Original Article

Genetic Variations of Drug Transporters Can Influence on Drug Response in Patients Treated with Docetaxel Chemotherapy

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Purpose

Dose-limiting toxicities of docetaxel are widely considered to be neutropenia, anemia, skin toxicity, and nausea. One of the factors that limit the use of docetaxel is its unpredictability of inter-individual variation in toxicity.

Materials and Methods

In order to identify the genetic factors that affect the risk of docetaxel-induced toxicities, we recruited patients who received docetaxel chemotherapy. We genotyped 92 patients with single-nucleotide polymorphisms (SNPs) in 5 genes: CYP3A4 (CYP3A4*1B, CYP3A4*18, and CYP3A4*3), CYP3A5 (CYP3A5*2 and CYP3A5*3), ABCB1 (C1236T, G2677G/T, and C3435T), SLCO1B3 (rs11045585), and ABCC2 (rs12762549).

Results

Out of 92 patients, 70 had grade 3 or 4 neutropenia; 4 had grade 1 or 2; and 18 had no toxicity (76.1%, 4.3%, and 19.6%, respectively). The findings of the SNP analysis showed that patients with TT genotype of ABCB1 3435C>T polymorphism showed significantly higher risk of neutropenia and anemia (p=0.029 and p=0.044, respectively). There were significant associations between docetaxel-induced leucopenia and 2677G/T of ABCB1 and rs12762549 of ABCC2 (p=0.025 and p=0.028, respectively). In a multivariate analysis, we observed that patients carrying 2677G>T in ABCB1 might be associated with higher risk of chemo-resistance when treated with docetaxel (odds ratio [OR], 6.48; confidence interval, 1.92 to 21.94; p=0.003). In a subgroup analysis of non-small cell lung cancer patients, a significant association of tumor response with G2677T/A (OR, 4.54) in ABCB1 and SLCO1B3 (OR, 9.44) was observed.

Conclusion

Our data suggest that ABCB1 (2677G/T) and SLCO1B3 (rs11055585) might be major genetic predictors of docetaxel-related toxicities in patients receiving docetaxel chemotherapy.

Introduction

Different patients respond in different ways to the same medication. Although many nongenetic factors, including age, concomitant therapy, drug interactions, and the nature of the disease, may influence the outcomes of medications, there are many inter-individual differences in drug response owing to the sequence variants of genes that encode drug-metabolizing enzymes, drug transporters, or drug targets [1].

Most of the drug-metabolizing enzymes and transporters have a broad range of genetic polymorphisms, which may cause inter-individual variability with different concentrations of drugs. In addition, anticancer therapies are known to have a narrow therapeutic range; a high concentration in a patient's body increases the toxicity, and a low concentration decreases the effect of the drug [2]. Some of the single-nucleotide polymorphisms (SNPs) have already been correlated with substantial changes in the metabolism or efficacy of the drug, and some are being utilized to predict clinical outcomes [1].

Docetaxel has an effective antitumor activity against many cancers, such as locally advanced or metabolic breast cancer, non-small-cell lung cancer (NSCLC), and androgen-independent prostate cancer, and can induce response rates between 20% and 40% [3]. However, despite its widespread use, an inter-individual variability in the toxicities of docetaxel has been a major challenge in clinical practice. Dose-limiting toxicities of docetaxel are considered to be neutropenia, anemia, nausea, asthenia, and skin toxicity [4]. Among the severe toxicities, neutropenia is one of the dose-limiting adverse reactions and is often observed at a frequency of approximately 36% [4,5]. The other side effects include alopecia, asthenia, dermatologic reactions, fluid retention, hypersensitivity reactions, and stomatitis. One of the most important factors that limit the use of docetaxel use is its unpredictability of inter-individual variation in toxicity. The potential causes of variability include pathogenesis and disease severity, occurrence of unintended drug interactions, and impairment of hepatic and/or renal functions [4].

The elimination of docetaxel occurs mainly through a metabolic conversion by *CYP3A4* and *CYP3A5*, which results in a formation of metabolites with reduced cytotoxic activity [5,6]. The biotransformation of docetaxel at the hepatic level leads to the inactivation of the molecule and reduction of its therapeutic effect [6]. Biotransformation is the main route for elimination of docetaxel, which makes it an interesting drug for the investigation of the genetic polymorphism in CYP450 enzymes [5]. Moreover, the correlation between high *CYP3A4* mRNA expression and low chemical susceptibility of docetaxel in breast cancer tissues has been shown by real-time polymerase chain reaction and immunohistochemistry. A high *CYP3A4* mRNA expression in tumor tissues can be predicted to accelerate the speed of docetaxel metabolism, and thus, results in resistance [7].

The elimination pathway is widely known to be mediated by the drug efflux ABC transporter, *ABCB1* (also known as P-glycoprotein or *MDR1*) [8]. Moreover, the expression of these genes is regulated by the nuclear hormone receptors pregnane X receptor and constitutive androstane receptor encoded by *NR1I2* and *NR1I3*, respectively [9]. Other transporters, *ABCC2* (*MRP2*) and *SLCO1B3* (OTAP1B3 or OATP8), are responsible for the efflux and uptake of docetaxel *in vitro*. Consequently, these genes are considered to be candidates that may affect the toxicity of docetaxel. There have been a few reports concerning the association between the toxicity of docetaxel and genetic variants of *CYP3A4*, *CYP3A5*, and *ABCB1*, and there were no reports on *NR1I2*, *NR1I3*, *ABCC2*, and *SLCO1B3* [4]. In this study, we investigated the role of *CYP3A4*, *CYP3A5*, *ABCB1*, *SLCO1B3*, and *ABCC2* polymorphisms on docetaxel toxicity.

Materials and Methods

1. Study subjects

We recruited a total of 92 patients, who were treated with docetaxel as a single agent or combination therapy between 2009 and 2011; clinical characteristics of patients are shown in Table 1. Ethical permission for this study was obtained from the Institutional Review Boards of Seoul St. Mary's Hospital. All patients who were admitted for chemotherapy at the Seoul St. Mary's Hospital provided written informed consent, in accordance to the Declaration of Helsinki. Other eligibility criteria included age (18 years or older), normal liver function, and performance status of less than 3 in accordance to the Eastern Cooperative Oncology Group criteria. Ineligibility criteria include cytotoxic chemotherapy in the previous 4 weeks and corticoid treatment in the past 2 weeks. The demographics of age and gender, as well as indications for docetaxel therapy, additional medical problems, and concurrent medications were also recorded during the clinic visit.

The dose of docetaxel was 60 mg/m^2 or less in 12 patients and 60-80 mg/m^2 in 80 patients. Patients had lung, stomach, head and neck, as well as esophagus cancer, and who received docetaxel concomitantly with capecitabine, doxorubicin, cisplatin, cisplatin-cetuximab, and ifosfamide. We obtained hematologic toxicities, such as neutropenia, leukopenia, anemia, and thrombocytopenia, and also collected non-hematologic toxicities, including stomatitis, neuropathy, alopecia, diarrhea, and anorexia at the baseline of the pretreatment and nadir (10-14 days post-treatment). Furthermore, clinical data, such as white blood cell count, neutrophil, and platelet counts, as well as hemoglobin values, were collected as the first baseline before chemotherapy and again at 10-14 days after the first chemotherapy cycle, if and when available.

Table 1. Clinical characteristics of cancer patients (n=92)

Variable	No. of patients (%)
Age (range, yr)	58.4 (28-78)
Gender (male:female)	71 (77.2):21 (22.8)
ECOG performance status	
0-1	87 (94.6)
2	5 (5.4)
Tumor type	
Lung	55 (59.8)
Stomach	18 (19.6)
Head and neck	13 (14.1)
Esophagus	4 (4.3)
Other	2 (2.2)
Tumor stage	
I-II	2 (2.2)
III-IV	90 (97.9)
Docetaxel dose (mg/m^2)	
≤ 60	12 (13.0)
60-80	80 (87.0)
Response rate	
CR+PR	31 (33.7)
SD	25 (27.2)
PD	31 (33.7)
ND	3 (3.3)
Concomitant medication	
Yes	39 (42.4)
No	53 (57.6)

ECOG, Eastern Cooperative Oncology Group; CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease; ND, not determined.

2. Analysis of the *CYP3A4, CYP3A5, ABCB1, SLCO1B3,* and *ABCC2* genomic polymorphism

The polymorphisms for the *CYP3A4* (*CYP3A4*1B, CYP3A4*18,* and *CYP3A4*3*), *CYP3A5* (*CYP3A5*2* and *CYP3A5*3*), *ABCB1* (C1236T, G2677G/T, and C3435T), *SLCO1B3* (rs11045585), and *ABCC2* (rs12762549) genes were analyzed (http://www.ncbi.nlm.gov/). For each sample, the genomic DNA was isolated from the whole blood, using the QIAamp DNA blood mini kit (Qiagen, Germantown, MD) in accordance with the supplier's instructions. Polymerase chain reaction (PCR) was performed using a hot start Ace Taq DNA Polymerase Kit (Genenmed, Seoul, Korea). All the primers for PCR amplification and DNA sequencing were designed using a Primer3 software (http://Frodo.wi.mit.edu/cgi-bin/primer3/primer3); the sequences are available upon request. PCR reaction was carried out in a final volume of 25 μL containing 10× buffer, 1.5 mmol/L MgCl$_2$, 20 μmol/L dNTP, 0.5 μmol/L of each primer, 10 ng of genomic DNA as

template, and 0.5 U polymerase. Each PCR product was purified and subjected to DNA sequencing by using BigDye Terminator v3.1 Cycle Sequencing Kit (Applied Biosystems, Foster City, CA) and the ABI Prism 3730 genetic analyzer (Applied Biosystems) after confirming the purity and mobility of each PCR product by agarose gel electrophoresis. Each sample was sequenced for both strands to confirm the results.

3. Statistical analysis

All statistical analyses were conducted using a statistical program, SPSS ver. 10.0 (SPSS Inc., Chicago, IL). The chi-square test or Fisher's exact test was used to determine the associations between different side effects after docetaxel treatment and the polymorphisms of the *CYP3A4, CYP3A5, ABCB1, SLCO1B3,* and *ABCC2* genes in accordance with suitable conditions. A 2-tailed $p < 0.05$ was considered with be statistically significant. The odds ratio (OR) and 95% confidence intervals (CI) of the polymorphisms of the *CYP3A4, CYP3A5, ABCB1, SLCO1B3,* and *ABCC2* genes for different side effects were estimated using a logistic regression.

Results

1. Study subjects' clinical characteristics

Table 1 describes the general characteristics of the eligible study subjects. We included 92 cancer patients (71 men and 21 women) with a median age of 58.4 years (range, 28 to 78 years). In brief, most of the cases had a single site (right or left) tumor, and 59.8% of the cases were diagnosed with lung cancer. The clinical stages of nearly 90% of the cases were stage III and stage IV. The dose of docetaxel was ≤ 60 mg/m^2 in 12 patients (13.0%), and 60-80 mg/m^2 in 80 patients (87.0%).

The occurrence frequencies of the side effects, including hematologic toxicities, such as neutropenia, leucopenia, anemia, and thrombocytopenia, after docetaxel treatment in patients were investigated (data not shown). We analyzed all grades of toxicities, as well as grade 2 or higher. At nadir, 10-14 days after the first chemotherapy cycle, 74 out of the 92 patients were evaluated with regard to the occurrence of neutropenia, the main adverse effect.

Twenty-five patients (33.8%) had grade 3 neutropenia and 45 (60.8%) had grade 4 neutropenia. Fifty-eight patients (85.3%) had grades 1 and 2 anemia, and 38 (41.3%) had non-hematologic toxicities, such as alopecia (Appendix 1).

Table 2. Association of genetic polymorphisms and hematologic toxicities (n=92)

SNP	Genotype	Neutropenia	p-value	Leukopenia	p-value	Anemia	p-value	Thrombopenia	p-value
*CYP3A5*3*	GG	1.62±2.88	0.506	3.35±3.06	0.265	10.97±1.56	0.700	235.50±121.4	0.167
	GA+AA	1.10±1.46		2.70±2.06		10.97±2.02		201.64±86.74	
ABCB1	CC	2.01±4.07	0.564	3.43±4.19	0.791	10.54±1.34	0.415	193.52±93.27	0.269
1236C>T	CC+TT	1.21±1.63		2.94±2.14		11.07±1.88		224.56±109.05	
ABCB1	GG	2.06±3.56	0.203	4.04±3.63	0.025	11.50±1.88	0.086	215.61±82.77	0.767
2677G>T/A	GG+TT+GA+AA+TA	1.13±1.61		2.69±2.11		10.79±1.70		219.8±113.92	
ABCB1	CC	1.85±2.95	0.029	3.62±3.25	0.074	11.42±2.02	0.044	212.45±88.30	0.955
3435C>T	CT+TT	0.97±1.49		2.57±1.91		10.62±1.53		223.72±119.47	
ABCC2	CC	0.68±0.98	0.164	1.57±.1.04	0.028	10.53±0.58	0.672	264.80±163.75	0.626
rs12762549	CG+GG	1.41±2.34		3.13±2.67		11.00±1.85		215.51±101.94	
SLCO1B3	AA	1.39±2.57	0.246	3.09±2.90	0.685	11.05±1.84	0.729	228.95±113.80	0.124
rs11045585	AG+GG	1.27±1.25		2.86±1.64		10.76±1.67		190.30±77.85	

Table 3. Relative contributions of clinical factors and genetic polymorphisms to docetaxel-induced leukopenia (n=92)

Variable	OR	95% CI	p-value
Age	0.97	0.93-1.02	0.560
Gender	0.98	0.33-2.88	0.800
Tumor stage	1.95	0.77-4.94	0.330
Dose of docetaxel (mg/m^2)	2.77	0.65-11.92	0.170
Chemotherapy regimen[a]	1.03	0.60-1.76	1.030
ABCB1 2677G>T (A)	6.48	1.92-21.94	0.003
ABCC2 rs12762549	0.37	0.03-4.54	0.433

OR, odds ratio; CI, confidence interval. [a]Docetaxel single vs. combination.

2. Association between polymorphisms of *CYP3A4*, *CYP3A5*, *ABCB1*, *SLCO1B3*, and *ABCC2* genes and the frequencies of adverse effects after docetaxel treatment

The frequencies of the side effects, such as neutropenia, leucopenia, anemia, and thrombopenia, after docetaxel treatment in patients carrying various SNPs of *CYP3A5* (*CYP3A5*3*), *ABCB1* (1236C>T, 2677G>T/A, and 3435C>T), *ABCC2* (rs12762549), and *SLCO1B3* (rs11045585) genes are shown in Table 2. The associations between the different SNPs of the *ABCB1* and *ABCC2* genes and the side effects after docetaxel treatment were analyzed. There were significant differences (p < 0.05) between *ABCB1* 2677G> T/A and patients with leucopenia (p=0.025), as well as the *ABCB1* 3435C>T SNP and patients with neutropenia (p=0.029) and anemia (p=0.044). However, we found no statistical significance between the frequencies of neutropenia and *CYP3A5*3*, as well as *ABCB1* 1236C>T and *SLCO1B3* rs11045585 SNPs. These results are shown in Table 2. Additionally, we estimated the OR and 95% CI of the *ABCB1* and *ABCC2* SNPs, showing significant results.

3. Risks of toxicity between *ABCB1* (2677G>T/A) and *ABCC2* (rs12762549) SNPs and other clinical factors after docetaxel treatment

Based on the results shown in Table 2, we conducted a multiple analysis to estimate the relative contributions of age, gender, tumor stage, dose of docetaxel, chemotherapy regimen, and two genetic polymorphisms to the docetaxel-induced leucopenia. These results are presented in Table 3. Leucopenia was dominant in the *ABCB1* 2677G>T/A SNP T/A allele carriers with OR of 6.48-fold (95% CI, 1.92 to 21.94; p=0.003). There were no significant associations between the side-effect occurrences and clinical factors, such as age, gender, tumor stage, dose of docetaxel, and chemotherapy regimen. The OR (95% CI) of leucopenia was 2.77 (range, 0.65 to 11.92) for the dose of docetaxel; however, there was no significant association.

4. Associations between genetic polymorphisms and tumor response in the 92 cancer patients

The frequencies of estimated tumor response, including

Table 4. Associations between the genetic polymorphisms and the tumor response after docetaxel treatment in the 92 patients

SNP	Genotype	CR+PR (%)	SD (%)	PD (%)	p-value
*CYP3A4*1B*	AA	23	19	12	-
*CYP3A4*18A*	TT	22	19	12	0.259
	TC	1			
*CYP3A4*3*	TT	23	19	12	-
*CYP3A5*2*	CC	23	19	12	-
*CYP3A5*3*	GG	12 (41.4)	9 (31.0)	8 (27.6)	0.625
	GA+AA	11 (44.0)	10 (40.0)	4 (16.0)	
ABCB1 1236C>T	CC	3 (37.5)	5 (62.5)	-	0.668
	CT+TT	20 (43.5)	14 (30.4)	12 (26.1)	
ABCB1 2677G>T/A	GG	11 (68.7)	3 (18.8)	2 (12.5)	0.020
	GT+TT+GA+AA+TA	12 (31.6)	16 (42.1)	10 (26.3)	
ABCB1 3435C>T	CC	13 (52.0)	9 (36.0)	3 (12.0)	0.300
	CT+TT	10 (34.5)	10 (34.5)	9 (31.0)	
ABCC2 rs12762549	CC	2 (100)	-	-	0.107
	CG+GG	21 (40.4)	19 (36.5)	12 (23.1)	
SLCO1B rs11045585	AA	20 (48.8)	16 (39.0)	5 (12.2)	0.075
	AG+GG	3 (23.1)	3 (23.1)	7 (53.8)	

CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease.

complete response, partial response, stable disease, and progressive disease, after docetaxel treatment in patients carrying various SNPs of *CYP3A4* (3 different sites), *CYP3A5* (2 different sites), *ABCB1* (3 different sites), *ABCC2* (rs12762549), and *SLCO1B* (rs11045585) genes are shown in Table 4. The associations between SNPs of the *ABCB1* and the tumor response were observed. There was a significant difference between the partial disease and patients with the *ABCB1* 2677TT/GT/GA/AA/TA genotype (p=0.020). In addition, we found a marginal association between tumor response and patients with the *SLCO1B* (rs11045585) GG genotype, although without statistical significance (Table 4). In a subgroup analysis of NSCLC patients, significant associations of tumor response and G2677T/A (OR, 4.54) in *ABCB1* and *SLCO1B3* (OR, 9.44) were observed (data not shown).

5. Multivariate analysis to estimate the relative contributions of clinical factors to docetaxel toxicity

A multivariate analysis was performed to estimate the relative contributions of gender, tumor stage, chemotherapy regimens, and two genetic polymorphisms to the inter-individual variations of docetaxel-induced toxicity. These results are presented in Table 5. The associations between the SNPs of *ABCB1* genes and docetaxel-induced toxicity were observed, and there was a significant difference between

docetaxel-induced toxicity and patients with the *SLCO1B3* rs11045585 GG genotype (p=0.022). In addition, we found an association between toxicity and chemotherapy regimen (Table 5).

Discussion

Although several studies have shown an association between the polymorphisms and toxicity of anticancer drugs, such as docetaxel, the genetic determinants of the adverse reaction of docetaxel has not been elucidated. In this study, we genotyped 10 polymorphisms located in 5 candidate genes involved in the metabolism (*CYP3A4* and *CYP3A5*) and transport (*ABCB1*, *ABCC2,* and *SLCO1B3*) of docetaxel to identify the genes related to the docetaxel-induced toxicity. We determined that 2677G/T in *ABCB1* and rs12762549 in *ABCC2* are significantly associated with severe docetaxel-induced leucopenia. In the subgroup analysis of NSCLC patients, significant associations of tumor response and G2677T/A in *ABCB1* and rs11045585 in *SLCO1B3* were also observed, suggesting that *ABCB1* and *SLCO1B3* may be largely involved in the transport of docetaxel.

Most of the genes that encode the enzymes involved in the activation and detoxification pathways are considered to be

Table 5. Multivariate analysis estimating the relative contributions of clinical factor to docetaxel-induced toxicity

Factor	OR	95% CI	p-value[a]
Gender	4.09	0.71-23.78	0.116
Tumor stage	2.04	0.39-10.54	0.394
Chemotherapy regimens[b]	0.38	0.17-0.83	0.016
ABCB1 2677G>T/A	4.54	0.98-21.13	0.054
SLCO1B3 rs11045585	9.44	1.39-64.01	0.022

OR, odds ratio; CI, confidence interval. [a]Logistic regression analysis, [b]Docetaxel single vs. combination.

highly polymorphic [2]. In cancer treatment, drug therapy is an essential tool in disease regulation. However, the therapeutic window of anticancer drugs is generally narrow. Inter-individual variations in a drug-metabolizing capacity and drug response can complicate the outcome of the same treatment even in patients who have been diagnosed with the same disease [5].

In the present study, we found no association between the genotypes of the *CYP3A4* and *CYP3A5* genes and an increase in docetaxel toxicity. The disposition of docetaxel is mediated by *CYP3A4* and *CYP3A5* enzymes and transporters, such as *ABCB1*, *ABCC2*, and *SLCO1B3* [10]. The estimated quantitative contribution of *CYP3A4/5* to the metabolism of docetaxel in the human liver is 64%-93%, making it the major CYP450 subfamily in docetaxel elimination [5,11]. Previously, several studies on patients with the *CYP3A4*1A/1B* (rs2740574) and *CYP3A5*1/*3* (rs776746) haplotypes showed an association with an increased clearance and/or decreased exposure to docetaxel [10,12]. Both rs2710574 and *CYP3A5*1* alleles have shown to be in a linkage disequilibrium in Caucasians and African Americans [12]. Previous studies have shown that *CYP3A4-CYP3A5* haplotypes may be correlated to certain diseases, impaired drug clearance, or undesirable adverse drug events [12]. In Asian cancer patients, some studies suggested a correlation between the inactive *CYP3A5*3* allele and docetaxel clearance. However, another study observed no association between the clearance and *CYP3A5*3* genotype status in *CYP3A5*1/*1*, *CYP3A5*1/*3*, and *CYP3A5*3/*3* patients [13].

Generally, variants of the coding regions in *CYP3A4* have 5% allele frequencies as heterozygous with the wild-type allele. Due to low allele frequencies, these coding variants are not likely to be the major cause of inter-individual differences in CYP3A-dependent clearance and limited alterations in enzyme expression or catalytic function. The most common variant, *CYP3A4*1B*, an A-392G transition in the 5'-flanking region, has an allele frequency that ranges from 0% (Chinese and Japanese) to 45% (African Americans) [14]. In our population, we observed that *CYP3A4*1B* and

*CYP3A4*3* have 0% of allele frequency. In contrast, a linkage disequilibrium between *CYP3A4*1B* and another *CYP3A* allele (*CYP3A5*1*) may be the cause of clinical phenotype. *CYP3A5* is polymorphically expressed in adults: approximately 10%-20% in Caucasians, 33% in Japanese, and 55% in African-Americans [15]. However, it is unlikely that *CYP3A4* and *CYP3A5* polymorphisms will be of clinical benefit in influencing docetaxel disposition in our patients.

Drug transporters consist of uptake and efflux transporters, indicating intracellular or extracellular transport directions. These transporters play an essential role as the defense mechanisms against penetration of xenobiotics or transmembrane transportation of various endogenous compounds [16]. In our study, 2677G/T in *ABCB1* and rs12762549 in *ABCC2* are significantly associated with severe docetaxel-induced leucopenia. Among the ABC proteins, some members, such as *ABCB1*, *ABCC1*, *ABCC2*, and *ABCG2*, are considered to contribute to multidrug resistance of cancer chemotherapy [17]. Recently, genetic polymorphisms in the *ABCB1* gene and their association with the P-gp level have been investigated [18,19]. Some studies examined 15 SNPs, including 6 in the coding region of healthy Caucasians and found a significant association of polymorphism in exon 26 (C3435T) of *ABCB1* with the expression levels and function of *ABCB1* [18]. In a Japanese population, 8 SNPs have been identified in the region of *ABCB1*, and among these SNPs, –2410T>C, –1910T>C, and 692T>C are in perfect linkage disequilibrium [17]. In addition, several studies have shown that the inter-individual variations in activity and expression levels of *ABCB1* and *ABCC2* may have an effect on drug response and response to toxic agents. Therefore, our results are similar to those obtained in previous studies.

The *SLCO1B3* gene is highly polymorphic, exhibiting high variations across the ethnic groups [20]. The allelic frequencies of the non-synonymous variants 334T>G (Ser112Ala; rs4149117) and 699G>A (Met233lle; rs7311358) display a great degree of heterogeneity across diverse ethnic populations, ranging from 41% in African-Americans to approximately 71%-90% in Caucasians and Chinese. However, we

estimate that the allelic frequency of *SLCO1B3* (G2677T/A; rs11045585) is almost 1% in this population compared to that of the previous studies. This study shows a significant association of tumor response with G2677T/A and *SLCO1B3* in a subgroup of lung cancer patients. This study highlights the importance of *SLCO1B3* polymorphic variations in influencing docetaxel disposition in cancer patients.

An important limitation associated with docetaxel use is the unpredictability of inter-individual efficacy and toxicity. In spite of the potential importance of the clinical variables in determining the drug effects, it is considered that inherited differences in metabolism and excretion can have a greater effect on the efficacy and toxicity of drugs [21]. Several studies have attempted to identify the genetic polymorphisms in genes encoding drug metabolizing enzymes and transporters accounting for the remarkable inter-individual variation. The studies are conflicting and inconclusive. For example, some researchers reported an increase in docetaxel clearance in carriers of *CYP3A4* polymorphisms (rs2740574) [6,13], a finding that was not supported by others [21]. Differences in the sample size, various tumor types, different treatment regimens (single agent vs. combination of drugs interacting with docetaxel) and various ethnic groups might be an explanation for these conflicting findings. Additionally, most of these results were obtained from only a few SNPs in genes involved in docetaxel disposition [22].

Recently, Maemondo et al. [23] suggested that carboplatin and paclitaxel (CP) regimen achieved a longer progression-free survival with less toxicity, excluding moderate anemia and thrombocytopenia than single-agent docetaxel. Considering the results of this phase II and IFCT-0501 trials, they selected the CP regimen as a candidate for a future phase III trial in elderly patients with advanced NSCLC [23]. Although monotherapy with the third-generation agents has been regarded as the preferred treatment option for elderly patients with NSCLC, Quoix et al. [24] recently reported the results of IFCT-0501, a phase III study comparing a similar CP regimen with monotherapy with either vinorelbine or gemcitabine in an elderly population. They demonstrated a significant superiority of the CP regimen in terms of the efficacy (overall survival); however, severe toxicity in the CP arm, including a treatment-related death rate of 4.4%, was observed [24]. In this study, we found an association between toxicity and chemotherapy regimen as the previous studies in a multivariate logistic regression analysis, and docetaxel monotherapy might be more toxic than the combination therapy.

Conclusion

Our data suggest that *ABCB1* (2677G/T) and *SLCO1B3* (rs11055585) may be major genetic predictors of docetaxel-related adverse events in patients receiving docetaxel chemotherapy. Further studies are warranted to determine the usefulness of genotyping for docetaxel treatment.

Conflicts of Interest

Conflict of interest relevant to this article was not reported.

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Appendix

Appendix 1. Distribution of the adverse effects (n=92)

Toxicity	Grade 1-2	Grade 3	Grade 4
Hematologic toxicities			
Neutropenia	4 (5.4)	25 (33.8)	45 (60.8)
Leukopenia	6 (12.8)	30 (63.8)	11 (23.4)
Anemia	58 (85.3)	9 (13.2)	1 (1.5)
Thrombocytopenia	24 (88.9)	-	3 (11.1)
Non-hematologic toxicities			
Alopecia	38 (41.3)	-	-
Fatigue/asthenia	35 (37.0)	-	-
Neuropathy	19 (20.7)	-	-
Skin rash	19 (20.7)	1 (11.0)	-
Nausea/vomiting	18 (19.6)	-	-
Dyspnea	17 (18.5)	-	-
Myalgia, mucositis	16 (17.4)	-	-
Anorexia	12 (13.0)	-	-
Diarrhea	11 (12.0)	-	-

Values are presented as number (%).