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Influence of Concomitant Polypharmacy on Docetaxel-induced Febrile Neutropenia

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Abstract. *Background/Aim: Docetaxel (DTX) is metabolized by liver cytochromes P450 (CYP) 3A4 (CYP3A4) and 3A5 (CYP3A5) CYP3A4 activity is considered the main factor affecting the effectiveness in DTX clearance. We, therefore, explored the association between DTX-induced febrile neutropenia (FN) and concomitant polypharmacy involving CYP3A4 inhibitors in cancer patients. Patients and Methods: Among patients who received docetaxel, we compared the number of concomitant medications between patients with and without FN, and risk factors associated with FN were identified. Results: The total number of concomitant CYP3A4 inhibitors and substrates used was significantly higher in patients with FN [mean: 2.1 (95% confidence interval (CI)=1.5-2.9)] than in those without FN [mean: 1.4 (95% CI=1.0-1.8)] (p=0.01). The only risk factor for FN was the use of ≥2 concomitant CYP3A4 inhibitors and substrates in total (OR=4.82, 95% CI=1.77-14.1; p=0.002). Conclusion: Polypharmacy involving CYP3A4 inhibitors and substrates increases the risk of DTX-induced FN.*

With developments in cancer treatment, the survival time of cancer patients is prolonging. Polypharmacy is regarded as a social problem because many cancer patients develop complications as survival time increases and are elderly (1). Polypharmacy is not just the use of multiple concomitant medications; it is characterized by comprehensive problems such as increased side-effects and drug–drug interactions caused by medications and decreased adherence to necessary medications (2). It has been identified as one of the domains commonly included in the Comprehensive Geriatric Assessment, likely because of its potential influence in oncology treatment outcomes (3). Adverse drug reactions caused by drug–drug interactions have been reported to account for 20-30% of all side-effects of drug therapy in cancer patients (4). In a previous study among hospitalized cancer patients, it was reported that the majority of patients were receiving at least eight medications on average and more than half of the drug interactions were classified as moderate-to-severe risk (5). Sokol *et al*. reported that elderly outpatients receiving chemotherapy received nine medications on average, which included at least three chemotherapeutic and/or supportive medications (mainly antiemetics), and identified several potential chemotherapy–drug interactions (6).

Docetaxel (DTX) is a widely used chemotherapeutic agent for patients with several solid tumors (7), including breast, non-small cell lung, ovarian, gastric, esophageal, and prostate cancer; however, neutropenia is a factor of dose-limiting toxicity. In particular, febrile neutropenia (FN) is a life-threatening complication of cancer chemotherapy (8, 9). DTX clearance and the area under the curve (AUC) for DTX were associated with the risk of FN development (10, 11). The drug is metabolized by liver cytochromes P450 (CYP) 3A4 and 3A5 (12, 13). CYP3A4 activity is considered the main factor underlying interpatient variability in DTX clearance (14-16). Moreover, coadministration of ketoconazole, a strong and specific CYP3A4 inhibitor (17, 18), has been reported to cause a 40-50% decrease in the clearance of DTX (19-21). Rudek *et al*. reported that concomitant administration of the CYP3A4 inhibitors ritonavir and ketoconazole in mice resulted in a 6.9- and 3.1-fold increase in the AUC of DTX, respectively (22). However, to our knowledge, no study has explored the risk of DTX-induced toxicity in cases in which multiple moderate-to-weak inhibitor drugs of CYP3A4 and/or substrates of CYP3A4 are concomitantly used. Therefore, in this study, we explored the association between DTX-induced FN development and concomitant polypharmacy involving CYP3A4 inhibitors or substrates in cancer patients.

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Key Words: Polypharmacy, docetaxel, febrile neutropenia, drug interaction, CYP3A4.

Patients and Methods

Patient characteristics. This retrospective study was conducted in patients who were treated with DTX monotherapy or DTX combined with trastuzumab at the Yodogawa Christian Hospital between November 2012 and April 2019. The eligibility criteria included histologically or cytologically confirmed solid tumors, age ≥20 years, Eastern Cooperative Oncology Group (ECOG) performance status (PS) of 0-2, absolute neutrophil count (ANC) ≥1,500/μl, platelet count ≥100,000/μl, total bilirubin level ≤1.5× upper limit of normal (ULN), alanine transaminase/aspartate transaminase (ALT/AST) levels <60 IU/l, and both alkaline phosphatase (ALP) level <1.5× ULN and ALT/AST level <1.5× ULN. The exclusion criteria included an active infection or seropositivity for the human immunodeficiency virus, hepatitis C virus, or hepatitis B surface antigen; syphilis; or serious comorbidities (severe heart disease, uncontrolled hypertension, or diabetes mellitus). Patients who received prophylactic granulocyte colony–stimulating factors (G-CSFs) and antibiotics before the development of FN were excluded from the analysis. The data sets were collected from de-identified electronic medical records at Yodogawa Christian Hospital. This study was approved by the ethical review board of Yodogawa Christian Hospital (approval number: 2019-016).

Treatment. DTX was infused intravenously over 1 h every 3 weeks. Most patients received a dose of ≥60 mg/m^2, while some patients were received reduced doses depending on ECOG PS, their age, the degree of adverse events experienced due to previous chemotherapy, or the physician's discretion. In cases in which the treatment included trastuzumab, trastuzumab was administered at an initial dose of 8 mg/kg, followed by triweekly infusions of 6 mg/kg.

Safety assessment and categories of concomitant medications. The data used for the study were obtained during the first course of DTX treatment. We collected baseline patient characteristics from the electronic medical records on the last visit before day 1 of DTX treatment or on day 1 of such therapy. Concomitant medications were defined as therapeutic drugs used to manage comorbid conditions besides cancer. Concomitant medications continuously administered at least 1 week before the start of DTX treatment until after day 1 of chemotherapy were recorded on the basis of the patients' electronic charts. Topically applied medications were excluded. Premedications for DTX treatment such as steroids and antiemetics and medication to be taken as needed were also excluded. The categories of concomitant drugs were classified using the SuperCYP website, a comprehensive database on cytochrome P450 enzymes including a tool for analyzing CYP-drug interactions (23), and the Lexicomp® drug interaction software. In case of outpatient chemotherapy, blood chemistry tests and complete blood cell count were performed at least before each cycle of chemotherapy. In case in which the neutrophil count was unavailable because of the patient was an outpatient, FN was defined as an axillary temperature of ≥37.5˚C after day 5. If the neutrophil count was available, FN was defined as an axillary temperature of ≥37.5˚C and an absolute neutrophil count (ANC) of <0.5×10^9/l.

Statistical analysis. The number of concomitant medications was compared between patients with and without FN by using the Wilcoxon rank-sum test. To identify the factors associated with FN, categorical variables were evaluated with the Fisher's exact test or the chi-squared test. The categorical variables included for statistical analysis were as follows: age, sex, ECOG PS, tumor type, number of previous treatment regimens, DTX dose, number of comorbidities, metastatic tumor, Charlson comorbidity index score (24), number of concomitant medications, and total number of concomitant CYP3A inhibitors and substrates. Variables with *p*-values higher than 0.2 were excluded in the stepwise multivariate logistic regression model. Two-sided *p*-values lower than 0.05 were considered statistically significant. Odds ratios (ORs) were calculated with the corresponding 95% confidence intervals (CIs). Statistical analyses were performed using JMP v. 10 (SAS Institute, Inc., Cary, NC, USA).

Results

Patient characteristics. One hundred and seventy patients fulfilled the inclusion criteria and were initially selected for inclusion in this retrospective analysis. Fifty-seven patients were excluded from the study: 52 and five patients were excluded because they received prophylactic G-CSFs and antibiotics before FN development, respectively. The final study population consisted of 113 patients, whose characteristics are summarized in Table I. The median age of patients was 64 years (range=30-83), and 13 patients (11.5%) had an ECOG PS of 2. Forty (35.4%) patients received adjuvant chemotherapy, and 73 (64.6%) received palliative chemotherapy. Twenty-five patients (22.1%) received DTX at a dose less than 60 mg/m^2. Breast cancer (40) was the most common primary tumor type in the patients, followed by lung (37), gastric (14), and other cancers (22). Almost 80% of patients were administered concomitant medications, of whom 48 (42.5%) were receiving four or more medications. Furthermore, 57 (50.4%) patients were administered concomitant CYP3A4 inhibitors, and the top 10 CYP3A4 inhibitors frequently administered are shown in Table II.

Number of concomitant medications and DTX-induced FN. Of the 113 patients, 29 (25.7%) developed FN. Figure 1 shows that the number of concomitant medications was significantly higher in patients who developed FN [mean: 5.6 (95% CI=4.3-6.8)] than in those who did not [mean: 3.2 (95% CI=2.6-4.0); p=0.0005]. Similarly, the total number of concomitant CYP3A4 inhibitors and substrates administered was significantly higher in patients who developed FN [mean: 2.1 (95% CI=1.5-2.9)] than in those who did not [mean: 1.4 (95% CI=1.0-1.8); p=0.01].

Associations of patient characteristics with FN. Univariate analyses were performed to evaluate the association between patient characteristics and DTX-induced FN. As shown in Table III, when the characteristics of patients who developed FN were compared to those who did not, the distribution of the DTX dose factor, which was set to <60 mg/m^2, 60-70 mg/m^2, or ≥70 mg/m^2, was significantly different. Moreover, the number of concomitant

Table I. *Patient demographic and clinical characteristics.*

Characteristic	n (%)
Total no. of patients	113
Age, years	
Median (range)	64 (30-83)
Gender	
Male	46
Female	67
ECOG PS	
0-1	100
2	13
Treatment category	
Adjuvant	40
Palliative	73
Number of previous treatment regimens	
0-1	84
≥2	29
DTX dose (mg/m^2)	
<60	25
60-<70	46
70-75	42
Tumor type	
Breast	40
Lung	37
Gastric	14
Others	22
Number of concomitant medications	
0	22
1-3	43
≥4	48

ECOG PS, Eastern Cooperative Oncology Group performance status; DTX, docetaxel.

Table II. *CYP3A4 inhibitors concomitantly used in patients receiving docetaxel.*

Concomitant medications	n*
Lansoprazole	18
Amlodipine	14
Atorvastatin	8
Rabeprazole	5
Benidipine	5
Metformin	4
Ambroxol	3
Nifedipine	3
Irbesartan	3
Others	31

*There is some overlapping.

medications and total number of concomitant CYP3A4 inhibitors and substrates were significantly associated with DTX-induced FN. Since, these two variables are covariates, categorical variables used for multivariate analysis were selected: Age ≥70 years, female, ECOG PS of 0-1, lung cancer, number of previous treatment regimens ≥1, DTX dose ≥60 mg/m^2, metastatic tumor, number of comorbidities ≥1, Charlson comorbidity index score ≥3, and total number of concomitant of CYP3A4 inhibitors and substrates ≥2. Although the five risk factors for FN exhibited a level of $p<0.2$ in the stepwise multivariate logistic regression, total number of concomitant CYP3A4 inhibitors and substrates ≥2 (OR=4.82, 95% CI=1.77-14.1; $p=0.002$) was the only independent risk factor for FN (Table IV).

Discussion

In the present study, we investigated the risk of increased FN when administering the anticancer drug DTX concomitantly with other medications, especially CYP3A4 inhibitors and substrates. Patients who developed FN were the ones who received more concomitant medications, and the concomitant use of multiple CYP3A4 inhibitors and substrates was a risk factor for DTX-induced FN. Several studies have demonstrated that polypharmacy is significantly associated with severe chemotherapy-induced toxicity. In a meta-analysis of three phase II/III trials, which included 1,213 patients with advanced ovarian cancer, polypharmacy was associated with grade 3-4 hematological and non-hematological toxicities (25). In a single-center prospective study of 78 breast cancer patients receiving first-line chemotherapy, ≥5 concomitant medications was associated with grade 3-4 toxicities (26). However, it is reported that polypharmacy in older patients receiving palliative radiotherapy did not influence on failure to complete radiotherapy by adverse reactions (27). These studies indicate that polypharmacy during chemotherapy increases the risk of adverse events caused by drug–drug interactions or toxicity due to concomitant drugs. In our study, the use of ≥6 concomitant medications was more common among patients who developed FN compared to that among those who did not. The mechanisms of drug–drug interactions caused by polypharmacy are complicated, and even a drug that may have a small influence alone may have a great influence when multiple drugs interact with each other. Although DTX is metabolized by CYP3A4, in clinical practice, there is little opportunity to co-administer anticancer drugs with strong inhibitors of CYP3A4, such as ritonavir and ketoconazole. As shown in Table II, all of the top 10 concomitantly administered CYP3A4 inhibitors in the present study were reported to have weak inhibitory activities. Furthermore, of the 57 patients who were concomitantly administered with CYP3A4 inhibitors, only one was administered with clarithromycin, which is reported to be a moderate CYP3A4 inhibitor (18). On the other hand, even weak inhibitors of CYP3A4, such as pazopanib and

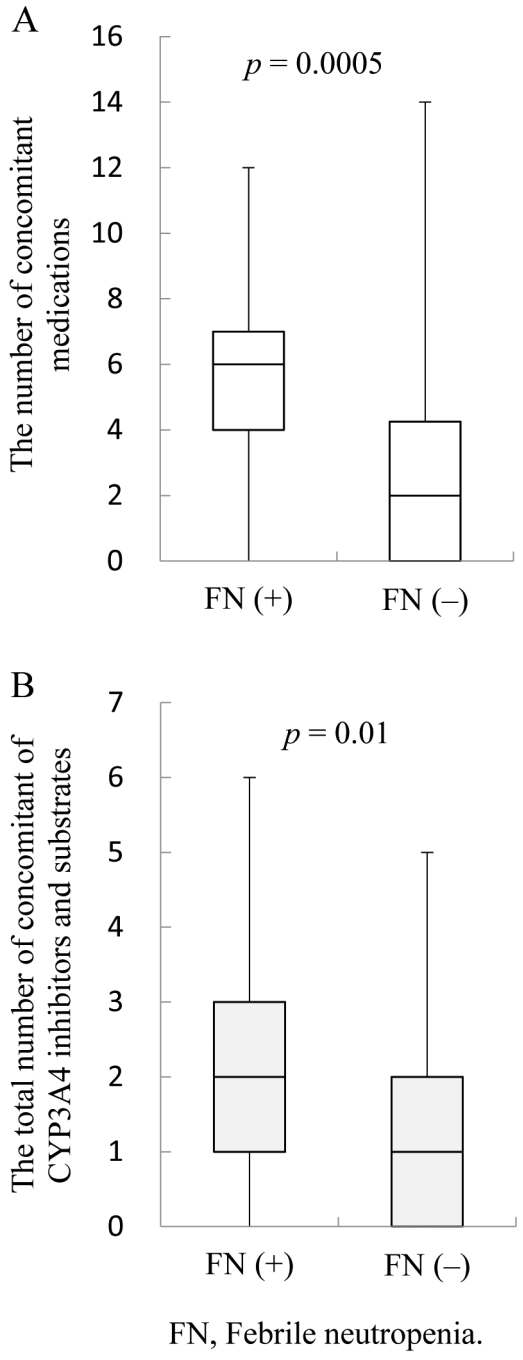

Figure 1. *Comparison of (A) the number of concomitant medications and (B) the total number of concomitant of CYP3A4 inhibitors and substrates between patients with and without febrile neutropenia (FN). FN, Febrile neutropenia.*

Table III. *Associations of patient characteristics with docetaxel-induced febrile neutropenia.*

	FN (+) (n=29)	FN (–) (n=84)	*p*-Value
Age, years			
<70	16 (55)	61 (73)	0.11[a]
≥70	13 (45)	23 (27)	
Gender			
Male	12 (41)	34 (40)	1.0[a]
Female	17 (59)	50 (60)	
ECOG PS			
0-1	24 (83)	76 (90)	0.31[a]
2	5 (17)	8 (10)	
Tumor type			
Breast	5 (17)	35 (42)	0.05[b]
Lung	12 (41)	25 (31)	
Gastric	3 (10)	11 (13)	
Others	12 (31)	12 (14)	
Number of previous treatment regimens			
0	6 (21)	13 (15)	0.27[b]
1	13 (45)	52 (62)	
≥2	10 (34)	19 (23)	
DTX dose (mg/m^2)			
<60	7 (24)	18 (21)	0.03[b]
60-<70	17 (59)	29 (35)	
≥70	5 (17)	37 (44)	
Metastatic tumor			
Yes	16 (55)	42 (50)	0.67[a]
No	13 (45)	42 (50)	
Number of comorbidity			
0	17 (59)	54 (64)	0.84[b]
1	6 (21)	16 (19)	
≥2	6 (21)	14 (17)	
Charlson comorbidity index score			
2	7 (24)	33 (39)	0.2[b]
3-6	16 (55)	31 (47)	
≥7	6 (21)	20 (24)	
Number of concomitant medications			
0-2	7 (24)	50 (60)	0.001[b]
3-5	6 (21)	16 (19)	
≥6	16 (55)	18 (21)	
Total number of concomitant of CYP3A4 inhibitors and substrates			
0-1	10 (34)	57 (68)	0.002[a]
≥2	19 (66)	27 (32)	

FN, Febrile neutropenia; ECOG PS, Eastern Cooperative Oncology Group performance status; DTX, docetaxel; CYP3A4, cytochrome P450 3A4. [a]Fisher's exact test. [b]Chi-squared test.

lapatinib (28, 29), have been reported to increase the AUC of DTX (30, 31). Sasaki *et al*. reported that concomitant polypharmacy was significantly associated with severe irinotecan-induced toxicity and that CYP3A4 substrates might cooperatively interact to inhibit CYP3A4, which is involved in the generation of inactive metabolites of irinotecan (32). The results of our study partly support their views. That is, it is possible that coadministration of DTX with multiple weak inhibitors of CYP3A4 and substrate drugs causes an increase in the AUC of DTX, resulting in an increased risk of FN. In general, patients with multiple

Table IV. *Multivariate logistic regression analysis of risk factors for febrile neutropenia.*

Factor	Multivariate analysis	
	Odds ratio (95% confidence interval)	*p*-Value
Age (≥70)	2.28 (0.81-6.57)	0.12
Metastatic tumor	0.29 (0.06-1.29)	0.1
Number of comorbidity (≥1)	0.29 (0.07-1.06)	0.06
Charlson comorbidity index score (≥3)	4.11 (0.62-27.7)	0.14
Total number of concomitant of CYP3A4 inhibitors and substrates (≥2)	4.82 (1.77-14.1)	0.002

CYP3A4, Cytochrome P450 3A4.

comorbidities tend to receive more medications. In general, such patients are expected to have a high incidence of adverse events due to anticancer drugs because they are elderly or have a poor PS. However, our study did not indicate an association between age, PS, and number of comorbidities, and the risk of DTX-induced FN. This might be due to dose reduction depending on PS, patient age, or comorbidities, based on the physician's discretion. In any case, it was suggested that concomitant use of multiple CYP3A4 inhibitors and substrates is an independent risk factor for DTX-induced FN.

The present study has certain limitations. Because this study was a retrospective analysis based on data from electronic medical records, we were unable to assess the neutrophil count at the time of fever in outpatients. In other words, some outpatients who were diagnosed with FN might not have fulfilled the criterion of ANC $<0.5\times10^9$/l. Moreover, we did not evaluate the serum concentrations of DTX. Therefore, it would be necessary to confirm our findings in future investigations.

In conclusion, concomitant polypharmacy involving CYP3A4 inhibitors and substrates during DTX treatment increases the risk of developing FN. Therefore, it is necessary to ensure the safety of DTX treatment by reducing inappropriate medications or changing to drugs with metabolic pathways different from those related to DTX in patients with polypharmacy.

Conflicts of Interest

The Authors alone are responsible for the content and writing of this article and declare that they have no conflicts of interest.

Authors' Contributions

Conception and design: K Makihara; Collection and assembly of data: K Makihara; Data analysis and interpretation: K Makihara; Manuscript writing: K Makihara and Y Shimeda; All Authors have read and approved the final article.

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