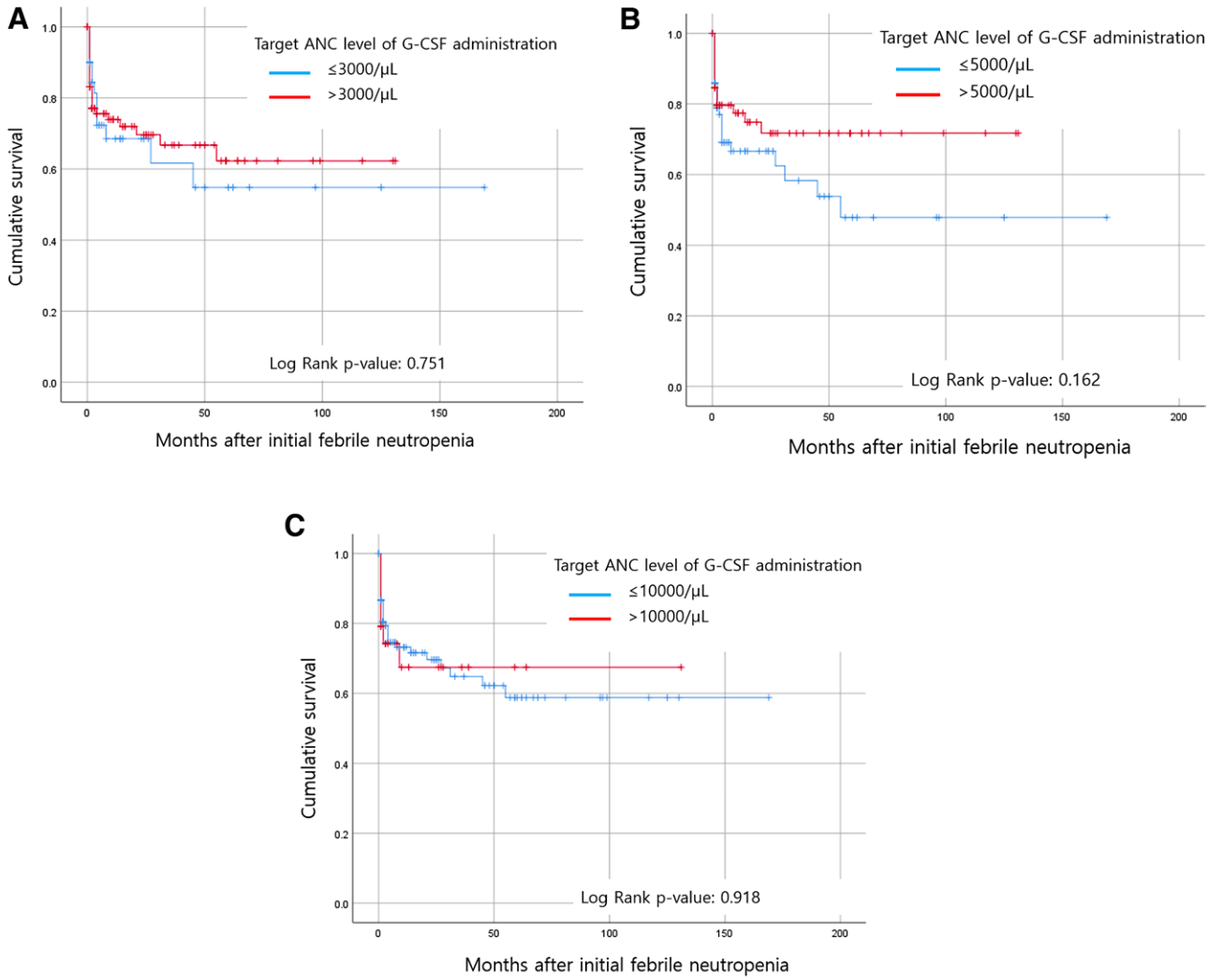

Figure 2. Kaplan–Meier curves for recurrence-free survival of febrile neutropenia according to different target ANC level of G-CSF (A, 3000/μL; B, 5000/μL; C, 10,000/μL). ANC = absolute neutrophil count, G-CSF = granulocyte colony-stimulating factor.

Table 5

Recovery time from recurrence of FN and side effects of G-CSF according to maximum daily dose of G-CSF at initial FN.

	MDD ≤ 600 μg (n = 133)	MDD > 600 μg (n = 23)	*P*
Recovery time from first recurrence of FN*	4.12 ± 2.26 (n = 42)	3.00 ± 2.83 (n = 2)	.500
Side effects of G-CSF			
Pain	51 (38.3)	5 (21.7)	.125
Diarrhea	17 (12.8)	4 (17.4)	.517
Thrombosis	2 (1.5)	1 (4.3)	.382

Values are presented as mean ± standard deviation or number (%). Of 49 patients with recurrent FN, 3 who died at the second FN event and one who was discharged with ANC 1029 were excluded from analysis.

ANC = absolute neutrophil count, FN = febrile neutropenia, G-CSF = granulocyte colony-stimulating factor, MDD = maximum daily dose.

*The days from diagnosis of FN to ANC ≥1500/μL.

It is necessary to consider whether a high dose of therapeutic G-CSF is feasible in terms of dose and toxicity. The NCCN guidelines recommend a therapeutic filgrastim dose of 5 μg/kg/d and duration until post-nadir ANC recovery to normal or near normal levels by laboratory standards. This dose and duration were the same as those for prophylactic use. For mobilization and posthematopoietic cell transplantation, a daily dose of filgrastim can be administered at a dose of 10 to 16 μg/kg, which is 2 to 3 times higher than that used in FN.[1] In a previous study on hematopoietic recovery according to various G-CSF doses in patients with autologous bone marrow transplant, the administered G-CSF dose range was 4 to 64 μg/kg/d and was tolerable even at high doses. The researchers suggested that the optimal dose of G-CSF to stimulate ANC recovery after transplant was 4 to 8 μg/kg/d.[21] For the treatment of severe congenital and acquired neutropenia, the G-CSF daily dose may be increased to >20 μg/kg/d or more depending on the clinical conditions of the patient.[22] In practice, a high dose of G-CSF is used in several clinical situations. Mild-to-moderate bone pain, which can be alleviated with analgesics, is the most common G-CSF-related adverse event and is reported in 10% to 30% of cases.[1,14] Splenic rupture, a very rare and potentially fatal complication of G-CSF, has been mostly reported in the treatment of hematologic malignancies or bone marrow transplantation rather than solid tumors.[23,24] Although several epidemiological studies have suggested that G-CSF may increase the risk of AML/MDS, no association has been reported in individual randomized trials, and it is difficult to determine whether secondary hematologic malignancies are due to G-CSF use or long-term chemotherapy.[1,23,25] Most of the studies on G-CSF-related adverse events were case reports and case series based on varied study populations and cancer types. In addition, there has been no evidence of G-CSF dose-dependent toxicity to date. Our study showed no

significant difference in adverse events of G-CSF between maximum daily dose of G-CSF ≤600 and >600 μg, and no splenic rupture or AML/MDS was observed in the study population. Therefore, we suggest that a high dose of G-CSF is feasible.

This is the first study to focus on the effect of various doses of therapeutic G-CSF on the subsequent recurrence of FN in patients with gynecologic cancer receiving cytotoxic chemotherapy. However, this study had several limitations. First, the disease state and chemotherapy regimens were mixed in our study. The advanced disease state of cancer is known as a disease-related risk factor associated with FN. The use of myelosuppressive chemotherapy agents such as doxorubicin, docetaxel, cyclophosphamide, etoposide, or gemcitabine has also been reported as a significant predictor of FN.[16] Because of the small sample size of the study population, analysis considering these risk factors was limited. Second, prophylactic G-CSF use before the initial FN event was included in the analysis, but the change in the use of prophylactic G-CSF after FN treatment with high-dose therapeutic G-CSF was not considered in the current study. The method of prophylactic G-CSF administration and outpatient check-up using a complete blood cell count test differed among gynecological oncologists in our institute; thus, the analysis was limited. Further limitations include the retrospective design of the study and the relatively small sample size of the study population.

5. Conclusions

Dose-dense administration of G-CSF >600 μg/d could prevent the recurrence of FN in patients with gynecologic cancer. Old age and FN at early lines of chemotherapy seem to be associated with FN recurrence. Because the risk of FN varies according to the chemotherapy regimen, further analysis is required depending on the individual regimen used predominantly in gynecologic cancer. In addition, further studies are needed to determine whether the use of high-dose therapeutic G-CSF has advantages in terms of cost or quality of life compared to prophylactic G-CSF.

Author contributions

NKK made substantial contributions to data acquisition, analysis, interpretation of data, and drafting and revising the manuscript. DHS made substantial contributions to the conception and design of the work, analysis and interpretation of data, and revision and confirmation of the manuscript. KK, JHN, and YBK made substantial contributions to the drafting, revising, and final confirmation of the manuscript. All authors have read and approved the final manuscript.

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