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ORIGINAL ARTICLE

An SNP in *CYP39A1* is associated with severe neutropenia induced by docetaxel

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Abstract
Purpose Docetaxel is one of the most widely used chemotherapy drugs for gynecological cancers. A dose-limiting factor of docetaxel is severe neutropenia, and previous reports showed that grade 4 neutropenia was observed in approximately 70 % of Japanese patients treated with docetaxel. In order to elucidate a valid biomarker for docetaxel-induced neutropenia, we analyzed 42 Japanese patients with gynecological cancers such as ovarian cancer and endometrial cancer of the uterus.
Methods As a first step, AUC of docetaxel was examined in 10 patients and 1,936 SNPs of 225 genes were genotyped using DMET Plus^{TM} genotyping systems.
Results The first screening revealed that 28 SNPs were associated with the AUC ($P < 0.05$), and we analyzed the associations between the 28 SNPs and neutrophil counts in the other 32 patients, with the result that *CYP39A1* (rs7761731) was found to be the only SNP significantly associated ($P = 0.049$ OR = 9.0) with the incidence of grade 4 neutropenia among 28 SNPs.
Conclusions This SNP in *CYP39A1* may be a useful biomarker for predicting the risk of docetaxel-induced neutropenia.

Keywords Docetaxel · Gynecological cancers · DMET · Neutropenia

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Introduction

The current standard regimen for gynecological cancers such as ovarian cancer and endometrial cancer is a combination of taxane- and platinum-based chemotherapy [1, 2]. Docetaxel is a semi-synthetic taxane and one of the most commonly used drugs [3–5]. The taxanes are potent anticancer agents that block tubulin depolymerization, leading to cell cycle arrest and finally cell death [6]. Both docetaxel and paclitaxel are widely used for the first- and second-line chemotherapy of gynecological cancers; however, critical side effects such as severe neutropenia and peripheral neuropathy [7], respectively, are becoming dose-limiting factors. Docetaxel has a great advantage over paclitaxel in that it can be used for a short-term 1-h infusion, which is convenient in outpatient oncology units.

Docetaxel's clinical target is not only gynecological cancer but also breast cancer, non-small-cell lung cancer, gastric cancer, prostatic cancer, and squamous cell carcinoma of the head and neck. Dose-limiting toxicities of docetaxel include neutropenia, anemia, asthenia, skin lesion, and gastrointestinal symptoms. Among these, neutropenia is one of the most common and serious problems, and approximately 70 % of patients were shown to be affected in Japanese studies [8–10].

Several studies have revealed that docetaxel is metabolized through CYP3A4 [11–13]. Inter-individual variation in docetaxel clearance has been recognized as being as high as 3.5-fold [14]. Several groups [15–17] have attempted to elucidate genetic polymorphisms of *CYP3A4*, *CYP3A5*, or *ABCB1* that are responsible for pharmacokinetic variation, and the presence of both *CYP3A4*1B*/*CYP3A5*1A* and *ABCB1*8* reportedly has an association with increased docetaxel clearance [16, 17]. Subsequently, several pharmacogenomic studies [18–20] have been undertaken, resulting in the identification of single-nucleotide polymorphisms (SNPs) positively associated with various side effects, including neutropenia, in genes such as *ATP7A*, *ABCB1*, *ABCC2*, *ABCC6*, *CHST3*, *CYP2D6*, *CYP3A4*, *CYP3A5*, *CYP4B1*, *NAT2*, *SLCO1B3*, *SLC10A2*, and *SPG7*. On the other hand, a large-scale study has been carried out to analyze the association between toxicities induced by either docetaxel or paclitaxel and polymorphisms in *ABCB1*, *ABCC1*, *ABCC2*, *ABCG2*, *CDKN1A*, *CYP1B1*, *CYP2C8*, *CYP3A4*, *CYP3A5*, *MAPT*, and *TP53*, in which no significant association was found [21].

A Japanese study reported that the SNPs in *ABCC2* and *SLCO1B3* are significantly associated with severe neutropenia induced by docetaxel [20]. However, upon re-examination of whether the SNPs in *ABCC2* and *SLCO1B3* are significantly associated with the combined chemotherapy for gynecological cancer, we were unable to reproduce the positive association between two SNPs and neutropenia, which was probably due to the combined use of taxane and platinum. This observation led us to apply a two-step pharmacogenomic analysis: In the first step, we performed pharmacokinetic analysis of docetaxel using 10 patients and screened the SNPs significantly associated with area under the curve (AUC) using the DMET-plus system. In the second step, we examined the association between severe neutropenia and the candidate SNPs selected in the first screening. Since genotyping using a microarray such as DMET-plus is capable of analyzing crucial gene polymorphisms including genes for cytochrome P450 or drug transporters, it is preferable over candidate gene strategy for examining hitherto unknown gene polymorphisms that are associated with docetaxel-induced neutropenia. In this paper, we describe that the two-step strategy successfully elucidated a single SNP that can predict severe neutropenia in combined taxane- and platinum-based chemotherapy.

Materials and methods

Patients

Forty-two Japanese gynecological cancer patients who were treated by the combination chemotherapy of docetaxel and carboplatin from September 2009 to March 2011 were enrolled in this study. The study was approved by the Institutional Review Board of Tokyo Women's Medical University. All patients were treated with a combination of docetaxel and carboplatin. The dose of docetaxel was 70 mg/m^2 every 3 weeks, and carboplatin was AUC 6.

In order to re-evaluate the association between *SLCO1B3* (rs11045585), *ABCC2* (rs12762549), and severe neutropenia, we determined the sample size as follows. The previous study [20] showed that docetaxel-induced neutropenia can be predicted by examining the two SNPs and that the odds ratio was 7.0 when compared the high-risk with the low-risk group. The study also showed that the genetic frequency of the high-risk group in control subjects was 0.351. Taken together, we calculated that in order to have a power of 80 %, at least 30 patients (15 per group) were required to detect the difference at the 5 % significance level with one-sided test.

Data collection

After the first administration of docetaxel, neutrophil counts were made every other day in order to determine the nadir of each patient. The blood concentration of docetaxel was measured for 10 among 42 patients, who voluntarily agreed with sampling. After 1-h dripped infusion of docetaxel, venous blood was sampled at 6 time points: right after infusion, 30 min, 1, 3, 7, and 24 h after infusion. A non-compartment model was assumed, and AUC (area under the blood concentration–time curve) from 0 to 24 h was calculated using the linear trapezoidal rule. Since the blood concentration of docetaxel became almost zero at the last time points, we calculated AUC as the area until the final measurement time.

Genotyping

We adopted a strategy to determine SNPs in most drug-metabolizing enzymes and transporters, and for this purpose, the DNA chip DMET^{TM} Plus (Affymetrix, USA) was used for genotyping. The system is capable of analyzing 1,936 SNPs in 225 genes associated with drug metabolism.

Statistical analysis

We examined the relationship between the lowest absolute neutrophil count (ANC) and docetaxel AUC using a scatter plot, and Pearson's correlation coefficient was calculated. The SNPs that correlated with neutropenia were identified by two-step explorations: In the first step, we performed the association analysis between genotypes and docetaxel AUC using 10 among 42 patients whose pharmacokinetics were analyzed. Wilcoxon signed-rank test was used for dominant and recessive inheritance models, whereas Jonckheere–Terpstra trend test was utilized for the additive inheritance model. If one of the three P values was significant, we looked upon the SNPs as significant in the first screening. In the second step, for 32 among 42 patients, we performed the association analysis between the genotypes and grade 4 neutropenia (ANC $< 500/mm^3$) using exact MAX test [22] of 2×3 contingency table for the SNPs selected in the first step. This test is robust under various inheritance models. Odds ratios were calculated using logistic regression. As a supplementary approach, we performed the association analysis using Fisher's exact test under dominant and recessive inheritance models and using the Cochran–Armitage trend test under an additive inheritance model. Statistical analyses were performed using SAS version 9.1. A P value less than 0.05 was considered as statistically significant. We performed first-step tests as two-sided tests, while second tests were one-sided tests because a risk allele was detected in the first step. All genotypes were checked for deviation from Hardy–Weinberg equilibrium.

Results

Patient characteristics and outcomes

The backgrounds of patients are shown in Table 1. Cases for which AUC was calculated ($N = 10$) and not calculated ($N = 32$) were revealed not to differ in terms of age, primary site of cancer, clinical stage, and days to nadir. We noticed that the lowest neutrophil counts were slightly different in the two groups; this was found to be not significant by Fisher's exact test. Although the cases were randomly assigned, the prevalence of severe neutropenia was found to be lower than expected in a group for which AUC was calculated. It should be noticed that linearity between neutrophil counts and AUC was obtained as shown in Fig. 1.

SNP typing by DMET

Among the 1,936 SNPs included in the DMET system, we obtained the genotyping data of 1,931 SNPs with over 99 % call rate; 1,232 SNPs were found to be identical in all patients tested in this study. As a result, we used genotyping data of the remaining 699 SNPs for statistical analysis.

Associations between clinical outcome and blood concentrations of docetaxel

Correlations between the log-transformed ANC and AUC of docetaxel are shown in the scatter plots of Fig. 1. Although the number of tested cases was only 10, Pearson's correlation coefficient showed a significant value, -0.82 ($P = 0.004$), suggesting that larger AUC causes lower neutrophil counts. All tested patients showed normal neutrophil counts before the chemotherapy. We hypothesized that some SNPs of genes for drug-metabolizing enzymes and drug transporters showing a positive association with large AUC may also be associated with severe neutropenia.

Associations between genotypes and blood concentrations

Table 2 depicts the results of the first-step selection of SNPs that are associated with large AUC. We were unable to predict an appropriate genetic model, so 3 genetic models were examined for the association study using three signed-rank tests: a Jonckheere–Terpstra trend test and two Wilcoxon signed-rank tests. We selected 28 SNPs of 16 genes, which showed $P < 0.05$ in at least one of the three genetic models tested. Table 2 shows genotype frequencies, median of AUC, P values, and risk alleles for increased AUC. In this analysis, several genes were listed as having multiple significant SNPs: 4 SNPs in *ABCB1* and *PON3*; 3 SNPs in *ABP1* and *SLCO1B1*; and 2 SNPs in *ATP7B* and *SLC19A1*. The other SNPs in *ABCC5*, *AOX1*, *CYP19A1*, *CYP39A1*, *CYP7B1*, *FMO3*, *GSTA5*, *MAOA*, *SLCO4A1*, and *XDH* were unique in each gene.

Associations between genotypes and clinical outcome

Table 3 shows the results of the second-step analysis involving the investigation of the candidate SNPs linked with AUC and their association with severe neutropenia, that is, below $500/mm^3$. In this table, we show the associations between the risk alleles of 28 SNPs and severe neutropenia as follows: genotype frequencies, P value of the MAX test, and odds ratio of each group. In addition, results of Fisher's exact test and the Cochran–Armitage trend test are shown. We did not test the P values of 10 SNPs that showed linkage disequilibrium with 18 neighboring SNPs.

Through the two-step tests, only one SNP, namely 56503T > A (rs7761731) of *CYP39A1*, showed a

Table 1 Patient demographics and clinical characteristics

Demographic or clinical characteristics	AUC calculated ($N = 10$) No. of patients (%)	AUC not calculated ($N = 32$) No. of patients (%)	Total ($N = 42$) No. of patients (%)
Age at surgery (year)			
Mean (SD)	60.5 (12.8)	57.7 (13.3)	58.4 (13.1)
Median (min–max)	57.5 (46–87)	59.0 (31–83)	58.5 (31–87)
Primary site of cancer			
Uterine corpus	3 (30.0 %)	10 (31.3 %)	13 (31.0 %)
Uterine cervix	0 (0.0 %)	3 (9.4 %)	3 (7.1 %)
Peritoneal	1 (10.0 %)	1 (3.1 %)	2 (4.8 %)
Ovarian	6 (60.0 %)	15 (46.9 %)	21 (50.0 %)
Unknown	0 (0.0 %)	3 (9.4 %)	3 (7.1 %)
Clinical stage			
Ia	3 (30.0 %)	6 (18.8 %)	9 (21.4 %)
IIa	3 (30.0 %)	5 (15.6 %)	8 (19.0 %)
IIIa	2 (20.0 %)	12 (37.5 %)	14 (33.3 %)
IV	2 (20.0 %)	5 (15.6 %)	7 (16.7 %)
Unknown	0 (0.0 %)	4 (12.5 %)	4 (9.5 %)
ANC (/mm^3)			
Mean (SD)	635.7 (358.0)	586.6 (572.3)	598.3 (525.6)
Median (min–max)	588.5 (74–1,280)	420.5 (0–2,227)	486.2 (0–2,227)
<500/mm^3	3 (30.0 %)	20 (62.5 %)	23 (54.8 %)
≧500/mm^3	7 (70.0 %)	12 (37.5 %)	19 (45.2 %)
Days to nadir (day)			
Mean (SD)	8.9 (1.9)	8.5 (1.7)	8.6 (1.7)
Median (min–max)	8.5 (6–12)	8.0 (6–15)	8.0 (6–15)
AUC (ng h/ml)			
Mean (SD)	818.3 (234.0)		
Median (min–max)	799.0 (551–1,314)		

AUC area under the blood concentration–time curve of docetaxel, *SD* standard deviation, *ANC* absolute neutrophil count

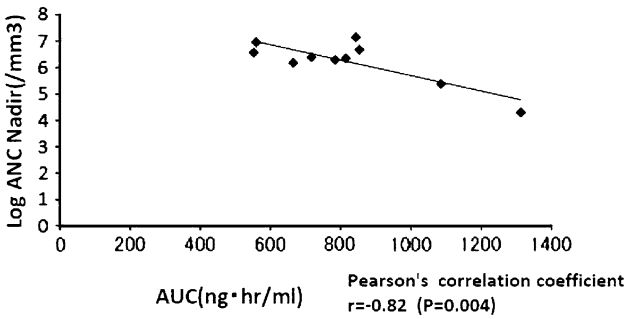

Fig. 1 AUC of docetaxel against the first-cycle neutrophil nadir. *Solid line* linear regression line

significant association with both large AUC and severe neutropenia ($P = 0.049$), suggesting that the *CYP39A1* genotypes of A/A and A/T conveyed greater susceptibility to severe neutropenia than those of T/T; the odds ratio was approximately 9.0. In Fig. 2, with the 42 cases categorized into two groups, severe neutropenia and others, genotype frequency and odds ratio are shown.

Discussion

Pharmacological responses to drugs vary among individuals, and drug-metabolizing enzymes and transporters play essential roles in drug actions. To obtain a comprehensive understanding of docetaxel-induced neutropenia, we undertook a strategy to search for genomic biomarkers using the DMET^{TM} Plus system [23], which enables us to analyze approximately 2,000 known SNPs in genes for drug-metabolizing enzymes as well as transporters.

Previous clinical studies have revealed that over 70 % of the patients administered docetaxel faced severe neutropenia [8–10]. A study by Goh et al. [15] showed that AUC of docetaxel correlated with neutrophil nadir and that Pearson's correlation coefficient was −0.48. These researchers examined the associations of genotypes of *ABCB1* (*MDR1*) and *CYP3A5* with docetaxel clearance; however, no significant association between SNPs and docetaxel clearance was found in the candidate gene analysis. In the present study, the observed correlation between AUC of docetaxel and neutrophil nadir was

Table 2 Associations between genotypes and blood concentrations

Gene	Common name	Genotypes frequency, $N = 10$				Median of AUC			P value			Risk allele
		11	12	22	MAF	11	12	22	12/22 versus 11	11/12 versus 22	Trend	
ABCB1	rs10276036	3	6	0	0.3	853	690	NA	0.028	NA	0.02	1
	rs1128503	4	6	0	0.3	969	690	NA	0.014	NA	0.011	1
	rs2235033	4	6	0	0.3	969	690	NA	0.014	NA	0.011	1
	rs2235013	4	6	0	0.3	969	690	NA	0.014	NA	0.011	1
ABCC5	rs3805114	8	2	0	0.1	750	1,120	NA	0.05	NA	0.037	2
ABP1	rs10893	4	5	1	0.35	843	637	1,086	0.07	0.296	0.035	2
	rs4725373	4	5	1	0.35	843	637	1,086	0.07	0.296	0.035	2
	rs1049793	4	5	1	0.35	843	637	1,086	0.07	0.296	0.035	2
AOX1	rs7563682	2	7	1	0.45	634	814	1,314	0.151	0.164	0.033	2
ATP7B	rs1801244	3	5	2	0.45	716	784	1,120	0.254	0.05	0.039	2
	rs2277448	3	6	1	0.4	1,086	724	716	0.023	0.728	0.029	1
CYP19A1	rs700519	5	4	1	0.3	664	964	853	0.037	0.486	0.035	2
CYP39A1	rs7761731	2	8	0	0.4	555	829	NA	0.05	NA	0.037	2
CYP7B1	rs8192907	8	2	0	0.1	750	1,120	NA	0.05	NA	0.037	2
FMO3	rs909530	2	6	2	0.5	671	765	1,120	0.361	0.05	0.04	2
GSTA5	rs7746993	8	2	0	0.1	829	555	NA	0.05	NA	0.037	1
MAOA	rs1137070	4	3	3	0.45	964	814	558	0.11	0.068	0.028	1
PON3	rs11764079	7	2	1	0.2	843	633	558	0.04	0.296	0.033	1
	rs11770903	7	2	1	0.2	843	633	558	0.04	0.296	0.033	1
	rs17882539	7	2	1	0.2	843	633	558	0.04	0.296	0.033	1
	rs13226149	7	2	1	0.2	843	633	558	0.04	0.296	0.033	1
SLC19A1	rs1051266	6	3	1	0.25	690	843	1,086	0.11	0.296	0.049	2
	rs12659	6	3	1	0.25	690	843	1,086	0.11	0.296	0.049	2
SLCO1B1	rs2306283	3	5	2	0.45	558	814	1,120	0.04	0.05	0.004	2
	rs4149057	3	5	2	0.45	558	814	1,120	0.04	0.05	0.004	2
	rs3764006	6	3	1	0.25	834	664	551	0.07	0.164	0.029	1
SLCO4A1	rs3787537	3	4	3	0.5	558	799	1,086	0.023	0.023	0.002	2
XDH	rs1884725	5	4	1	0.3	664	969	843	0.022	0.728	0.035	2

11: Major allele was defined as allele 1; *MAF* minor allele frequency; 12/22 versus 11: Wilcoxon signed-rank test; 11/12 versus 22: Wilcoxon signed-rank test; trend: Jonckheere–Terpstra trend test; *P* value: two-sided; *NA* not available

−0.82, as shown in Fig. 1. The observation suggested that neutropenia induced by docetaxel–carboplatin combination therapy was due mainly to docetaxel, though we have not measured the AUC of carboplatin. The pharmacogenomic study for patients who are treated with docetaxel as a single agent such as those with prostate cancer might be useful for confirmation of the positive association between the SNP and neutropenia.

In the next step, we examined SNPs that are associated with both AUC and grade 4 neutropenia by extensively analyzing 1,936 SNPs of 225 genes, resulting in the identification of an SNP of *CYP39A1* (rs7761731) associated with severe neutropenia induced by docetaxel, as shown in Table 3.

A recent study [18] using the DMET genotyping platform elucidated that 11 SNPs in eight genes were associated with toxicities induced by docetaxel in the treatment of prostate cancer: *ABCC6*, *ATP7A*, *CHST3*, *CYP2D6*, *CYP4B1*, *NAT2*, *SLC10A2*, and *SPG7*. In this study, none of these SNPs was associated with neutropenia caused by docetaxel. The discrepancy seems to be attributable to patients' ethnic groups, gender, definitions of toxicity, regimen of chemotherapy, or different origins of cancer [18].

According to the results of the clinical trials, the frequencies of docetaxel-induced grade 3 and grade 4 neutropenia were 90.9 and 73.7 %, respectively [8–10]. In the data from the International HapMap Project, the genotype frequencies of rs7761731 of *CYP39A1* in Japanese are as follows: A/A 0.326, A/T 0.512, and T/T 0.163 (HapMap Data Rel 24/phase II on November 8, on NCBI B36 assembly, dbSNP b126), suggesting that the combined genotype frequency of A/A and A/T, both of which were found to convey higher risk for severe neutropenia, is

Table 3 Associations between genotypes and grade 4 neutropenia

Gene	Common name	Grade 4 neutropenia, $N = 20$				Grade 1–3 neutropenia, $N = 12$				*P* value				Odds ratio	
		11	12	22	MAF	11	12	22	MAF	Max	12/22 versus 11	11/12 versus 22	Trend	12/22 versus 11	11/12 versus 22
ABCB1	rs10276036	3	9	8	0.63	1	5	6	0.71	0.512	0.515	0.426	0.252	0.52	1.50
	rs1128503	3	9	8	0.63	1	5	6	0.71						
	rs2235033	3	9	8	0.63	1	5	6	0.71						
	rs2235013	3	9	8	0.63	1	5	6	0.71						
ABCC5	rs3805114	15	4	1	0.15	10	2	0	0.08	0.486	0.465	0.625	0.233	1.67	0.00
ABP1	rs10893	8	11	1	0.33	6	4	2	0.33	0.516	0.426	0.956	0.528	1.50	3.80
	rs4725373	8	11	1	0.33	6	4	2	0.33						
	rs1049793	8	11	1	0.33	6	4	2	0.33						
AOX1	rs7563682	4	11	5	0.53	4	6	2	0.42	0.392	0.332	0.465	0.193	2.00	0.60
ATP7B	rs1801244	5	8	7	0.55	3	7	2	0.46	0.329	0.656	0.242	0.245	1.00	0.37
	rs2277448	7	10	3	0.4	1	9	2	0.54	0.104	0.1	0.634	0.109	0.17	1.13
CYP19A1	rs700519	9	11	0	0.28	6	3	3	0.38	0.622	0.536	1	0.801	1.22	NA
CYP39A1	rs7761731	1	13	5	0.58	4	5	3	0.46	0.049 *	0.06	0.638	0.107	9.00	0.93
CYP7B1	rs8192907	20	0	0	0	12	0	0	0	NA	NA	NA	NA	NA	NA
FMO3	rs909530	6	11	2	0.38	7	2	2	0.25	0.117	0.093	0.874	0.175	3.79	1.89
GSTA5	rs7746993	15	4	1	0.15	8	3	1	0.21	0.566	0.454	0.617	0.295	0.67	1.73
MAOA	rs1137070	6	9	4	0.43	4	8	0	0.33	0.742	0.692	1	0.832	1.08	0.00
PON3	rs11764079	9	8	3	0.35	6	6	0	0.25	0.818	0.739	1	0.801	1.22	0.00
	rs11770903	9	8	3	0.35	6	6	0	0.25						
	rs17882539	9	8	3	0.35	6	6	0	0.25						
	rs13226149	9	8	3	0.35	6	5	1	0.29						
SLC19A1	rs1051266	10	7	3	0.33	5	6	1	0.33	0.516	0.794	0.515	0.526	0.71	0.52
	rs12659	9	7	3	0.33	4	7	1	0.38						
SLCO1B1	rs2306283	7	7	6	0.48	5	5	2	0.38	0.402	0.497	0.344	0.241	1.33	0.47
	rs4149057	7	7	6	0.48	4	6	2	0.42						
	rs3764006	13	7	0	0.18	8	4	0	0.17	0.737	0.681	NA	0.538	1.08	NA
SLCO4A1	rs3787537	6	11	3	0.43	6	5	1	0.29	0.284	0.225	0.515	0.135	2.33	0.52
XDH	rs1884725	16	4	0	0.1	6	4	2	0.33	0.998	0.984	1	0.984	0.25	NA

*P value less than 0.05

11: Major allele was defined as allele 1 in Table 2; MAF: minor allele frequency in Table 2; P value: one-sided; max: max test; 12/22 versus 11: Fisher's exact test; 11/12 versus 22: Fisher's exact test; trend: Cochran–Armitage trend test; grade 4 neutropenia: ANC $< 500/mm^3$; grade 1–3 neutropenia: ANC $\geq 500/mm^3$; *NA* not available; if SNPs show linkage to other SNPs, then P value and odds ratio were not calculated

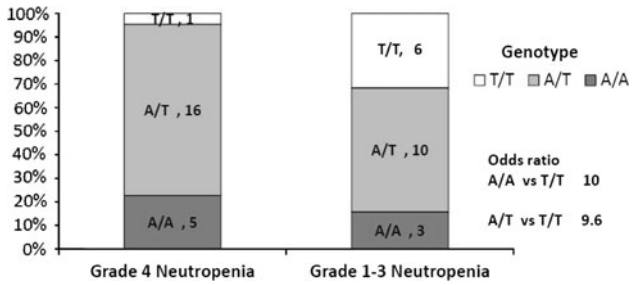

Fig. 2 Associations between CYP39A1 genotypes and grade 4 neutropenia

83.8 %. In this study, we observed that the genotype frequency of A/A and A/T was 82.9 %. These observations suggested that the genotype frequencies of A/A and A/T are almost compatible with the occurrence of grade 4 neutropenia during clinical trials. As a result, predicted occurrence of grade 4 neutropenia using the genotype frequency and the odds ratio obtained in this study are 82 % for A/A, 81 % for A/T, and 31 % for T/T.

CYP39A1 encodes a member of the cytochrome P450 superfamily of enzymes, and it is involved in the conversion of cholesterol to bile acids. The synthesis and

excretion of bile acids comprise the major pathway of cholesterol catabolism in human. The synthesis of bile acids requires 17 enzymes, including CYP7A1, CYP7B1, CYP27A1, CYP39A1, and CYP46A1. The SNP, rs7761731, causes non-synonymous single amino acid substitution, Asn324Lys. The effect of this amino acid change has been predicted by the use of two programs, SIFT [24] and PolyPhen [25]. Each program predicted this structural variation as tolerated and benign, respectively. The observation suggests that either another SNP on *CYP39A1* or a polymorphism on the distinct gene close to rs7761731 may be responsible for the docetaxel-induced neutropenia.

Another taxane, paclitaxel, reportedly induces peripheral neuropathy, and several laboratories have investigated the association between SNPs and neurotoxicities [26, 27]. Our present results may be useful for choosing safer taxanes, docetaxel or paclitaxel, for patients who are treated for gynecological cancers as well as other types of malignancy.

In conclusion, we suggest that the identified SNP in *CYP39A1* may be a good biomarker for the prediction of severe neutropenia induced by docetaxel, and a prospective study to confirm its diagnostic significance is in progress.

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