Received: 16 March 2022 | Revised: 8 June 2022 | Accepted: 5 July 2022

DOI: 10.1111/cas.15490

Cancer Science WILEY

ORIGINAL ARTICLE

Decreased febrile neutropenia during inpatient chemotherapy for urologic cancer during coronavirus disease 2019 pandemic

Ren Toriumi | Hiroshi Yaegashi | Suguru Kadomoto | Hiroaki Iwamoto | Masashi Iijima | Shohei Kawaguchi | Takahiro Nohara | Kazuyoshi Shigehara | Kouji Izumi | Yoshifumi Kadono | Atsushi Mizokami

Department of Integrative Cancer Therapy and Urology, Kanazawa University Graduate School of Medical Science, Kanazawa, Japan

Correspondence
Hiroshi Yaegashi, Department of Integrative Cancer Therapy and Urology, Kanazawa University Graduate School of Medical Science, 13-1 Takaramachi, Kanazawa, Ishikawa 920-8640, Japan.
Email: hyae2002jp@yahoo.co.jp

Abstract

Since 2020, the coronavirus disease 2019 pandemic has led to the widespread practice of hand hygiene and wearing face masks, not only among medical personnel, but also among the general population. Thus, the impact of the coronavirus disease 2019 pandemic on the incidence of febrile neutropenia should be verified. This study aimed to examine the incidence of febrile neutropenia in hospitalized patients receiving chemotherapy at Kanazawa University Hospital. Among inpatients at the Department of Urology receiving chemotherapy, we compared the incidence of febrile neutropenia between 317 cases in 2018–2019 and 276 cases in 2020. We retrospectively analyzed the factors of febrile neutropenia via binomial logistic regression analysis based on patient characteristics and the characteristics of primary diseases, with statistical significance set at $p < 0.05$. Febrile neutropenia occurred in 20/317 cases in 2018–2019 and 1/276 cases in 2020, with a significant decrease in the latter ($p = 0.005$). In a multivariate analysis, we identified the following independent risk factors for febrile neutropenia: non-coronavirus disease 2019 era ($p = 0.005$), first course of therapy ($p = 0.005$), malnutrition ($p = 0.032$), and past history of febrile neutropenia ($p = 0.018$). Due to the coronavirus disease 2019 pandemic, hygiene policies for medical personnel and quarantine measures for patients were thoroughly implemented. Therefore, the incidence of febrile neutropenia in 2020 decreased to 1/15 of the previous incidence. Thus, the hygiene for medical personnel and patients during the expected period of chemotherapy-induced neutropenia is important for febrile neutropenia prevention.

KEYWORDS
Coronavirus disease 2019, drug therapy, febrile neutropenia, fever of unknown origin, hygiene

Abbreviations: COVID-19, coronavirus disease 2019; CTCAE, Common Terminology Criteria for Adverse Events; CVC, central venous catheter; FN, febrile neutropenia; FUO, fever of unknown origin; G-CSF, granulocyte-colony stimulating factor; HSCT, hematopoietic stem cell transplant; MASCC, Multinational Association of Supportive Care in Cancer; PER, protective environment room; PS, performance status; SmCC, small cell carcinoma; VeIP, vinblastine, ifosfamide, and cisplatin combination therapy.

1 | INTRODUCTION

The global coronavirus disease 2019 (COVID-19) pandemic has led to the widespread practice of hand hygiene and wearing face masks, not only among medical personnel, but also among the general public.[1,2] To avoid the nosocomial spread of COVID-19, infection prevention awareness among medical personnel has been further enhanced. The incidence of some community-acquired infections has decreased during the COVID-19 pandemic, probably due to the infection prevention measures practiced by the general public. For example, seasonal influenza virus infections in Japan dramatically decreased during 2020–2021.[3–5]

COVID-19 was first reported in Wuhan, China, on December 8, 2019. The infection then spread worldwide, and was first reported in Japan on January 16, 2020. In April 2020, when the government first declared a state of emergency in seven prefectures in Japan, the mask-wearing rate in public places was 84%.[2] In Ishikawa Prefecture, where our hospital (Kanazawa University Hospital) is located, the first case of COVID-19 was reported in February 2020. At about the same time, our hospital started infection prevention measures against COVID-19. These included the strict mask-wearing and hand disinfection by medical personnel and patients, prohibiting visits, outings, and staying out overnight, as well as COVID-19 PCR testing for all patients immediately before hospitalization. These were new rules compared to those before the COVID-19 pandemic. Specifically, patients with cancer are more susceptible to severe events if they develop COVID-19 infection because of their systemic immunosuppressive state caused by the malignancy and anticancer treatments (i.e., chemotherapy or surgery).[6] Therefore, infection prevention measures are very important in such patients.

In terms of infections for cancer patients treated by cytotoxic agents, febrile neutropenia (FN) is also an important issue. FN is one of the most alarming side-effects of chemotherapy.[7–9] When chemotherapy causes neutropenia, there is a high risk of fever, which can rapidly become severe and lead to death.[7] Although there is a 20%–30% probability that the microorganism that causes the fever will be identified, broad-spectrum antimicrobial agents improve symptoms in most cases.[10–12] In recent years, FN guidelines have been developed, and proper use of antimicrobial agents has decreased the mortality rate of FN.[12] Because the worldwide COVID-19 pandemic has recently forced us to drastically review hygiene management, we intuitively hypothesized that the number of severely infected patients undergoing inpatient chemotherapy would decrease. Thus, this study aimed to investigate the impact of the COVID-19 pandemic on the incidence of FN.

2 | MATERIALS AND METHODS

2.1 | Patient criteria

For inpatient chemotherapy in the Department of Urology, Kanazawa University Hospital, one admission event was counted as one case. The incidence of FN among 317 cases in 2018–2019 was retrospectively compared with that among 276 cases in 2020. We included patients receiving cytotoxic chemotherapy regimens (both oral and intravenous), and excluded those treated with immune checkpoint inhibitors and molecular targeted therapies. Patients who were discharged after inpatient chemotherapy and hospitalized again due to FN were also counted as one case. FN was diagnosed based on the definition of The Infection Diseases Society of America.[12] There was no unified rule on what to do before and after the onset of FN; this depended on each attending physician's decision.

2.2 | Risk factors of FN

The patient-related risk factors of FN have already been reported in several guidelines.[12–15] Treatment regimen and dosage are also known as the main treatment-related risk factors of FN. Based on this, we made a list of the possible risk factors of FN, and divided them into three categories: patient characteristics, tumor characteristics, and treatment characteristics.

2.3 | Patient characteristics

We evaluated the following patient characteristics: COVID-19 era (2020 vs. 2018–2019), age (≥65 years), gender, Eastern Cooperative Oncology Group Performance Status (ECOG-PS), obesity (body mass index ≥25), diabetes mellitus, hypertension, human immunodeficiency virus infection, malnutrition (albumin <3.5 g/dl), renal dysfunction (estimated-glomerular filtration rate $<50\,ml/min/1.73\,m^2$), liver dysfunction (total bilirubin >2.0 mg/dl), cardiovascular disease, hematological disease, chronic obstructive pulmonary disease, neutropenia at treatment (neutrophil count $<2.0\times10^9/L$), history of FN, surgery within the last 3 months, and radiotherapy, use of a central venous catheter (CVC), and administration of primary prophylactic granulocyte-colony stimulating factors (G-CSF), steroids, immunosuppressive agents, or antimicrobial agents.

2.4 | Tumor characteristics

We evaluated tumor characteristics, such as the type of cancer and its histology, lymph node metastasis, and distant metastasis. Regarding cases of small cell carcinoma (SmCC), we counted cases of both pure histological type and concomitant with other histological type.

2.5 | Treatment characteristics

Treatment characteristics included regimen, number of treatment lines, treatment courses, and total treatment courses, and the existence of dose reduction in chemotherapy. The number of treatment lines included immune checkpoint inhibitors and molecular targeted therapies and excluded hormone therapy for prostate cancer.

[Corrections made on 02 December 2022, after first online publication: The word "excluded" in the text "and hormone therapy for prostate cancer" has been added. Also, some of the abbreviations have been corrected in this version.]. The number of treatment courses was defined as the number of courses in the current regimen, and the number of total treatment courses was defined as the total number of past and present courses of single cytotoxic chemotherapy.

2.6 | Evaluation of cytopenia

We collected the data on blood cell counts before and after chemotherapy, and evaluated the Common Terminology Criteria for Adverse Events (CTCAE) grade of cytopenia for each group. Nadir blood cell counts were defined as those that are decreased to the lowest point of each value after chemotherapy compared with before chemotherapy. Cases wherein blood cell counts were not measured after chemotherapy were excluded.

2.7 | Diagnosis and treatment of FN

We collected the clinical data of FN cases about diagnoses and treatments retrospectively, as well as assessed the risk of severe FN using the Multinational Association of Supportive Care in Cancer (MASCC) score.[16]

TABLE 1 Characteristics of patients undergoing inpatient chemotherapy for urological cancer in 2020 and 2018–2019

	2020	2018–2019	
	n (%)	*n* (%)	*p* value
Total, *n*	276	317	
Gender			
Male	219 (79)	212 (67)	0.177
Female	57 (21)	105 (33)	Reference
Age, years			
Median (range)	73 (25–86)	70 (18–86)	
≥65	214 (78)	219 (69)	0.362
ECOG-PS			
0–1	258 (93)	306 (97)	0.785
≥2	18 (7)	11 (3)	Reference
Obesity	74 (27)	68 (22)	0.233
Diabetes mellitus	40 (14)	43 (14)	0.778
Hypertension	120 (43)	138 (44)	0.993
HIV infection	0 (0)	0 (0)	N/A
Malnutrition	88 (32)	83 (26)	0.257
Renal dysfunction	78 (28)	114 (36)	0.152
Liver dysfunction	0 (0)	1 (0.3)	0.351
Cardiovascular disease	79 (29)	52 (16)	0.004
Hematological disease	3 (1)	21 (7)	0.001
COPD	21 (8)	15 (5)	0.169
Past history of FN	7 (3)	9 (3)	0.825
Neutropenia at treatment	18 (7)	45 (14)	0.006
History of surgery (within the last 3 months)	51 (18)	69 (22)	0.418
Past history of radiotherapy	57 (21)	58 (18)	0.552
Use of CVC	63 (23)	119 (38)	0.005
Administration of G-CSF	33 (12)	44 (14)	0.542
Administration of steroids	45 (16)	36 (11)	0.128
Administration of immunosuppressive agents	0 (0)	0 (0)	N/A
Administration of antimicrobial agents	2 (0.7)	2 (0.6)	0.89

Abbreviations: COPD, chronic obstructive pulmonary disease; CVC, central venous catheter; G-CSF, granulocyte-colony stimulating factors; N/A, not applicable; PS, performance status.

2.8 | Statistical analysis

The χ^2-test was used to compare the 2020 and 2018–2019 groups. We analyzed the factors of FN via binomial logistic regression analysis. The GraphPad Prism 7 software (GraphPad Software Inc.) and SPSS software for Windows (SPSS Inc.) were used to analyze data and obtain figures. Statistical significance was set at $p < 0.05$ for each analysis.

3 | RESULTS

3.1 | Three categories of characteristics

Patient characteristics were approximately equal in both groups, but there were significant differences in four factors, namely: cardiovascular disease, hematologic disease, neutropenia at treatment, and use of CVC (Table 1).

In terms of tumor characteristics, there were significant differences in the type of cancer (i.e., prostate cancer) and in the histological type (i.e., adenocarcinoma and SmCC). There were no significant differences in lymph node metastasis or distant metastasis between the two groups (Table 2).

Regarding treatment characteristics, there were no significant differences in the number of lines and courses, or in dose reduction. Significantly more patients in the 2018–2019 group received carboplatin monotherapy for germ cell tumors compared to those in the 2020 group, whereas the percentage of patients receiving other regimens was not significantly different between the groups (Table 3).

TABLE 2 Tumor characteristics among patients undergoing inpatient chemotherapy for urological cancer in 2020 and 2018–2019

	2020	2018–2019	
	n (%)	*n* (%)	*p* value
Total, *n*	276	317	
Type of cancer			
Urinary tract cancer	198 (72)	259 (82)	0.299
Prostate cancer	53 (19)	31 (10)	0.005
Germ cell tumor	15 (5)	15 (5)	0.711
Others	10 (4)	12 (4)	0.920
Type of histology			
Urothelial carcinoma	198 (72)	234 (74)	0.822
Adenocarcinoma (of the prostate)	49 (18)	28 (9)	0.009
Derived from germ cell	15 (5)	15 (5)	0.711
Small cell carcinoma[a]	4 (1)	30 (9)	<0.001
Others	10 (4)	10 (3)	0.761
Lymph node metastasis	175 (63)	187 (59)	0.589
Distant metastasis	135 (49)	171 (54)	0.489
Bone metastasis	80 (29)	75 (24)	0.261
Lung metastasis	63 (23)	100 (32)	0.073
Visceral metastasis	91 (33)	132 (42)	0.142

[a]Small cell carcinoma includes both pure and concomitant cases. Other histology types exclude pure and concomitant cases of small cell carcinoma.

3.2 | Evaluation of neutropenia

185 cases in the 2020 group and 248 cases in the 2018–2019 group with confirmed nadir neutrophil counts were analyzed (Table 4). Median [interquartile range] nadir neutrophil counts were 0.96×10^9/l [$0.56–1.68 \times 10^9$/l] in the 2020 group and 0.97×10^9/l [$0.50–1.54 \times 10^9$/l] in the 2018–2019 group. CTCAE grade 3 or 4 neutropenia occurred in 96 cases in the 2020 group and 128 cases in the 2018–2019 group. Adverse events with regard to other blood cell counts are summarized in Supplementary Table S1.

3.3 | Incidence of FN

FN occurred in 20/317 cases (6.3%) in the 2018–2019 group and only 1/276 cases (0.4%) in the 2020 group, with a significant decrease in the latter ($p = 0.005$) (Figure 1). The characteristics of these 21 cases of FN are compared with those of non-FN and summarized in Table 5.

3.4 | Statistical analysis on the risk factors for FN

Nine risk factors of FN were identified in a univariate analysis. In a multivariate analysis, the following independent risk factors of FN were identified: non-COVID-19 era ($p = 0.005$), first course of therapy ($p = 0.005$), malnutrition ($p = 0.032$), and history of FN ($p = 0.018$) (Table 6).

3.5 | Diagnosis and treatment of FN

Among the 21 FN cases, the origin of fever was identified in eight cases (38.1%), whereas 13 cases (61.9%) were classified as having a fever of unknown origin (FUO). Blood culture was undertaken in 19 cases and was positive in five cases (26.3%). Sputum culture was undertaken in eight cases and was positive in one case (12.5%). Urine culture was undertaken in 11 cases and was positive in five cases (45.5%) (Table 7).

The case of FN in the 2020 group was diagnosed as FUO. Therefore, it is not possible to compare changes in causative microorganisms before and after the COVID-19 pandemic. Identified microorganisms are summarized in Supplementary Table S2.

Six patients were considered high-risk based on the MASCC score, which is an indicator of severe FN. However, all patients received antimicrobial therapy, and their condition improved. The median date of FN onset was day 11 (range, day 7–21) of any cytotoxic treatment, the median duration of antimicrobial therapy was 6 days

(range, 3–13 days), and the median time to fever resolution from the onset of FN was 3 days (range, 2–8 days).

Among the 21 FN cases, four were under outpatient management at the onset of FN after inpatient chemotherapy. All these cases belonged to 2018–2019 group, and their regimens were etoposide plus cisplatin, docetaxel, gemcitabine plus cisplatin, and cabazitaxel.

4 | DISCUSSION

In this study, we found four independent risk factors of FN. This is also the first evidence of a sufficiently large scale showing that the incidence of FN decreased during the COVID-19 pandemic. In the current guidelines, malnutrition and having a history of FN are risk factors for FN.[14,15] Being in the first course of the regimen was also identified as a risk factor in this study, with 116 and 150 patients with this risk factor identified in the 2020 and 2018–2019 groups, respectively (Table 3). Furthermore, 87 (75%) and 121 (81%) patients in the 2020 and 2018–2019 groups, respectively, had undergone their first course of chemotherapy without dose reduction. The differences in these characteristics could be the reason why this risk factor was extracted.

In the 2020 group, only one case developed FN while receiving vinblastine, ifosfamide, and cisplatin combination therapy. The incidence of FN in the 2018–2019 group was almost evenly present with each regimen. Carboplatin monotherapy for germ cell tumors is the only regimen that was administered significantly more frequently in the 2020 group (Table 3); however, this did not cause FN. In other words, the difference in the number of FN cases was not due to the differences in the treatment regimen. However, overall, there was a trend toward more high-risk regimens in the 2018–2019

TABLE 3 Treatment characteristics among patients undergoing inpatient chemotherapy for urological cancer in 2020 and 2018–2019

	2020	2018–2019	
	n (%)	*n* (%)	*p* value
Total, *n*	276	317	
First-line chemotherapy for primary cancer	164 (59)	227 (72)	0.156
First course of current treatment	116 (42)	150 (47)	0.425
First course of total treatment	78 (28)	105 (33)	0.352
Dose reduction	147 (53)	128 (40)	0.058
Regimen			
GC	102 (37)	132 (42)	0.443
GCarbo	42 (15)	63 (20)	0.215
MVAC	0 (0)	4 (1)	0.063
TC	30 (11)	28 (9)	0.451
GN	24 (9)	10 (3)	0.006
DTX	23 (8)	13 (7)	0.043
CBZ	6 (2)	10 (3)	0.474
EP	22 (8)	27 (9)	0.824
BEP	12 (4)	6 (2)	0.092
TIP	0 (0)	1 (0.3)	0.351
VeIP	3 (1)	3 (1)	0.866
Carboplatin monotherapy	0 (0)	5 (2)	0.038
CE	0 (0)	4 (1)	0.063
Irinotecan plus carboplatin	2 (1)	3 (1)	0.770
TS-1	1 (0.4)	4 (1)	0.236
ADM	2 (1)	3 (1)	0.770
Eribulin	6 (2)	0 (0)	0.009
Trabectedin	1 (0.4)	0 (0)	0.284
Mitotane	0 (0)	1 (0.3)	0.351

Abbreviations: ADM, doxorubicin; BEP, bleomycin, etoposide, and cisplatin; CBZ, cabazitaxel; CE, carboplatin plus etoposide; DTX, docetaxel; EP, etoposide plus cisplatin; GC, gemcitabine plus cisplatin; GCarbo, gemcitabine plus carboplatin; GN, gemcitabine plus nedaplatin; MVAC, methotrexate, vinblastine, doxorubicin, and cisplatin; TC, paclitaxel plus carboplatin; TIP, paclitaxel, ifosfamide, and cisplatin; TS-1, tegafur, gimeracil, and oteracil potassium; VeIP, vinblastine, ifosfamide, and cisplatin.

group, but the difference was not significant. Since the beginning of the COVID-19 pandemic, major clinical oncology societies (i.e., American Society of Clinical Oncology and European Society for Medical Oncology) have proposed treatment guidelines for malignant diseases under COVID-19 pandemic, thereby recommending the use of regimens resulting in as little FN as possible during the COVID-19 pandemic.[17,18] Reflecting on these guidelines, a safer regimen may have been selected during the COVID-19 pandemic in our study.

According to our examination of the risk factors of FN that were already reported in the guidelines,[12–15] the risk factor for the non-COVID-19 era (i.e., before 2020) was still an independent risk factor. Table 4 shows nadir neutrophil counts and CTCAE grade of neutropenia. Nadir neutrophil counts did not differ between the two groups, although they are influenced by various of other risk factors, such as regimen, dose reduction, and administration of G-CSF, thereby suggesting that this evidence supports our opinion. As the reduced incidence of FN in the COVID-19 era could not be attributed to patient or treatment characteristics, this was likely due to the environmental changes, specifically the infection prevention measures. If infection prevention measures reduce the incidence of FN cases, then most FN cases probably develop due to exposure to microorganisms in the environment, such as from human-to-human infection. Previous reports have stated that the origin of fever is not identified in 70%–80% of FN cases. However, most cases of FN improve with antimicrobial therapy.[10–12] Additionally, the practice of protective environment room (PER) implementation for patients undergoing allogenic hematopoietic stem cell transplant (HSCT) further supports the effectiveness of these infection prevention measures. PER is recommended for patients undergoing allogenic HSCT patients[19–21] and has reduced the incidence of FN and overall mortality.[22] In our study, infection prevention measures were considered to play a role similar to PER. In other words, many FN cases could have been prevented before the COVID-19 pandemic.

Our study had some limitations. We did not investigate cases of FN in patients undergoing outpatient chemotherapy. However, in our department, the first course of chemotherapy is always administered in the hospital, and the safety of the treatment is confirmed before moving them to outpatient chemotherapy. Thus, there are few patients who developed FN during outpatient chemotherapy.

Regarding patient characteristics (Table 1), four factors were significantly different between the two groups, but none of them were significant in the univariate or multivariate analysis, thereby suggesting that they could not be risk factors for FN.

Regarding treatment characteristics (Table 3), the *p* value of dose reduction was marginally significant, with a lower value in the 2018–2019 group. There were no fixed criteria for dose reduction, and that was implemented at the discretion of the attending physician based on the individual patient's FN risk factors. Focusing only on cases that

TABLE 4 Evaluation of neutropenia in patients undergoing inpatient chemotherapy for urological cancer in 2020 and 2018–2019

	2020	2018–2019
Total, *n*	**185**	**248**
Nadir neutrophil counts ($\times 10^9$/L)		
Mean (±SD)	1.37 (1.31)	1.23 (1.09)
Median (IQR)	0.96 (0.56–1.68)	0.97 (0.50–1.54)
CTCAE grade of neutropenia		
1	25	25
2	29	55
3	54	66
4	42	62
Any grade	150	208
Grade 3 or 4	96	128

Abbreviations: CTCAE, Common Terminology Criteria for Adverse Events; IQR, interquartile range.

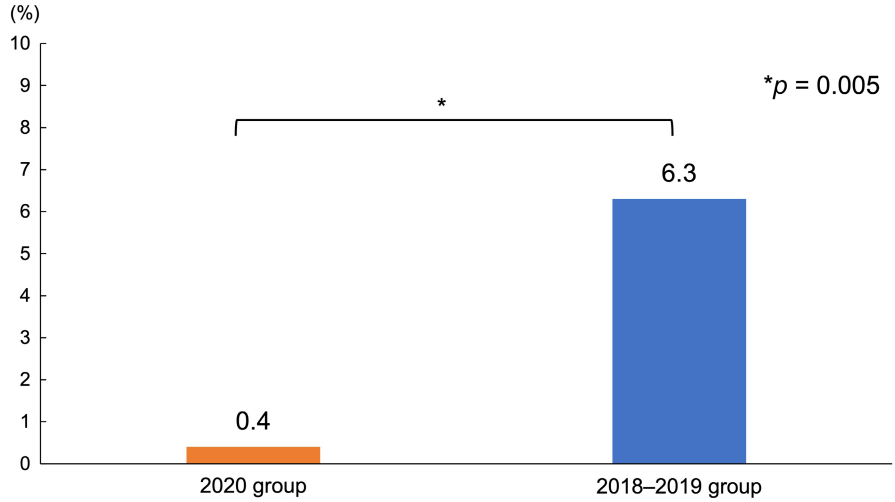

FIGURE 1 Incidence rate of febrile neutropenia among patients undergoing inpatient chemotherapy for urological cancer in 2020 and 2018–2019

TABLE 5 Comparison of febrile neutropenia (FN) and non-FN patients during inpatient chemotherapy for urological cancer

	FN	Non-FN		FN	Non-FN		FN	Non-FN
Patient characteristics	***n* (%)**	***n* (%)**	**Tumor characteristics**	***n* (%)**	***n* (%)**	**Treatment characteristics**	***n* (%)**	***n* (%)**
Total, *n*	21	572	Total, *n*	21	572	Total, *n*	21	572
Gender			Type of cancer			First-line chemotherapy for primary cancer	11 (52)	380 (66)
Male	19 (90)	412 (72)	Urinary tract cancer	9 (43)	448 (78)	First course of current treatment	17 (81)	249 (44)
Female	2 (10)	160 (28)	Prostate cancer	7 (33)	77 (13)	First course of total treatment	10 (48)	173 (30)
Age, years			Germ cell tumor	4 (19)	26 (5)	Dose reduction	7 (33)	268 (47)
Median (range)	66 (18–83)	71 (19–86)	Others	1 (5)	21 (4)	Regimen		
≥65	11 (52)	422 (74)	Type of histology			GC	3	231
ECOG-PS			Urothelial carcinoma	8 (38)	424 (74)	GCarbo	3	102
0–1	20 (95)	544 (95)	Adenocarcinoma (of the prostate)	7 (33)	70 (12)	MVAC	0	4
≥ 2	1 (5)	28 (5)	Derived from germ cell	4 (19)	26 (5)	TC	1	57
Obesity	2 (10)	140 (24)	Small cell carcinoma	2 (10)	32 (6)	GN	1	33
Diabetes mellitus	5 (24)	78 (14)	Others	0	20 (3)	DTX	3	33
Hypertension	6 (29)	252 (44)	Lymph node metastasis	17 (81)	346 (60)	CBZ	3	13
HIV infection	0 (0)	0 (0)	Distant metastasis	15 (71)	292 (51)	EP	2	47
Malnutrition	13 (62)	158 (28)	Bone metastasis	11 (52)	145 (25)	BEP	3	15
Renal dysfunction	6 (29)	186 (33)	Lung metastasis	6 (29)	158 (28)	TIP	0	1
Liver dysfunction	0 (0)	1 (0.2)	Visceral metastasis	12 (57)	212 (37)	VeIP	1	5
Cardiovascular disease	3 (14)	128 (22)				Carboplatin monotherapy	0	5
Hematological disease	1 (5)	23 (4)				CE	1	3
COPD	1 (5)	35 (6)						
Past history of FN	4 (19)	12 (2)						
Neutropenia at treatment	3 (14)	60 (10)						
History of surgery (within the last 3 months)	4 (19)	116 (20)						
History of radiotherapy	7 (33)	128 (22)						
Use of CVC	8 (38)	174 (30)						
Administration of G-CSF	7 (33)	70 (12)						
Administration of steroids	8 (38)	73 (13)						
Administration of immunosuppressive agents	0 (0)	0 (0)						
Administration of antimicrobial agents	2 (10)	2 (0.3)						

Abbreviations: BEP, bleomycin, etoposide, and cisplatin; CBZ, cabazitaxel; CE, carboplatin plus etoposide; COPD, chronic obstructive pulmonary disease; CVC, central venous catheter; DTX, docetaxel; EP, etoposide plus cisplatin; GC, gemcitabine plus cisplatin; GCarbo, gemcitabine plus carboplatin; G-CSF, granulocyte-colony stimulating factors; GN, gemcitabine plus nedaplatin; MVAC, methotrexate, vinblastine, doxorubicin, and cisplatin; PS, performance status; TC, paclitaxel plus carboplatin; TIP, paclitaxel, ifosfamide, and cisplatin; VeIP, vinblastine, ifosfamide, and cisplatin.

TABLE 6 Statistical analysis of the risk factors for febrile neutropenia (FN) during inpatient chemotherapy for urological cancer

	Univariate analysis		Multivariate analysis	
	OR (95% CI)	*p* value	OR (95% CI)	*p* value
COVID-19 era	0.054 (0.007–0.405)	0.005	0.041 (0.005–0.375)	0.005
Gender	3.689 (0.850–16.020)	0.081	NA	NA
Age	0.391 (0.163–0.939)	0.036	0.583 (0.200–1.695)	0.321
ECOG-PS	0.971 (0.126–7.501)	0.978	NA	NA
Obesity	0.325(0.075–1.412)	0.134	NA	NA
Diabetes mellitus	1.979 (0.705–5.556)	0.195	NA	NA
Hypertension	0.508 (0.194–1.328)	0.167	NA	NA
Malnutrition	4.258 (1.732–10.469)	0.002	3.113 (1.101–8.805)	0.032
Renal dysfunction	0.828 (0.316–2.168)	0.701	NA	NA
Cardiovascular disease	0.578 (0.168–1.994)	0.386	NA	NA
Hematological disease	1.142 (0.147–8.864)	0.899	NA	NA
COPD	0.767 (0.100–5.884)	0.799	NA	NA
History of FN	10.980 (3.209–37.573)	<0.001	11.030 (1.516–80.233)	0.018
History of treatment	1.422 (0.407–4.970)	0.581	NA	NA
History of surgery (within the last 3 months)	0.925 (0.305–2.801)	0.890	NA	NA
History of radiotherapy	2.148 (0.847–5.451)	0.108	NA	NA
Use of CVC	1.408 (0.573–3.457)	0.456	NA	NA
Administration of G-CSF	3.586 (1.399–9.190)	0.008	2.633 (0.661–10.484)	0.170
Administration of steroids	4.207 (1.686–10.496)	0.002	2.425 (0.527–11.160)	0.255
Administration of immunosuppressive agents	30.000 (4.009–224.472)	0.001	24.308 (0.997–592.509)	0.050
Lymph node metastasis	2.037 (0.752–5.521)	0.162	NA	NA
Distant metastasis	1.918 (0.763–4.822)	0.166	NA	NA
Bone metastasis	2.677 (1.114–6.434)	0.028	0.671 (0.166–2.711)	0.576
First line	0.556 (0.232–1.332)	0.188	NA	NA
First course	5.513 (1.832–16.590)	0.002	8.532 (1.937–37.574)	0.005
First course of total treatment	2.097 (0.874–5.028)	0.097	NA	NA
Dose reduction	0.567 (0.226–1.426)	0.228	NA	NA

Abbreviations: CI, confidence interval; COPD, chronic obstructive pulmonary disease; CVC, central venous catheter; G-CSF, granulocyte-colony stimulating factors; NA, not included in analysis; OR, odds ratio; PS, performance status.

did not receive dose-reduced chemotherapy, FN occurred in 13/189 cases in the 2018–2019 group and in 1/129 cases in the 2020 group. As the univariate analysis in Table 6 shows, the absence of dose reduction is not necessarily due to the increase in FN number.

The attending physicians managed FN cases, and they did not always undertake various tests such as cultures of certain specimens. If these tests had been carried out thoroughly, the number of FN cases diagnosed as FUO could have been decreased.

We used binomial logistic regression analysis as the statistical method, but the number of FN events was too small for multivariate analysis, thereby resulting in overfitting, which reduced the reliability of the data. However, the non-COVID-19 era as a risk factor had a *p* value of 0.005, indicating a strong correlation. Furthermore, it is unlikely that this confounded with other risk factors, such as neutrophil count and the use of G-CSF. To confirm our findings, further analysis that accumulates more cases are warranted in the future.

We considered the environmental changes before and after the COVID-19 pandemic to be the differences in infection prevention measures, but we could not quantify these changes. Thus, a prospective study stratified by the presence or absence of infection prevention measures is needed.

This is the first report in the world describing the incidence of FN decreased during the COVID-19 pandemic. Although more cases need to be analyzed in detail, our findings suggest that strict infection prevention measures reduces the incidence of bacterial infections in inpatient chemotherapy.

TABLE 7 Details of patients diagnosed with febrile neutropenia (FN) during inpatient chemotherapy for urological cancer

	FN
	n (% or range)
Total, *n*	21
Origin of the fever	
Identified	8 (38)
Unknown	13 (62)
Blood culture	
Performed	19 (90)
Positive	5 (24)
Undetected	14 (67)
Sputum culture	
Performed	8 (38)
Positive	1 (5)
Undetected	7 (33)
Urine culture	
Performed	11 (52)
Positive	5 (24)
Undetected	6 (29)
MASCC score	
Median score	21 (10–24)
High risk	6 (29)
Others	15 (71)
Median time from chemotherapy treatment to FN onset (days)	11 (7–21)
Median duration of antimicrobial drug treatment (days)	6 (3–13)
Median time to fever resolution (days)	3 (2–8)

Abbreviation: MASCC, Multinational Association of Supportive Care in Cancer.

ACKNOWLEDGMENTS

We would like to thank Enago for the English language editing.

DISCLOSURE

The authors have no conflict of interest.

APPROVAL OF THE RESEARCH PROTOCOL BY AN INSTITUTIONAL REVIEWER BOARD

The ethics committee of Kanazawa University Graduate School of Medical Science approved this study (Approved No. 113772-1).-Informed Consent: Patients' consents were waived because the analysis was a retrospective origin and used anonymous clinical data that were obtained after each patient agreed to treatment by written consent. And also, we applied Opt-out method to obtain consent on this study. The poster used in the opt-out method were approved by the Institutional Review Board.

ORCID

Ren Toriumi https://orcid.org/0000-0002-6951-8524
Suguru Kadomoto https://orcid.org/0000-0003-4136-8998
Hiroaki Iwamoto https://orcid.org/0000-0003-3599-2217
Shohei Kawaguchi https://orcid.org/0000-0001-6847-9861
Kouji Izumi https://orcid.org/0000-0002-8480-9100

REFERENCES

1. Rundle CW, Presley CL, Militello M, et al. Hand hygiene during COVID-19: recommendations from the American contact dermatitis society. *J Am Acad Dermatol*. 2020;83:1730-1737. doi:10.1016/j.jaad.2020.07.057
2. YouGov, COVID-19 behaviour changes tracker: Wearing a face mask when in public places Web site. Available at: https://yougov.co.uk/topics/international/articles-reports/2020/03/17/personal-measures-taken-avoid-covid-19. Accessed December 17, 2021.
3. Ministry of Health, Labour and Welfare, the incidence of Influenza virus infection Web site (in Japanese). Available at: https://www.mhlw.go.jp/stf/seisakunitsuite/bunya/kenkou_iryou/kenkou/kekkaku-kansenshou01/houdou.htm. Accessed December 17, 2021.
4. Sawakami T, Karako K, Song P. Behavioral changes adopted to constrain COVID-19 in Japan: what are the implications for seasonal influenza prevention and control? *Glob Health Med*. 2021;3:125-128. doi:10.35772/ghm.2021.01066
5. Sakamoto H, Ishikane M, Ueda P. Seasonal influenza activity during the SARS-CoV-2 outbreak in Japan. *JAMA*. 2020;323:1969-1971. doi:10.1001/jama.2020.6173
6. Liang W, Guan W, Chen R, et al. Cancer patients in SARS-CoV-2 infection: a nationwide analysis in China. *Lancet Oncol*. 2020;21:335-337. doi:10.1016/S1470-2045(20)30096-6
7. Bennet CL, Djulbegovic B, Norris LB, et al. Colony-stimulating factors for febrile neutropenia during cancer therapy. *N Engl J Med*. 2013;368:1131-1139. doi:10.1056/NEJMct1210890
8. Culakova E, Thota R, Poniewierski MS, et al. Patterns of chemotherapy-associated toxicity and supportive care in US oncology practice: a nationwide prospective cohort study. *Cancer Med*. 2014;3:434-444. doi:10.1002/cam4.200
9. Kuderer NM, Dale DC, Crawford J, Cosler LE, Lyman GH. Mortality, morbidity, and cost associated with febrile neutropenia in adult cancer patients. *Cancer*. 2006;106:2258-2266. doi:10.1002/cncr.21847
10. Tamura K, Matsuoka H, Tsukada J, et al. Cefepime or carbapenem treatment for febrile neutropenia as a single agent is as effective as a combination of 4th-generation cephalosporin + aminoglycosides: comparative study. *Am J Hematol*. 2002;71:248-255. doi:10.1002/ajh.10236
11. Tamura K, Imajo K, Akiyama N, et al. Randomized trial of cefepime monotherapy or cefepime in combination with amikacin as empirical therapy for febrile neutropenia. *Clin Infect Dis*. 2004;39(suppl 1):S15-S24. doi:10.1086/383046
12. Freifeld AG, Bow EJ, Sepkowitz KA, et al. Clinical practice guideline for the use of antimicrobial agents in neutropenic patients with cancer: 2010 update by the Infectious Diseases Society of America. *Clin Infect Dis*. 2011;52:427-431. doi:10.1093/cid/ciq147
13. Crawford J, Becker PS, Armitage JO, et al. Myeloid growth factors, version 2.2017, NCCN clinical practice guidelines in oncology. *J Natl Compr Canc Netw*. 2017;15:1520-1541. doi:10.6004/jnccn.2017.0175
14. Aapro MS, Bohlius J, Cameron DA, et al. 2010 update of EORTC guidelines for the use of granulocyte-colony stimulating factor to reduce the incidence of chemotherapy-induced febrile neutropenia in adult patients with lymphoproliferative disorders and solid tumours. *Eur J Cancer*. 2011;47:8-32. doi:10.1016/j.ejca.2010.10.013
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;33:3199-3212. doi:10.1200/JCO.2015.62.3488

16. Klastersky J, Paesmans M, Rubenstein EB, 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;18:3038-3051. doi:10.1200/JCO.2000.18.16.3038
17. American Society of Clinical Oncology. Cancer Treatment & Supportive Care Web site. Available at: https://www.asco.org/covid-resources/patient-care-info/cancer-treatment-supportive-care. Accessed May 25, 2022
18. Curigliano G, Banerjee S, Cervantes A, et al. Managing cancer patients during the COVID-19 pandemic: an ESMO multidisciplinary expert consensus. *Ann Oncol*. 2020;31:1320-1335. PMID: 32745693. doi:10.1016/j.annonc.2020.07.010
19. Tomblyn M, Chiller T, Einsele H, et al. Guidelines for preventing infectious complications among hematopoietic cell transplantation recipients: a global perspective. *Biol Blood Marrow Transplant*. 2009;15:1143-1238. doi:10.1016/j.bbmt.2009.06.019
20. Siegel JD, Rhinehart E, Jackson M, Chiarello L, Health Care Infection Control Practices Advisory Committee. 2007 guideline for isolation precautions: preventing transmission of infectious agents in health care settings. *Am J Infect Control*. 2007;35:S65-S164. doi:10.1016/j.ajic.2007.10.007
21. Sehulster L, Chinn RYW. Guidelines for environmental infection control in health-care facilities. Recommendations of CDC and the healthcare infection control practices advisory committee (HICPAC). *MMWR Recomm Rep*. 2003;52:1-42.
22. Stoll P, Silla LM, Cola CM, et al. Effectiveness of a protective environment implementation for cancer patients with chemotherapy-induced neutropenia on fever and mortality incidence. *Am J Infect Control*. 2013;41:357-359. doi:10.1016/j.ajic.2012.05.018

SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

How to cite this article: Toriumi R, Yaegashi H, Kadomoto S, et al. Decreased febrile neutropenia during inpatient chemotherapy for urologic cancer during coronavirus disease 2019 pandemic. *Cancer Sci*. 2023;114:201-210. doi: 10.1111/cas.15490