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ORIGINAL ARTICLE

Febrile neutropenia and role of prophylactic granulocyte colony-stimulating factor in docetaxel and cyclophosphamide chemotherapy for breast cancer

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Abstract

Purpose Febrile neutropenia (FN) incidence during docetaxel and cyclophosphamide (TC) chemotherapy, known as a high-risk regimen, differs among countries. The role of prophylactic granulocyte colony-stimulating factor (G-CSF) in FN is unclear. This study aimed to investigate FN frequency and relative dose intensity (RDI) of TC chemotherapy in patients with breast cancer and identify the correct population requiring prophylactic G-CSF.

Methods In total, 205 patients with breast cancer were scheduled for TC chemotherapy (docetaxel/cyclophosphamide 75/600 mg/m^2, every 3 weeks, 4 cycles) as adjuvant chemotherapy. Trastuzumab (8 mg/kg; continued with 6 mg/kg) was administrated intravenously for human epidermal growth factor receptor 2 (HER2)-positive cancer. Fifty-five patients received primary prophylactic measures (G-CSF: 20 and antibiotics: 35). We investigated the frequency of FN and hospitalization, RDI, and the factors related to FN, adverse events, hospitalization, and RDI.

Results FN occurred in 70 patients (35.7%). FN incidence was noted in 41.1% without any prophylactic measures and in 5.0% with prophylactic G-CSF. In multivariate analysis, the independent risk factors of FN were older age (≥ 60 years, $P = 0.017$) and without primary prophylactic G-CSF ($P = 0.011$). Eleven patients (5.6%) were hospitalized of which 8 (72.7%) were elderly. The median RDIs of docetaxel and cyclophosphamide were 96.7% and 99.7%, respectively.

Conclusion FN frequency during TC chemotherapy was high, and primary prophylactic G-CSF reduced FN incidence. Primary prophylactic G-CSF is an effective therapy for preventing FN during TC chemotherapy. However, prophylactic G-CSF should be considered for elderly patients based on the low hospitalization rate and the high RDI.

Keywords Breast cancer · Primary prophylactic G-CSF · Febrile neutropenia · TC chemotherapy · Relative dose intensity · Hospitalization

Introduction

Docetaxel and cyclophosphamide (TC) chemotherapy improves disease-free and overall survival after breast cancer surgery when compared with doxorubicin and cyclophosphamide (AC) chemotherapy. It is also one of the standard regimens of adjuvant chemotherapy for breast cancer [1, 2]. The incidence of febrile neutropenia (FN) caused by TC chemotherapy varies widely in clinical studies (5% in a US Oncology Research trial [3] and 68.8% in a Japanese trial [4]). This difference might be due to race or clinical trial settings such as frequent temperature measurements and blood tests. In addition, Asian patients are known to show strong hematological toxicity [5].

FN is one of the major life-threatening adverse events in chemotherapy. A high FN incidence rate increases infection, leading to mortality. G-CSF has been shown efficacy of reduction FN by production of granulocytes and enhancement of neutrophil function [6]. Therefore, the American Society of Clinical Oncology (ASCO), the European Organisation for Research and Treatment of Cancer (EORTC), and the National Comprehensive Cancer Network (NCCN) guidelines

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recommend the administration of prophylactic granulocyte colony-stimulating factor (G-CSF) in high-risk FN (> 20%) treatment regimens [7–9]. In addition, the FN incidence might lead to a reduction in treatment intensity [10]. High relative dose intensity (RDI) of perioperative chemotherapy is reported to be important to improve prognosis [10, 11].

G-CSF causes adverse events associated with bone pain, fever, leukocytosis, and allergic reactions [12–14]. In addition, the use of G-CSF adds considerable cost to adjuvant chemotherapy of breast cancer [15]. Therefore, it is important to select breast cancer patients who would benefit from prophylactic G-CSF treatment for TC chemotherapy.

Therefore, we aimed to retrospectively investigate FN frequency, RDI, and the potential risk factors related to FN onset in Japanese patients receiving TC chemotherapy in the clinical setting.

Patients and methods

Patients

A total of 205 patients with breast cancer who received adjuvant TC chemotherapy between April 2009 and June 2017 at Hiroshima University Hospital were retrospectively reviewed. Nine patients who discontinued the therapy due to allergic reaction during initial treatment were excluded from FN and RDI assessment. We evaluated the frequency and risk factors of FN, adverse events, hospitalization, and RDI.

Treatment

Docetaxel (75 mg/m^2) and cyclophosphamide (600 mg/m^2) were intravenously administered at day 1 of each cycle to all 205 patients. Chemotherapy was repeated every 3 weeks for four cycles. TC therapy was reduced and delayed as needed according to the choice of the physician. Trastuzumab 8 mg/kg (continued with 6 mg/kg after two cycles) was administered intravenously to 15 patients (7.3%) with human epidermal growth factor receptor 2 (HER2)-positive cancer. FN was diagnosed when the patient developed fever (axillary temperature of over 37.5°) and had grade 3/4 neutropenia (< 1.0 × 10^9/L) or fever during the neutropenic period (days 5-14) [4]. Other adverse events were defined according to the Common Terminology Criteria for Adverse Events (CTCAE), version 4.0 [16].

Statistical analysis

Data are presented as numbers and percentages unless otherwise stated. Frequencies of FN and RDI were compared using Fisher's exact test for categorical variables. Logistic regression was used to predict FN incidence and low RDI. The cutoff for age was defined as 60 years based on the receiver operating characteristic curves. $P < 0.05$ was considered to indicate statistical significance in all comparisons. All data were statistically analyzed using EZR (Saitama Medical Center, Jichi Medical University, Saitama, Japan), which is a graphical user interface for R (The R Foundation for Statistical Computing, Vienna, Austria) [17].

Results

Patient and characteristics

The characteristics of all 205 patients are shown in Table 1. The median patient age was 53 years, and 78 patients (38.0%) were aged ≥ 60 years. Most patients had stage I (33.7%) or stage II (57.6%) disease at diagnosis. Fifty-five patients (26.8%) received primary prophylactic measures (G-CSF 9.7% (n = 20) and antibiotics 17.1% (n = 35)).

Frequency and risk factors for FN

The frequency of FN incidence was 35.7% (70/196) in all patients, 41.1% (58/141) in patients who did not receive primary prophylactic measures, 5.0% (1/20) in patients who

Table 1 Patients' characteristics

Characteristics	Number (%)
Age (years), median (range)	53 (27-84)
Stage	
I	69 (33.7)
II	118 (57.6)
III	13 (6.3)
Locoregional recurrence	5 (2.4)
Histology	
Invasive carcinoma of no special type	190 (92.7)
Invasive lobular carcinoma	11 (5.4)
Others	4 (1.9)
Nuclear grade	
1	16 (7.8)
2	57 (27.8)
3	128 (62.4)
Estrogen receptor positive	184 (89.8)
HER2 positive	15 (7.3)
Ki-67 labeling index (%), median (IQR)	36 (21-54)
Primary prophylactic measures	
G-CSF	20 (9.7)
Antibiotics	35 (17.1)

G-CSF granulocyte colony-stimulating factor; *HER2* human epidermal growth factor receptor 2; *IQR* interquartile range

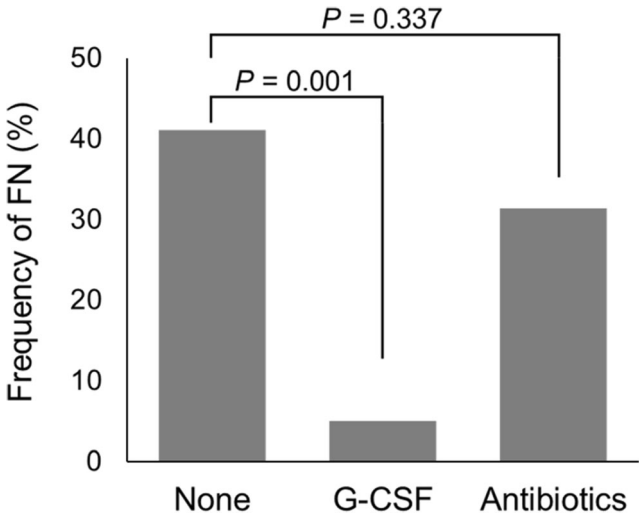

Fig. 1 Frequency of FN according to primary prophylactic measures. FN febrile neutropenia; G-CSF granulocyte colony-stimulating factor

received prophylactic G-CSF, and 31.4% (11/35) in patients who received prophylactic antibiotics. Prophylactic G-CSF significantly reduced the frequency of FN incidence (P = 0.001), whereas prophylactic antibiotics did not (P = 0.337) (Fig. 1).

From the multivariate analysis, we found that older age (≥ 60 years) and absence of primary prophylactic G-CSF administration were independent risk factors for FN (P = 0.017 and P = 0.011, respectively) (Table 2); however, hepatic dysfunction, renal dysfunction, and prophylactic antibiotics were not associated with FN incidence. Other adverse events are listed in Supplementary Table S1. No treatment-related death occurred.

Hospitalization

During TC chemotherapy, hospitalization was observed in 5.6% of the patients for the following reasons: 3 (1.5%) were diagnosed with FN, 3 (1.5%) had an infection, 3 (1.5%) had anorexia, and 2 (1.0%) were admitted for other reasons (Table 3). The frequency of overall hospitalization and neutropenia-related hospitalization was low.

Relative dose intensity and risk factors

Discontinuation of TC chemotherapy occurred in 20 patients (9.8%), delay in 23 (11.2%), and dose reduction in 41 (20.0%) (Supplementary Table S2). The major reason for discontinuation of the therapy was an allergic reaction and it occurred in 13 patients. Although there were no cases of discontinuation due to FN, it was the most common cause for delay (8 patients) and dose reduction (15 patients). The median RDIs of docetaxel and cyclophosphamide treatments were 96.7% and 99.7%, respectively (Fig. 2). There was no difference in RDIs regardless of the use of G-CSF (with G-CSF: 99.7% and 99.9%, and without G-CSF: 96.6% and 99.7%). Among patients with a low RDI (< 85%), there were 36 patients (18.4%) in the docetaxel treatment group and 20 (10.2%) in the cyclophosphamide treatment group.

Multivariate analysis revealed that older age (≥ 60 years) was an independent risk factor for a low RDI (odds ratio (OR) 5.16, 95% confidence interval (CI) 2.32-11.5, P = 0.001), whereas primary prophylactic measures were not (G-CSF: OR 0.39, 95% CI 0.08-1.92, P = 0.247 and antibiotics: OR 1.08, 95% CI 0.43-2.72, P = 0.862) (Supplementary Table S3). Hepatic dysfunction and renal dysfunction were also not associated with low RDI.

Discussion

This study demonstrated the high incidence rate of FN and the benefits of primary prophylactic G-CSF in breast cancer patients treated with TC chemotherapy in Japanese clinical practice. We also showed that a high frequency of FN does not always lead to an increased probability for hospitalization or reduction of RDI. Our findings support the importance of an adequate decision for prophylactic G-CSF administration, which should be based on the risk factors in the particular case, such as age.

Adjuvant chemotherapy is important for reducing recurrence and mortality in breast cancer patients. Although anthracycline- or taxane-based regimens are key treatments in breast cancer chemotherapy [18, 19], regimens excluding

Table 2 Predictive factors of febrile neutropenia incidence

Factors	Univariate analysis		Multivariate analysis	
	Odds ratio (95% CI)	P	Odds ratio (95% CI)	P
Age ≥ 60 years	5.16 (2.32-11.50)	< 0.001	2.19 (1.15-4.17)	0.017
Hepatic dysfunction	1.85 (0.40-8.62)	0.44	2.39 (0.56-10.10)	0.237
Renal dysfunction	0.28 (0.06-1.38)	0.12	0.82 (0.29-2.30)	0.708
Prophylactic G-CSF	0.39 (0.08-1.92)	0.25	0.07 (0.01-0.54)	0.011
Prophylactic antibiotics	1.08 (0.43-2.72)	0.86	0.59 (0.26-1.34)	0.206

CI confidence interval; *G-CSF* granulocyte colony-stimulating factor

Table 3 Frequency of hospitalization according to primary prophylactic measures

Prophylactic measures	Number (%)	*P*
Total (n = 196)	11 (5.6)	
None (n = 141)	3 (2.1)	
G-CSF (n = 20)	4 (20.0)	0.005
Antibiotics (n = 35)	4 (11.4)	0.030

G-CSF granulocyte colony-stimulating factor

anthracycline are being developed as it can cause severe adverse events such as cardiotoxicity and secondary malignancies [20]. TC chemotherapy has been reported to improve disease-free and overall survival compared to AC chemotherapy in the US Oncology Research trial 9735 [2]. Among the chemotherapy regimens used for breast cancer, TC chemotherapy is known to have a high risk for FN. The frequency of FN incidence related to TC chemotherapy was reported to be 68.5% in the Japanese trial [4] and 5% in the US Oncology Research trial [3], showing a significant difference in the results. Population-based studies have shown that the incidence of FN associated with TC chemotherapy was higher (20.9–38.0%) in patients who did not receive primary prophylactic G-CSF than in those who did receive G-CSF (4.2–8.1%) [21–23]. A systematic review has shown that the median FN rates with and without primary prophylaxis were 6.6% and 31.3%, respectively [24]. The present study showed that the frequency of FN in TC chemotherapy without any primary prophylactic measures was 41.1% and prophylactic G-CSF reduced the FN incidence by 36.1%. Asian patients who received TC chemotherapy have been reported to develop strong hematological toxicity, and an appropriate neutropenic management was needed [5]. The frequency of hospitalization in US patients treated with TC chemotherapy was reported to be 16.5% despite the use of prophylactic G-CSF in 62.1% of them [25]. In addition, patients older than 65 years had approximately twice the risk of hospitalization compared to patients below the age of 65 years [26]. The present study showed low frequency of hospitalization, with a hospitalization rate of 72.7% for older patients and no treatment-related mortality during TC chemotherapy.

Dose reduction was often performed as a measure against FN before pegfilgrastim had been approved in Japan in 2014. However, reducing RDI of adjuvant chemotherapy worsens the prognosis of breast cancer [11]. Therefore, avoiding discontinuation, treatment delays, and dose reduction is important for maintaining the treatment effect. Dose intensity of TC chemotherapy has been reported to be 99.8% in US Oncology Research trial [3]. A previous study has reported that prophylactic G-CSF prevented dose reduction in chemotherapy [25]. The present study showed a high RDI (docetaxel 96.7% and cyclophosphamide 99.7%) despite the high frequency of FN. Prophylactic G-CSF was not related to RDI. Therefore, primary prophylactic G-CSF is an effective therapy for preventing FN during TC chemotherapy.

G-CSF has some limitations. The most relevant and harmful adverse events of G-CSF are bone and musculoskeletal pain [12]. Among the patients who received chemotherapy with G-CSF for breast cancer, the prevalence of bone pain was reported to be 46.6% [27]. In addition, G-CSF has cost issue. In Japan, the cost of G-CSF is around $1000 per dose and approximately $4000 entire course of four cycles of TC chemotherapy. G-CSF administration in all chemotherapy cycles is associated with high costs; the cost effectiveness of this therapy should be considered [15]. Our findings support a selective use of prophylactic G-CSF in patients with breast cancer who received TC chemotherapy. We propose prophylactic G-CSF administration for elderly patients because older age was the only risk factor for both FN and low RDI.

The limitations of this study arose from its retrospective design. FN might have been overestimated because neutrophil count during fever was not taken owing to outpatient care in many cases. A prospective cohort study in Japan reported that

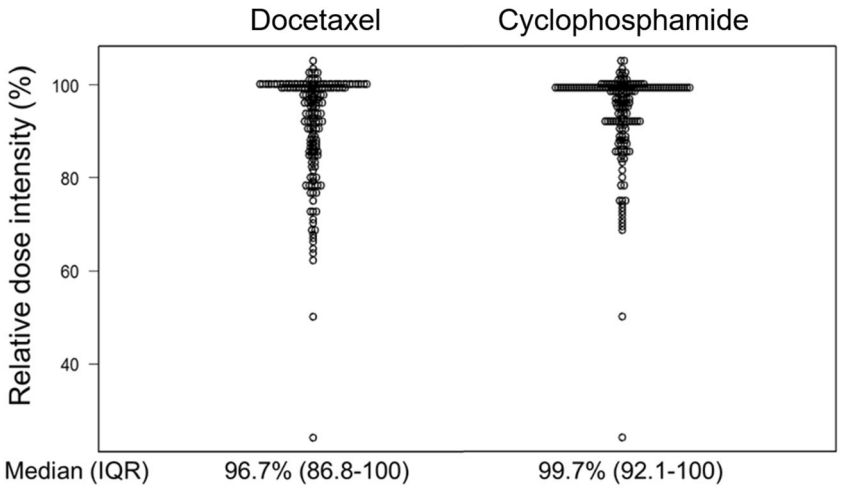

Fig. 2 Relative dose intensity of docetaxel and cyclophosphamide chemotherapy. IQR interquartile range

FN was surveyed based on two different definitions, namely, true FN: ≥ 37.5 °C and grade 4 neutropenia, and surrogate FN: ≥ 37.5 °C and oral antibiotic and antipyretic intake [28, 29]. This study showed that no differences were found in the incidence of FN in the two groups (36.6% and 31.5%, respectively). Hence, the definition of FN in this study is reasonable.

Conclusion

FN incidence in TC chemotherapy is high, and primary prophylactic G-CSF was effective in reducing FN events. TC chemotherapy was well-tolerated and administrated at the appropriate dosage in Japanese clinical practice. Primary prophylactic G-CSF should be applied selectively, such as in patients at an older age.

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Author contributions Yuri Kimura and Shinsuke Sasada contributed to the study conception and design. Yuri Kimura, Shinsuke Sasada, Akiko Emi, Norio Masumoto, and Takayuki Kadoya collected the clinical data. Yuri Kimura and Shinsuke Sasada analyzed the data and wrote the manuscript. All authors read and approved the final manuscript.

Data availability Not applicable.

Compliance with ethical standards

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

Ethics approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. The study was approved by the Bioethics Committee of the Medical University of Hiroshima (No. 1157).

Consent to participate For this type of study, formal patient consent was not required.

Consent for publication Not applicable.

Code availability Not applicable.

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