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Lesson from COVID-19 outbreak; importance of standard precautions to febrile neutropenia prevention in patients with breast cancer who received adjuvant chemotherapy: a retrospective observational study

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Purpose: Intensive cytotoxic chemotherapy increases the risk of infection in patients with cancer by inducing bone marrow suppression and mucosal injury. Febrile neutropenia (FN) is the most important clinical adverse event in patients with cancer receiving cytotoxic chemotherapy. To prevent FN, standard precautions including hand and respiratory hygiene are generally recommended, but the exact effect of non-pharmacologic intervention has not been clearly proven in the clinical setting. We aimed to compare the incidence of FN between the pre-coronavirus disease 19 (COVID-19) era *vs*. the post-COVID-19 era.
Methods: We retrospectively enrolled patients with breast cancer who received an adriamycin and cyclophosphamide (AC) regimen containing adjuvant chemotherapy at Jeju National University Hospital. We compared the incidence of FN between the pre- and post-COVID-19 period and analyzed characteristics of the event and other clinical risk factors.
Results: In total, 149 patients were enrolled, including 94 who received AC chemotherapy in the pre-COVID-19 era and 55 who received it in the post-COVID-19 era. Sixteen patients (10.7%) experienced FN. Fourteen (14.9%) and 2 events (3.6%) occurred in pre-COVID-19 and post-COVID-19 eras, respectively. The post-COVID-19 era was the only risk factor for FN (P = 0.032).
Conclusion: We found an association between FN occurrence and the COVID-19 outbreak, providing indirect evidence of the importance of non-pharmacological measures to reduce FN risk in patients with breast cancer. Further research is required to confirm the standard precautions for FN prevention in patients with cancer.
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Key Words: Febrile neutropenia, Universal precautions, COVID-19

INTRODUCTION

The outcome of cancer treatment has remarkably improved with the development of various treatment modalities and contributes greatly to the improvement of cancer survival rates along with efforts for early screening [1,2]. From the perspective of chemotherapy, many improvements have been made in terms of efficacy and toxicity with the development of various targeted therapies and immunotherapy. However cytotoxic agents still occupy the backbone of the cancer therapy; nevertheless, they are accompanied by various unavoidable side effects such as myelosuppression. Febrile neutropenia (FN),

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which is related to chemotherapy-induced myelosuppression in patients with cancer, is one of the most important and serious side effects of chemotherapy. FN is associated with infection-related morbidity and mortality, increased medical cost, and can indirectly impair oncologic outcomes by affecting chemotherapy intensity [3,4]. Therefore, the prevention of FN remains the most critical clinical issue in the oncologic era. Based on evidence from high-risk patients, the use of antibiotics and colony-stimulating factors (CSFs) is actively recommended in various guidelines [5,6]. Other approaches to prevent FN, including standard precautions, neutropenic diet, patient's skin and oral care, and environmental control, are also recommended in several guidelines; however, direct evidence of this measure is lacking [5,7,8]. Owing to the lack of evidence, patients and even clinicians often overlook the importance of the non-pharmacological approach and tend to have inconsistent policies. Standard precautions, including hand and respiratory hygiene, are also being implemented uniformly and routinely based on past historical experience; evidence of their efficacy in preventing FN is also lacking.

Since social distancing and precaution measures, such as hand and oral hygiene, were emphasized after the outbreak of coronavirus disease 19 (COVID-19), we hypothesized that if the incidence of FN decreased during this period; the clinical importance of these non-pharmacological approaches could be evaluated indirectly but effectively.

METHODS

Ethics statements

The study protocol was reviewed and approved by the Institutional Review Board of the Jeju National University Hospital (No. 2023-08-004). The study was conducted according to the recommendations of the Declaration of Helsinki for biomedical research and written informed consent was waived due to its retrospective nature.

Study populations and data collection

We retrospectively collected data from patients with breast cancer, who received an adriamycin and cyclophosphamide (AC) containing adjuvant chemotherapy regimen from January 2016 to March 2022 at Jeju National University Hospital in Jeju, Korea. Patients with inadequate organ function and those taking immunosuppressive drugs were excluded. The following data were retrospectively collected from electronic medical records: age, sex, body weight, height, performance status, comorbidities, disease stage, treatment, and laboratory examination. We also reviewed the occurrence of FN and its related outcome during AC chemotherapy.

The study patients were divided into 2 groups; pre-COVID-19 or post-COVID-19 eras, from March 22, 2020, when national social distancing began in South Korea. From the data, social distancing and personal quarantine guidelines were strongly recommended including masking, hand hygiene, and cough etiquette that is similar to the standard precaution measures in medical practice.

FN was defined according to the guidelines of the Infectious Disease Society of America (IDSA) and was divided into 3 categories: microbiologically documented infection [8], clinically documented infection, and unexplained fever. We also classified FN episodes based on the risk of serious complications by the Multinational Association for Supportive Care in Cancer (MASCC) scoring tool [8,9]. To categorize patient comorbidities, we used the Charlson Comorbidity Index (CCI) method [10].

Statistical analyses

Continuous variables were expressed as means ± standard deviation at baseline, while categorical variables were expressed as percentages. The Student t-test and 1-way analysis of variance were used to analyze continuous variables, whereas the chi-square or Fisher exact tests were used to analyze categorical variables. After performing univariate analysis to identify the risk factors for FN, multivariate analysis was performed with multiple logistic regression using the enter method. Disease-free survival (DFS) and overall survival (OS) were analyzed using the Kaplan-Meier method and the log-rank test. DFS was calculated as the interval between the first day of chemotherapy and the date of documented disease recurrence or death from any cause, whereas OS was calculated as the interval between the first day of adjuvant chemotherapy and the date of death. A P-value of ≤0.05 was considered statistically significant. All statistical analyses were performed using the IBM SPSS Statistics for Windows, ver. 21 (IBM Corp.).

RESULTS

Patient characteristics

One hundred and forty-nine patients were enrolled in this study, with 94 and 55 in the pre- and post-COVID-19 era groups, respectively. The characteristics of patients in both groups are shown in Table 1. Mean age for the pre- and post-COVID-19 ear groups were 52 and 54 years, and body mass index was 24.6 and 25.5 kg/m^2, respectively. AC monotherapy and AC followed by taxane treatment were introduced to 43 and 106 patients, respectively, and 47 patients received anti-human epidermal growth factor receptor 2 (HER2) agent after AC chemotherapy. Comorbidities, disease stage, hormone receptor status, HER2 status, type of surgery, and chemotherapy regimen were not significantly different in the 2 groups. AC followed by taxane chemotherapy was administered in both groups.

Characteristics of febrile neutropenia events and outcome

Sixty FN episodes occurred including 14 in the pre-COVID-19 group and 2 in the post-COVID-19 group. In total, 81.3% of the cases (13 of 16) developed FN in the first cycles of AC chemotherapy, and most episodes (14 of 16) developed FN without prophylactic CSF administration. A total of 87.5% of the FN episodes (14 of 16) were categorized as unexplained fever, and each event (6.3%) was defined as clinically documented infection and microbiologically documented infection. Only 2 FNs were classified as high-risk episodes by the MASCC scoring system. Most patients (15 of 16) were admitted and treated for FN. All episodes were resolved without any morbidity or mortality, but 62.5% of the patients (10 of 16) had a delayed chemotherapy schedule (Table 2). Patients who experienced FN events showed a minimal compromise in DFS, but both DFS and OS were not significantly different according to the occurrence of FN events (Fig. 1).

Table 1. Baseline characteristics of patients (n = 149)

Characteristic	Pre-COVID-19 era	Post-COVID-19 era	P-value
No. of patients	94	55	
Female sex	93 (98.9)	55 (100)	>0.999
Age (yr)	52 ± 11	54 ± 10	0.413
Body mass index (kg/m^2)	24.6 ± 3.1	25.5 ± 4.1	0.160
Menopausal state			0.604
Premenopausal	41 (45.1)	21 (40.4)	
Postmenopausal	50 (54.9)	31 (59.6)	
Comorbidities			
Diabetes mellitus	7 (7.4)	7 (12.7)	0.384
Hypertension	18 (19.1)	9 (16.4)	0.670
Pulmonary tuberculosis	0 (0)	1 (1.8)	0.369
HBV	1 (1.1)	3 (5.5)	0.142
HCV	2 (2.1)	1 (1.8)	>0.999
Ischemic heart disease	1 (1.1)	1 (1.8)	>0.999
Cerebrovascular disease	1 (1.1)	1 (1.8)	>0.999
COPD	1 (1.1)	3 (5.5)	0.142
Other malignancies	9 (9.6)	4 (7.3)	0.768
Stage			0.093
Stage I	19 (20.2)	15 (27.3)	
Stage IIA	32 (34.0)	22 (40.0)	
Stage IIB	27 (28.7)	13 (23.6)	
Stage III	16 (17.0)	5 (9.1)	
HR positive	79 (84.0)	39 (70.9)	0.063
HER2 positive	25 (26.9)	23 (41.8)	0.055
Surgery			0.293
Breast-conserving surgery	52 (55.3)	37 (67.3)	
Mastectomy	41 (43.6)	18 (32.7)	
Lumpectomy	1 (1.1)	0 (0)	
Chemotherapy regimen			0.673
AC	26 (27.7)	17 (30.9)	
AC followed by docetaxel/weekly paclitaxel	68 (72.3)	38 (69.1)	
Anti-HER2 agent, yes	24 (25.5)	23 (41.8)	0.047

Values are presented as number only, number (%), or mean ± standard deviation.
COVID-19, coronavirus disease 19; COPD, chronic obstructive pulmonary disease; HR, hormone receptor; HER2, human epidermal growth factor receptor 2; AC, adriamycin and cyclophosphamide.

Risk factor of febrile neutropenia

Univariable analysis to investigate the risk factors of FN found that pre-COVID-19 era, age of ≥60 years, and CCI of ≥4 were the only significant risk factors (Table 3). Multivariate logistic regression analysis revealed that the pre-COVID-19 era was the only independent risk factor for FN development. In the post-COVID-19 era, the odds ratio for the development of FN was 0.183 (95% confidence interval, 0.039–0.864; P = 0.032); thus, signifying that the risk of FN decreased in the post-COVID-19 era (Table 4).

DISCUSSION

We found that the incidence of FN was significantly reduced in the post-COVID-19 era and that it was the only significant clinical risk-reducing factor. Since personal quarantine guidelines, including social distancing, masking, and hand hygiene, were strongly recommended in South Korea after the COVID-19 outbreak, our study suggests that standard precautions in medical practice are an effective strategy to prevent FN. A similar pattern was also observed in seasonal respiratory virus infection rates [11]. Although these non-

Table 2. Characteristics of FN and its outcome (n = 16)

Characteristic	Data
Cycles of FN	
1st cycles	13 (81.3)
2nd cycles	3 (18.7)
Prophylactic G-CSF administration in FN event cycle	2 (12.5)
Category of FN syndrome	
Clinically documented infection	1 (6.3)
Microbiologically documented infection	1 (6.3)
Unexplained fever	14 (87.5)
MASCC risk	
Low	14 (87.5)
High	2 (12.5)
Admit for FN	15 (93.8)
Dose reduction after FN	1 (6.3)
Chemotherapy delay due to FN	10 (62.5)
Discontinuation after FN	0 (0)
Death from FN	0 (0)

FN, febrile neutropenia; G-CSF, granulocytes colony-stimulating factor; MASCC, multinational association of supportive care in cancer.

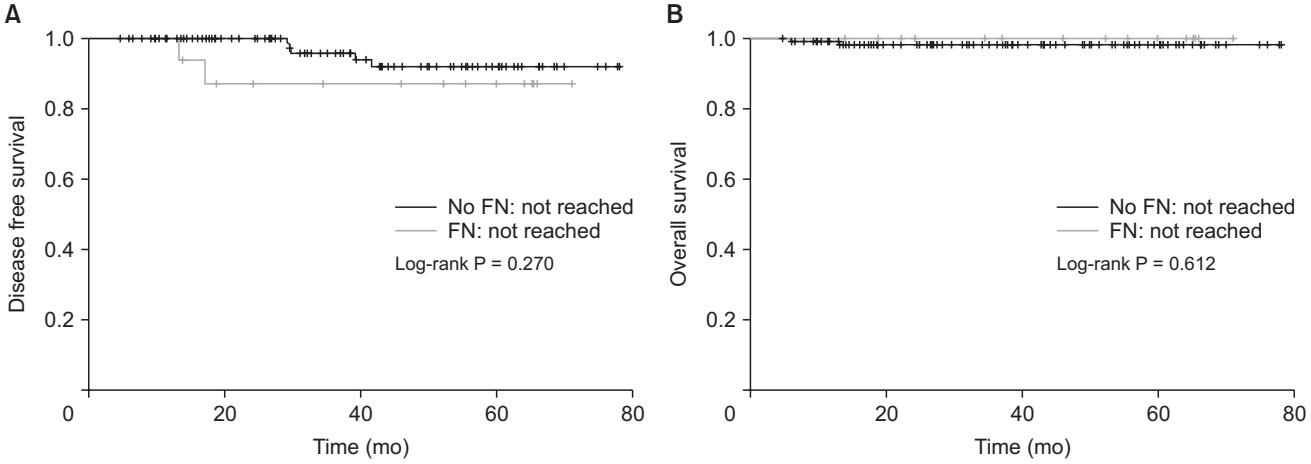

Fig. 1. (A) Disease-free survival and (B) overall survival based on occurrence of febrile neutropenia (FN).

Table 3. Univariable analysis to investigate risk factors of FN event

Characteristic	No FN (n = 133)	FN (n = 16)	P-value
COVID-19 era			0.052
Pre-COVID-19 era	80 (60.2)	14 (87.5)	
Post-COVID-19 era	53 (39.8)	2 (12.5)	
Age (yr)			0.022
<60	97 (72.9)	7 (43.8)	
≥60	36 (27.1)	9 (56.2)	
Body mass index (kg/m^2)			0.777
<23	42 (31.6)	4 (25.0)	
≥23	91 (68.4)	12 (75.0)	
Menopausal state			0.790
Premenopausal	56 (44.1)	6 (37.5)	
Postmenopausal	71 (55.9)	10 (62.5)	
Charlson Comorbidity Index			0.014
<4	91 (68.4)	6 (37.5)	
≥4	42 (31.6)	10 (62.5)	
Stage			0.485
Stage I	29 (21.8)	5 (31.2)	
Stage IIA	48 (36.1)	6 (37.5)	
Stage IIB	38 (28.6)	2 (12.5)	
Stage III	18 (13.5)	3 (18.8)	
HR positive	107 (80.5)	11 (68.8)	0.327
HER2 positive	44 (33.1)	4 (25.0)	0.513
Surgery			0.199
Breast-conserving surgery	76 (57.1)	13 (81.2)	
Mastectomy	56 (42.1)	3 (18.8)	
Lumpectomy	1 (0.8)	0 (0)	
WBC (/μL)			0.559
<4,000	6 (4.5)	1 (6.2)	
≥4,000	127 (95.5)	15 (93.8)	
Hemoglobin (g/dL)			0.527
<12	28 (21.2)	2 (12.5)	
≥12	104 (78.8)	14 (87.5)	
Platelet (K/μL)			0.185
<253	68 (51.5)	5 (31.2)	
≥253	64 (48.5)	11 (68.8)	
Albumin (g/dL)			0.819
<4.2	62 (47.0)	8 (50.0)	
≥4.2	70 (53.0)	8 (50.0)	
Total bilirubin (mg/dL)			0.107
<0.5	46 (34.8)	9 (56.2)	
≥0.5	86 (65.2)	7 (43.8)	
BUN (mg/dL)			0.650
<20	120 (90.9)	14 (87.5)	
≥20	12 (9.1)	2 (12.5)	
Creatinine (mg/dL)			0.185
<0.75	68 (51.5)	5 (31.2)	
≥0.75	64 (48.5)	11 (68.8)	
CRP (g/dL)			0.708
<0.30	91 (84.3)	9 (90.0)	
≥0.30	17 (15.7)	1 (10.0)	
ESR (mm/hr)			0.340
≤20	42 (44.7)	7 (63.6)	
>20	52 (55.3)	4 (36.4)	

FN, febrile neutropenia; COVID-19, coronavirus disease 19; HR, hormone receptor; HER2, human epidermal growth factor receptor 2.

pharmacological interventions are routinely recommended in medical practice and have not changed, there has been a significant alteration in the awareness of the importance and actual implementation after the COVID-19 outbreak. Above all, the fact that these policies were applied in social environments and for the general public, not patients, was a fundamental difference of the pre- and post-COVID-19 eras. These changes are thought to be the essential cause of the meaningful difference.

Cytotoxic chemotherapy-induced myelosuppression disrupts mucosal integrity related to FN development. Therefore,

Table 4. Multivariable logistic regression analysis on risk factor of FN events

Characteristic	Adjusted OR (95% CI)	P-value
COVID-19 era		0.032
Pre-COVID-19 era	1	
Post-COVID-19 era	0.183 (0.039–0.864)	
CCI		0.459
<4	1	
≥4	2.396 (0.238–24.152)	
Age (yr)		0.599
<60	1	
≥60	1.848 (0.187–18.249)	

FN, febrile neutropenia; OR, odds ratio; CI, confidence interval; COVID-19, coronavirus disease 19; CCI, Charlson Comorbidity Index.

although patients and tumor factors also affect FN occurrence and pathogenesis, seeding of normal gut flora in patients is considered the most important cause of FN. Approximately 80% of documented infectious organisms are considered to be of an endogenous origin [12]. For this reason, several guidelines for preventive strategies using CSFs and antibiotics are emphasized, and non-pharmacological measures, such as standard precaution, are usually less emphasized. Although the 2011 IDSA guidelines for neutropenic patients with cancer mentioned that hand hygiene is the most effective preventive measure, they do not provide direct evidence for FN and only provide indirect evidence for hospital-acquired infection prevention [5,8,13-15]. Because patients with cancer are a very heterogeneous disease group, the etiology of FN inevitably differs among patients, and reportedly viral agents are also an important etiology of FN [16-18]. In that respect, the preventive strategy for FN also needs to be applied differently depending on the patient's characteristics and expected etiology; however, the current practice is considered too simplistic and is focused on only a specific group. Our data and some recent studies have shown that the incidence of FN, especially upper respiratory infection, significantly decreased after the COVID-19 outbreak [19,20]. In our study, the pattern of our relatively lower-risk patients was different from the generally known epidemiological pattern of FN (unexplained fever, 87.5%; clinically documented infection, 6.3%; and microbiologically documented infection, 6.3%). These results imply that environmental infectious sources also play an important role in FN occurrence, and non-pharmacological intervention, such as standard precautions, may be more meaningful in some groups. This also suggests that preventive guidelines for FN should be more individualized according to the patient's clinical factors. For example, prophylactic antibiotics and CSFs should be strongly considered in higher-risk patients, and non-pharmacological intervention should be relatively emphasized in lower-risk patients.

At the beginning of our study, there were no reports on the relationship between FN and the COVID-19 outbreak. However, several recent research results have been reported. The result of each study though similar in some aspects, differed as highlighted in Table 5 [19-23]. Nessle et al. [19] reported only a reduced incidence of upper respiratory infection associated with FN and not overall FN episodes among pediatric patients with cancer during the post-COVID-19 era. Three other retrospective studies showed a reduction in the overall FN incidence after the COVID-19 outbreak in a relatively larger dataset. However, these data were derived from heterogeneous disease groups with different tumor types, chemotherapy regimens, and patient characteristics [20,21,23]. Therefore, it is somewhat difficult to apply these results to all cancer patients. Furthermore, Baracy et al. [21] reported an unexpected and different result in that FN episodes were reduced only in patients with hematologic malignancies. Another retrospective study in a homogenous patient group that received adjuvant docetaxel, AC chemotherapy after breast cancer surgery conducted by Gwak et al. [22] also reported a reduction in FN episodes that were very similar to our study. However, this study enrolled a relatively smaller number of patients and conducted somewhat different treatment and preventive strategies from that of routine clinical practice. Since our study enrolled very homogenous patients who received the same, well-standardized treatment, we may draw more confident conclusions. All the studies, including our study, were retrospective in design, and missing data bias is an important limitation. The hospital where this study was conducted is the only university hospital on Jeju Island. Thus, the study patients received almost all of their acute and chronic problem care at our hospital; missing data bias is expected to be relatively minimal. Additionally, because our study used more systematical assessment models to classify comorbidities, risk of FN episode, it is expected that better-controlled results can be derived.

Our study has some limitations. A retrospective, observational study with a small number of patients may have some potential bias. Another limitation is that the change in clinical practices after the COVID-19 outbreak (e.g., fewer hospital visits due to patient hesitation or higher institutional barriers to hospital visits) could have affected the reported FN episodes. However, a careful review of medical records would have considerably solved this problem. Survival analysis also has limitations in interpretation due to different follow-up periods. As our study enrolled a very limited patient population, these results cannot be applied to general cancer patients with diverse clinical characteristics. We believe that the results of this study can be applied to patients who expect to experience FN with low MASCC risk.

Since the incidence of FN has decreased after the COVID-19

Table 5. FN occurrence after COVID-19 outbreak, recent data

Study	Year	Study design	Patients and data	Results (compared with pre-COVID-19 ear)
Nessle et al. [19]	2023	Single center quasi-experimental 1-group pre-post study, retrospective	Pediatric oncologic patients Admitted with diagnosis of FN n = 236	No difference in FN admission (11.8/mo *vs.* 12.8/mo episode) No difference in the incidence of bacterial and bacterial bloodstream infection and PICU admission Decreased URI incidence among FN episodes (10.8% *vs.* 19.9%, P = 0.01) Increased high-risk episodes (63.6% *vs.* 44.2%) in respiratory seasons (November through February)
Baracy et al. [21]	2022	Retrospective cohort study Data from public health executive orders	Visit with FN among a total of 8,979,221 ED visits from March 1, 2019 to Apr 31, 2021	Reduction in the proportion of total ED visits with a diagnosis of FN (0.13% *vs.* 0.15%, P = 0.036) Reduction of FN episodes in only hematologic malignancy patients (17% *vs.* 22%, P = 0.02)
Gwak et al. [22]	2022	Single center retrospective observational study	Female patients with breast cancer who received TAC chemotherapy with prophylactic pegfilgrastim n = 85	No difference in chemotherapy-induced neutropenia Lower incidence of FN (9.5% *vs.* 27.9%, P = 0.05) Less hospitalization duration and total hospital cost
Baus et al. [20]	2023	Single center retrospective observational study	Admitted patients with solid tumors receiving chemotherapy with a risk of FN n = 8,337	Decreased FN-associated admission (0.63% *vs.* 1.26%, p<0.01) No difference pattern of outpatient antibiotics and CSFs use
Toriumi et al. [23]	2023	Single center retrospective observational study	Patients receiving inpatient cytotoxic chemotherapy in urologic department n = 593	Decreased FN episode rate (0.4 *vs.* 6.3%, P = 0.005)
Current study	2024	Single center retrospective observational study	Patients with breast cancer receiving adjuvant AC chemotherapy n = 149	Decreased FN events (3.6% *vs.* 14.9%) and pre-COVID-19 era was only independent risk factor (P = 0.032)

FN, febrile neutropenia; COVID-19, coronavirus disease 19; PICU, pediatric intensive care unit; URI, upper respiratory infection; ED, emergent department; TAC, docetaxel and adriamycin and cyclophosphamide; CSF, colony-stimulating factor; AC, adriamycin and cyclophosphamide.

outbreak and the pre-COVID-19 era was the only risk factor for FN occurrence in breast cancer patients who received AC regimen containing adjuvant chemotherapy, non-pharmacologic intervention, such as standard precaution, may contribute to the reduction of FN occurrence in specific populations. If additional research is conducted to confirm the results in various patients with cancer, we will be able to obtain indirect but strong evidence of the importance of these basic and non-pharmacologic interventions.

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Conflict of Interest

No potential conflict of interest relevant to this article was reported.

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