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ORIGINAL ARTICLE

Effectiveness and safety of the pre-prescription of garenoxacin in comparison to moxifloxacin for low-risk febrile neutropenia in breast cancer patients undergoing adjuvant and neoadjuvant chemotherapy

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Abstract

Purpose The purpose of this study was to compare the efficacy of the pre-prescription of garenoxacin mesylate hydrate (GRNX) with that of moxifloxacin hydrochloride (MFLX) in the management of breast cancer patients with low-risk febrile neutropenia.

Methods Data from female patients who had been instructed to take previously prescribed oral GRNX or MFLX for 3 days during adjuvant and neoadjuvant chemotherapy if their body temperature exceeded 38 °C were analyzed. This study compared the effectiveness between these fluoroquinolones using a propensity score matching analysis.

Results The 330 patients received 1192 administrations of chemotherapy between May 2007 and April 2014 and 136 (41.2%) patients had a total of 212 (17.8%) febrile episodes. The frequencies of febrile episodes were 19.5% (113/579) and 16.2% (99/613) in the GRNX and MFLX groups, respectively. After propensity score matching, 384 episodes were matched in each group. Febrile events occurred in 80 and 56 cases in the GRNX and MFLX groups, respectively. Treatment success was identified in 80.0% (64/80) of cases in the GRNX group and 64.3% (36/56) of cases in the MFLX group ($P = 0.0494$). Additionally, the therapeutic use of granulocyte-colony stimulating factor was 6.3% (5/80) of cases in the GRNX group and 17.9% (10/56) of cases in the MFLX group ($P = 0.0498$). There were few differences in the frequency of adverse effects between the two groups.

Conclusions These results indicate that the pre-prescription of GRNX may be a more effective option for the management of low-risk febrile neutropenia during adjuvant and neoadjuvant chemotherapy for breast cancer.

Keywords Pre-prescription · Garenoxacin · Moxifloxacin · Low-risk febrile neutropenia · Breast cancer · Adjuvant chemotherapy

Introduction

Febrile neutropenia is a potentially life-threatening complication of chemotherapy requiring the intravenous administration of antibiotics in the hospital [1]. However, low-risk patients can be managed at home with oral ciprofloxacin plus amoxicillin/clavulanic acid or oral moxifloxacin hydrochloride (MFLX) [2].

As outpatients undergoing adjuvant and neoadjuvant chemotherapy for breast cancer have controlled cancer and good performance status, they are likely to be classified as low-risk patients, if they have been diagnosed with febrile neutropenia [3]. Therefore, they are often instructed to take the medications which were previously prescribed for empirical use when they have a febrile episode in Japan. Recently, it was reported that the pre-prescription of oral antibiotics (oral ciprofloxacin plus amoxicillin/clavulanic acid or levofloxacin) without any initial assessment was a safe and convenient strategy [3].

However, oral ciprofloxacin 200 mg three times daily plus amoxicillin/clavulanic acid 250/125 mg three or four times daily were approved in Japan and were considerably lower than the recommended dose for the initial treatment of low-risk febrile neutropenia [2, 4]. Conversely, levofloxacin 500 mg once daily likely has inadequate activity against

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Pseudomonas aeruginosa and insufficient evidence as an empirical treatment [1, 2]. Levofloxacin 750 mg once daily may be sufficient but is not an approved dose in Japan. Therefore, a study was developed to focus on oral MFLX, which is shown to be equivalent to oral ciprofloxacin plus amoxicillin/clavulanic acid as an empirical treatment in patients with low-risk febrile neutropenia [5]. Besides, oral MFLX 400 mg once daily is approved in Japan and may decrease medication nonadherence compared to the combination therapy. A previously published study by the authors showed that the pre-prescription of oral MFLX might be an effective option for the management of low-risk febrile neutropenia in outpatients by reducing the number of hospital visits required [6]. However, the European Medicines Agency reported not only several adverse effects associated with oral MFLX, such as diarrhea, heart failure, skin toxicity, and lethal liver disorder but also death in eight patients [7]. In fact, the previous study reported that one patient receiving MFLX died due to etiologically unexplained cardiopulmonary arrest [5]. Since adjuvant and neoadjuvant chemotherapy regimens for breast cancer occasionally cause cardiotoxicity and hepatotoxicity [8, 9], it is possible that concurrent use of MFLX might increase the toxicity but this was not clarified due to a lack of sufficient cases and the difference in the target disease.

Garenoxacin mesylate hydrate (GRNX) is an oral desfluoro (6) quinolone that has been investigated in Japan and has a similar antibacterial spectrum as MFLX [10]. Although no clinical studies have been conducted to investigate whether GRNX has the same efficacy as initial empiric therapy for febrile neutropenia, GRNX may be effective for patients with low-risk febrile neutropenia. Additionally, the adverse effects of GRNX are less than or equal to those of other quinolones [11]. On the basis of these properties, GRNX could become the first-line agent for low-risk febrile neutropenia on behalf of oral ciprofloxacin plus amoxicillin/clavulanic acid, levofloxacin, and MFLX worldwide. Thus, it was also considered that a pre-prescription of GRNX might be more efficacious for low-risk febrile neutropenia.

This study analyzed the effectiveness of the pre-prescription of GRNX compared to the result of a previously published study by the authors, which showed that the pre-prescription of MFLX can be used to manage low-risk febrile neutropenia during adjuvant and neoadjuvant chemotherapy for breast cancer without hospital visits.

Methods

Study design and participants

This study was designed to compare the efficacy of the pre-prescription of GRNX with the result of the previously published study by the authors, regarding the effective management of low-risk febrile neutropenia using the pre-prescription of MFLX. The CONSORT diagram is shown in Fig. 1. This study performed a retrospective cohort analysis of consecutive female patients aged 18 years and older who had received adjuvant and neoadjuvant chemotherapy between May 2007 and April 2014 at Osaka City University Hospital (Osaka, Japan). The patients enrolled in this study received the following chemotherapy regimens: 5-fluorouracil 500 mg/m^2, epirubicin 100 mg/m^2, and cyclophosphamide 500 mg/m^2 every 3 weeks (FEC100); adriamycin 60 mg/m^2 and cyclophosphamide 600 mg/m^2 every 3 weeks (AC); and docetaxel 75 mg/m^2 and cyclophosphamide 600 mg/m^2 every 3 weeks (TC). Additionally, the patients enrolled in this study had been previously prescribed oral GRNX (400 mg once daily) or oral MFLX (400 mg once daily) for 3 days. All patients were instructed to take the antibiotics if their body temperature exceeded 38 °C and to visit the hospital if febrile episodes continued after 3 days of antibiotics. The patients who were administered chemotherapy in the hospital were excluded. The patients who had already been treated with any antibiotics or who were hospitalized before febrile episodes were also excluded. Additional exclusion criteria included receiving prophylactic granulocyte-colony stimulating factor (G-CSF) and loss to follow-up during the clinical course after chemotherapy administration for any reason (including death).

Data collection for efficacy and safety assessments

The following data were collected from the patients' medical records: age, body surface area (BSA), body mass index (BMI), previous use of other anti-cancer agents, timing of chemotherapy (adjuvant or neoadjuvant), administration cycles, chemotherapy regimen, laboratory data, clinical course, febrile episodes within 3 weeks, prescribed antibiotics, visits due to febrile episodes, response to treatment, therapeutic use of G-CSF, hospitalization due to febrile neutropenia, and adverse effects of antibiotics.

Outcome measures

A febrile episode was defined as a single self-measuring axillary temperature of greater than 38 °C or description of "fever" (not including "slight fever") in the medical record within 3 weeks of the start of chemotherapy. Treatment success was defined as an antipyretic effect that included recovering from a febrile episode without the provision of additional antibacterial antibiotics (including the same agents).

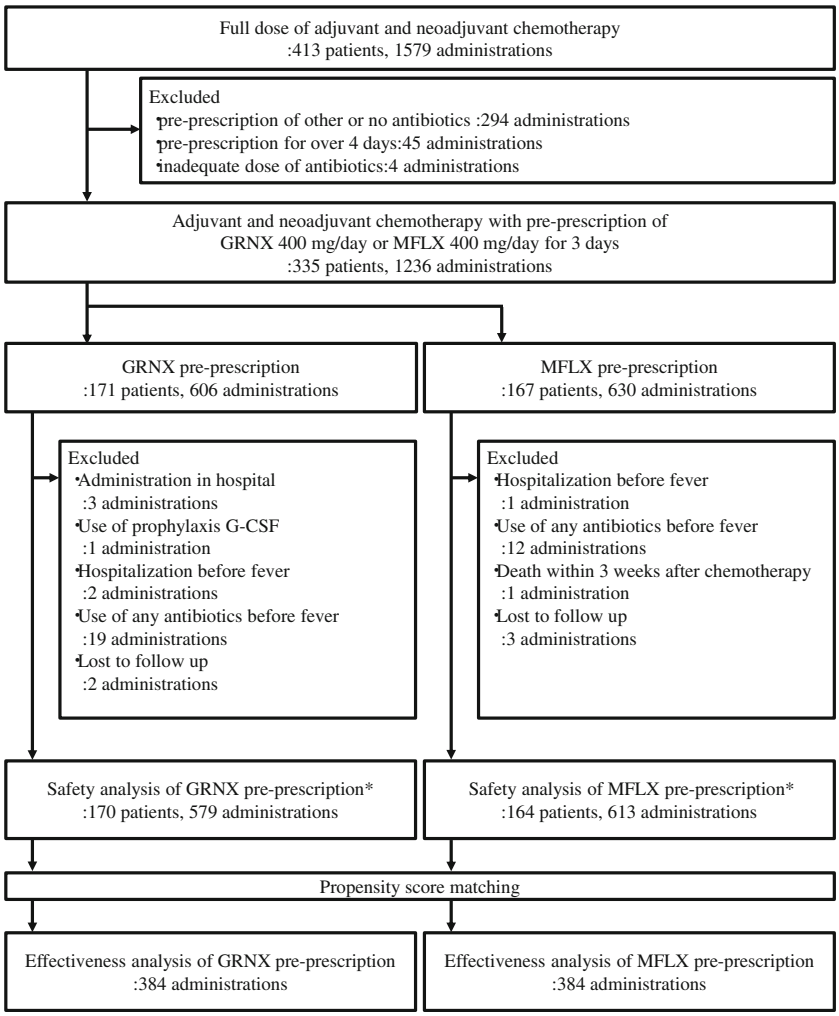

Fig. 1 Flow chart of participant recruitment for propensity score matching.
*Four patients were included in both GRNX and MFLX groups at the time of the safety analysis

Ethics

This study was approved by the institutional ethics committee (No. 3725).

Statistical analysis

The statistical analysis of categorical data was conducted using Fisher's exact or chi-squared tests for categorical data, while Mann-Whitney tests were used for the comparisons of continuous variables. The effects of selection bias and confounders were decreased by calculating the propensity score using a logistic regression analysis with 1:1 patient matching. The variables used in the propensity score analysis were age, BSA, BMI, previous treatment with other anti-cancer drugs, timing of chemotherapy, cycle number, chemotherapy regimen, neutrophil count, hemoglobin value, platelet count, serum albumin level, serum creatinine values, aspartate aminotransferase (AST) values, alanine aminotransferase (ALT) values, and total bilirubin. P values < 0.05 were considered statistically significant. All statistical analyses were conducted using IBM SPSS® Statistics 22.0 (SPSS Japan, Inc., Tokyo, Japan).

Results

Patients characteristics before propensity score matching analysis

Patients' characteristics before propensity score matching analysis are shown in Table 1. Adjuvant and neoadjuvant chemotherapy were administered 1579 times among 413 patients between May 2007 and April 2014. As 387 episodes met the exclusion criteria, this study included a total of 330 patients and 1192 episodes. Four patients received chemotherapies at different times due to recurrence and were duplicated in both the GRNX and MFLX groups. Thus, there were 170 patients in the GRNX group and 164 patients in the MFLX group, forming a total of 330 patients.

Table 1 Patients' characteristics before propensity score matching analysis

		GRNX	MFLX	*P* value
No. of patients		170	164	
No. of chemotherapies		579	613	
Age (years)	Median [25, 75%]	57 [46, 63]	57 [49, 63]	0.128
BSA (m^2)	Median [25, 75%]	1.54 [1.45, 1.60]	1.52 [1.45, 1.60]	0.253
BMI (kg/m^2)	Median [25, 75%]	21.8 [20.1, 24.7]	21.9 [20.2, 24.3]	0.726
Previous use of other anti-cancer agents	Yes No	58 (10.0%) 521 (90.0%)	7 (1.1%) 606 (98.9%)	< 0.001[a]
Timing of chemotherapy	Adjuvant Neoadjuvant	257 (44.4%) 322 (55.6%)	241 (39.3%) 372 (60.7%)	0.078[a]
Administration cycles	Median [25, 75%]	2 [1, 3]	3 [2, 4]	0.101
Chemotherapy regimen	FEC100 AC TC	359 (62.0%) 61 (10.5%) 159 (27.5%)	442 (72.1%) 65 (10.6%) 106 (17.3%)	< 0.001[b]
Neutrophil count (/μL)	Median [25, 75%]	3398 [2587, 4606]	3092 [2182, 4284]	< 0.001
Hemoglobin value (g/dL)	Median [25, 75%]	12.1 [11.3, 13.0]	12.1 [11.2, 12.9]	0.832
Platelet count ($\times 10^4$/μL)	Median [25, 75%]	26.9 [22.9, 32.1]	27.7 [22.6, 33.9]	0.161
Serum albumin level (g/dL)	Median [25, 75%]	4.2 [3.9, 4.4]	4.0 [3.8, 4.2]	< 0.001
Serum creatinine values (mg/dL)	Median [25, 75%]	0.58 [0.51, 0.64]	0.58 [0.52, 0.65]	0.192
AST values (IU/L)	Median [25, 75%]	18 [14, 24]	18 [13, 24]	0.863
ALT values (IU/L)	Median [25, 75%]	18 [14, 23]	19 [16, 24]	0.001
Total bilirubin (mg/dL)	Median [25, 75%]	0.30 [0.20, 0.40]	0.40 [0.30, 0.50]	< 0.001

a: Fisher's exact test; b: chi-squared test; other: Mann-Whitney *U* test

Frequency of febrile patients and episodes before propensity score matching analysis

The frequency of febrile episodes by chemotherapy regimens provided before propensity score matching analysis is summarized in Table 2. As seven patients received two chemotherapy regimens due to recurrence and adverse effects, 330 patients in total were enrolled. Among the 330 patients receiving 1192 chemotherapy administrations, 136 (41.2%) patients had a total of 212 (17.8%) febrile episodes before propensity score matching analysis. Overall, 44.7% (76/170) and 37.2% (61/164) of these febrile patients were in the GRNX and MFLX groups, respectively. The frequencies of febrile episodes were 19.5% (113/579) and 16.2% (99/613) in the

Table 2 Frequency of febrile episodes by chemotherapy regimens provided before propensity score matching analysis

(a) By patient				
Chemotherapy regimen		FEC100	AC	TC
No. of patients*		227	38	72
Median age [25, 75%]		54 [45, 61]	60 [52, 68]	60 [51, 67]
Febrile episodes, *n* (%)	Yes	92 (40.5%)	14 (36.8%)	30 (41.7%)
	No	135 (59.5%)	24 (63.2%)	42 (58.3%)
Visits due to febrile episodes, *n* (%)	Yes	39 (17.2%)	5 (13.2%)	11 (15.3%)
	No	188 (82.8%)	33 (86.8%)	61 (84.7%)
(b) By course				
Chemotherapy regimen		FEC100	AC	TC
No. of administrations		801	126	265
Median age [25, 75%]		54 [46, 60]	58 [50, 66]	60 [51, 69]
Febrile episodes, *n* (%)	Yes	144 (18.0%)	18 (14.3%)	50 (18.9%)
	No	657 (82.0%)	108 (85.7%)	215 (81.1%)
Visits due to febrile episodes, *n* (%)	Yes	48 (6.0%)	6 (4.8%)	19 (7.2%)
	No	753 (94.0%)	120 (95.2%)	246 (92.8%)

*Seven patients received two chemotherapy regimens and were included in both groups

GRNX and MFLX groups, respectively. Febrile episodes occupied in 40.5%, 36.8%, and 41.7% of the patients and in 18.0%, 14.3%, and 18.9% of the administrations by FEC100, AC, and TC regimens, respectively. Visits due to febrile episodes accounted for 17.2%, 13.2%, and 15.3% of the patients and 6.0%, 4.8%, and 7.2% of the administrations by FEC100, AC, and TC regimens, respectively.

Characteristics after propensity score matching analysis

Table 3 presents the characteristics after propensity score matching analysis. This study matched 384 episodes in each group using the propensity score matching analysis. Most of the differences in patient characteristics were no longer present. The value for total bilirubin was significantly lower in the GRNX group than MFLX group; however, the difference was very slight (median 0.30 mg/dL vs 0.40 mg/dL).

Outcome of febrile patients and episodes after propensity score matching analysis

Table 4 shows the outcomes of febrile patients by episodes for both groups after propensity score matching. There were 80 and 56 febrile episodes in the GRNX and MFLX groups, respectively. The frequency of visits due to febrile episodes did not significantly differ between the GRNX and MFLX groups (19/80 episodes [23.8%] vs 21/56 episodes [37.5%], $P = 0.090$). The frequency of treatment success was significantly higher in the GRNX group than the MFLX group (64/80 episodes [80.0%] vs 36/56 episodes [64.3%], $P = 0.0494$). Therapeutic use of G-CSF in the GRNX group was significantly infrequent compared with the MFLX group (5/80 episodes [6.3%] vs 10/56 episodes [17.9%], $P = 0.0498$). Finally, the rate of hospitalization due to low-risk febrile neutropenia did not significantly differ between the GRNX and MFLX groups (6/80 episodes [7.5%] vs 8/56 episodes [14.3%], $P = 0.255$).

Safety

Antimicrobial drugs were changed or stopped in two of the patients in the GRNX group due to skin rash and one of the patients in the MFLX group due to dizziness. There was no significant difference in discontinuation due to adverse effects between the GRNX and MFLX groups (2/113 episodes [1.8%] vs 1/99 episodes [1.0%], $P = 1$, Fisher's exact test). One patient in the MFLX group was lost to follow-up during the clinical course because of unexpected death within 3 weeks after the administration of chemotherapy and was therefore excluded from analysis.

Table 3 Patients' characteristics after propensity score matching analysis

		GRNX	MFLX	*P* value
No. of chemotherapies		384	384	
Age (years)	Median [25, 75%]	57 [47, 63]	56 [48, 63]	0.952
BSA (m^2)	Median [25, 75%]	1.54 [1.44, 1.60]	1.53 [1.47, 1.60]	0.913
BMI (kg/m^2)	Median [25, 75%]	21.5 [20.2, 24.9]	22.1 [20.5, 24.7]	0.271
Previous use of other anti-cancer agents	Yes No	7 (1.8%) 377 (98.2%)	7 (1.8%) 377 (98.2%)	1[a]
Timing of chemotherapy	Adjuvant Neoadjuvant	174 (45.3%) 210 (54.7%)	167 (43.5%) 217 (56.5%)	0.663[a]
Administration cycles	Median [25, 75%]	2 [1, 3]	2 [1, 3]	0.823
Chemotherapy regimen	FEC100 AC TC	253 (65.9%) 38 (9.9%) 93 (24.2%)	250 (65.1%) 49 (12.8%) 85 (22.1%)	0.413[b]
Neutrophil count (/μL)	Median [25, 75%]	3206 [2490, 4393]	3288 [2404, 4397]	0.942
Hemoglobin value (g/dL)	Median [25, 75%]	12.1 [11.3, 13.0]	12.2 [11.3, 12.9]	0.614
Platelet count ($\times 10^4/\mu L$)	Median [25, 75%]	26.8 [22.9, 32.8]	27.7 [22.4, 33.7]	0.427
Serum albumin level (g/dL)	Median [25, 75%]	4.1 [3.9, 4.3]	4.1 [3.9, 4.2]	0.144
Serum creatinine values (mg/dL)	Median [25, 75%]	0.58 [0.52, 0.64]	0.57 [0.51, 0.63]	0.439
AST values (IU/L)	Median [25, 75%]	18 [13, 24]	18 [13, 24]	0.587
ALT values (IU/L)	Median [25, 75%]	18 [14, 25]	19 [15, 24]	0.308
Total bilirubin (mg/dL)	Median [25, 75%]	0.30 [0.20, 0.50]	0.40 [0.30, 0.50]	0.001

a: Fisher's exact test; b:chi-squared test; other: Mann-Whitney *U* test

Table 4 Outcomes of febrile episodes after propensity score matching analysis

		GRNX	MFLX	*P* value
Visits due to febrile episodes	Yes	19 (23.8%)	21 (37.5%)	0.090
	No	61 (76.3%)	35 (62.5%)	
Treatment success	Yes	64 (80.0%)	36 (64.3%)	0.0494
	No	16 (20.0%)	20 (35.7%)	
Therapeutic use of G-CSF	Yes	5 (6.3%)	10 (17.9%)	0.0498
	No	75 (93.8%)	46 (82.1%)	
Hospitalization due to FN	Yes	6 (7.5%)	8 (14.3%)	0.255
	No	74 (92.5%)	48 (85.7%)	

all: Fisher's exact test

Discussion

Febrile neutropenia, which is a life-threatening complication of cancer chemotherapy, is relatively common in breast cancer patients [12]. Febrile neutropenia often causes dose reduction or a delay in the treatment schedule that may lead to impairing the survival benefit among patients with breast cancer [13, 14]. Thus, the appropriate management of febrile neutropenia is crucial, especially for breast cancer patients in the adjuvant setting [12]. Accordingly to the previous study, almost all of febrile patients during adjuvant and neoadjuvant chemotherapy for breast cancer would suffer low-risk febrile neutropenia and could be treated using oral antibiotics [3]. Additionally, early antibiotic administration is important in therapy for febrile neutropenia [15]. Therefore, the pre-prescription of quinolone antibiotics without initial assessment may be safe and convenient for febrile patients undergoing adjuvant and neoadjuvant chemotherapy for breast cancer [3, 6]. As GRNX is considered a better choice than MFLX due to its more favorable antibacterial activity and safety profile, this study investigated the efficacy and safety of GRNX without initial assessment, comparing it to those from a previously published study by the authors that investigated MFLX.

In this investigation, MFLX had a 64.3% treatment success rate in febrile patients. This was slightly lower than previously reported results that showed 72.9% and 80% treatment success rates [5, 16]. Regarding the treatment discontinuation rates due to MFLX intolerance or toxicity, our results were similar to those from previous studies, which reported that the ratio was 0% and 4% [5, 16]. Considering that the duration of treatment was 4 to 5 days in the previous reports, these results in the MFLX group were deemed to be valid and useful for comparisons with the GRNX group. As a result, this study demonstrated that the frequency of treatment success in the pre-prescription GRNX group was significantly higher than in the pre-prescription MFLX group. Additionally, the rate of the therapeutic use of G-CSF in the pre-prescription GRNX group was significantly lower than that in the pre-prescription MFLX group. There was no remarkable difference in the tolerability between patients treated with GRNX and MFLX. Therefore, the pre-prescription of GRNX was superior to MFLX for patients with low-risk febrile neutropenia during adjuvant and neoadjuvant chemotherapy for breast cancer.

Two explanations were considered to explain the differences between GRNX and MFLX. First, GRNX exhibits more potent activity against various bacterial species than MFLX. Previous studies have shown that GRNX has a higher free area under the curve/minimum inhibitory concentration than MFLX against many bacterial species [17, 18]. In particular, GRNX has more rapid bactericidal activity against *Bacteroides fragilis* strains and *Streptococcus pneumoniae*, including quinolone-resistant *S. pneumonia*, compared with MFLX [19, 20]. The second, GRNX is excreted mainly via renal routes and has an effective potential in the treatment of the urinary tract infections [21], which accounted for 5–15% of infections in a previous study of neutropenic patients [22]. Conversely, MFLX achieves considerably lower concentrations in the urine than other quinolones and is not recommend for urinary tract infections [23]. Although there was not a significant difference in the rate of visits due to febrile episodes, as this study was not powered to show this difference, there were trends suggestive of a decline.

The use of GRNX will allow for a reduction in the burden placed on the patient; they can save the time required for consultations, avoid additional blood test and X-rays, and save individual costs. Moreover, the provision of GRNX means an individual can start empiric therapy early and improve outcomes. This approach also assists in preventing dose reductions or delays in the treatment schedule.

This study was subject to several limitations. First, although this study performed propensity score matching analysis, there were still few differences, likely resulting from hidden confounders and biases due to the retrospective nature of the study. Second, the frequency of low-risk febrile neutropenia in this study was not clear due to the lack of an initial assessment. This study observed febrile events in 41.2% of patients; however certain patients may have had febrile episodes without neutropenia. Previous studies showed that the rate of patients with febrile neutropenia was 20.0% by FEC100 [9], 25.2% by AC [24], and 28.3% by TC [25]. Additionally, the median ages of participants from these past studies were approximately 5–10 years younger than in this study. In fact, these results were similar to those from a previous Japanese study which reported that 38.8% of patients had febrile neutropenia after FEC administration, all of whom had similar clinical and demographic characteristics [26]. In addition, the previous study mentioned that they were likely to be classified as low-risk patients when they developed febrile neutropenia [3]. In fact, almost all included febrile patients in this study satisfied the outpatient status and had solid tumors, no chronic obstructive pulmonary disease, were aged < 60 years. Therefore, they would be evaluated as having a

MASCC score≧ 21 and the majority of the febrile episodes in this study were likely to be low-risk febrile neutropenia. The prospective cohort study conducted by the Comprehensive Support Project for Oncological Research of Breast Cancer (UMIN 000017857) will resolve this issue. Third, some patients might not follow the instructions to take their previously prescribed oral antibiotics, despite their febrile status. However, this study could not determine antibiotic compliance due to the retrospective study design.

Finally, since MFLX had been mainly used before the first half of 2010 and GRNX has been used subsequently, progress in clinical practice during this period may have affected the findings from this study. However, it is reasonable to assume that these clinical advances were negligible, considering that there were minor differences in the Japanese guidelines for febrile neutropenia between 2004 and 2017 [27, 28]. A large-scale prospective study is necessary to confirm these results.

In conclusion, these results indicate that the pre-prescription of GRNX may be a superior alternative to MFLX for febrile patients with breast cancer undergoing adjuvant and neoadjuvant chemotherapy. This is the first study to show the possibility of GRNX as an empiric therapy for treating low-risk febrile neutropenia.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflicts of interest.

Research involving human participants and/or animals This study was approved by the Human Subjects Review Committee at Osaka City University (No. 3725).

Informed consent For this type of study, formal consent is not required.

Abbreviations in Figures and Tables GRNX, garenoxacin mesylate hydrate; MFLX, moxifloxacin hydrochloride; BSA, body surface area; BMI, body mass index; FEC100, 5-fluorouracil, epirubicin, cyclophosphamide; AC, adriamycin, cyclophosphamide; TC, docetaxel, cyclophosphamide; AST, aspartate aminotransferase; ALT, alanine aminotransferase; G-CSF, granulocyte-colony stimulating factor; FN, febrile neutropenia

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