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ORIGINAL ARTICLE

Prospective evaluation of the drug-metabolizing enzyme polymorphisms and toxicity profile of docetaxel in Korean patients with operable lymph node-positive breast cancer receiving adjuvant chemotherapy

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Abstract
Background Inter-individual variability of pharmacokinetics may account for unpredictable toxicities of docetaxel.
Methods From March 2007 to June 2008, female patients with operable lymph node-positive breast cancer receiving docetaxel-containing adjuvant chemotherapy were included in this study. The 4 cycles of planned dose of docetaxel (100 mg/m^2) was performed as adjuvant chemotherapy, following 4 cycles of adriamycin and cyclophosphamide. We evaluated toxicity profile of docetaxel and single nucleotide polymorphisms (SNPs) of CYP3A5 gene, ABCB1 gene, ABCC2 gene and SCLO1B3 gene. Toxicities during treatment of docetaxel were evaluated and defined according to the NCI CTCAE version 3.0.
Results Pharmacogenetic analysis was performed in 218 Korean women who had received the uniformly planned chemotherapy. With regard to ABCB1 3435 C>T, ABCB1 3435 T/T had significantly higher risks of neutropenia ($P = 0.015$). Meanwhile, allele frequencies for CYP3A5 6986 G and ABCB1 3435 T revealed a trend for neutropenia ($P = 0.107$ and 0.068). We could not find any other association between genotypes and other toxicities.
Discussion Although ABCB1 3435 T/T was significantly associated with docetaxel-related neutropenia in our study population, polymorphism of pharmacogenetic genes related to docetaxel metabolism did not appear to be evidently associated with docetaxel-related adverse events.

Keywords Docetaxel · Pharmacogenetics · Breast cancer · Adjuvant chemotherapy

Introduction

Since its initial approval in 1996, docetaxel had been shown to be effective in many cancers including breast, lung and prostate [1]. Despite this widespread use, however, inter-individual variability of toxicities related to docetaxel has been a major challenge in clinical practice. As a result, extensive investigations were performed to establish the relationship between toxicity, clinical activity and pharmacokinetics. Decrements in docetaxel clearance have increased the odds of developing grade 4 neutropenia, whereas smaller exposures of docetaxel have been associated with shorter time to progression of lung cancer [2, 3]. Moreover, population models with pharmacokinetic parameters have been built to explain inter-individual variability and pharmacokinetic-pharmacodynamic relationships [4, 5].

Several studies have explained the variability of pharmacokinetic parameters related to docetaxel by pharmacogenetics, the individual genetic difference in drug disposition and metabolism. Docetaxel is primarily metabolized in the liver, and CYP3A4 and CYP3A5 play major roles in this process. On the other hand, the main route of elimination of

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docetaxel and its metabolites is through biliary excretion through feces [6]. While ATP-binding cassette multidrug transporters ABCB1 and ABCC2 have been identified the efflux of docetaxel into bile acid, the key influx transporter of docetaxel into hepatocytes has been shown to be SLCO1B3. Various studies have evaluated the relationship between the polymorphism of these genes.

Node-positive early breast cancer patients benefit from adjuvant chemotherapy, which includes taxanes [7]. While investigations that apply the pharmacogenetic knowledge into individualized taxane therapy have been performed, reports have been limited partly because of different schedules and combinations for chemotherapy and heterogeneity in study populations [8]. In the present study, we analyzed the relationship between polymorphisms of CYP3A5, ABCB1, ABCC2 and SLCO1B3 genes and the toxicities of docetaxel in a homogenous Korean population of operable lymph node-positive breast cancer treated with adriamycin and cyclophosphamide followed by docetaxel as adjuvant chemotherapy after surgery.

Materials and methods

Study population and treatment

From March 2007 to June 2008, a prospective multinational observational study (Asia Pacific Breast Initiatives I, Sanofi-aventis) to evaluate toxicity profile of docetaxel in women with operable lymph node-positive breast cancer who received adriamycin and cyclophosphamide followed by sequential docetaxel as adjuvant chemotherapy. Patients were eligible if they were female with histologically proven lymph node-positive breast cancer, age 18–70 years at diagnosis, Eastern Cooperative Oncology Group (ECOG) performance status 0–1, and possessed adequate baseline hematologic function (absolute neutrophil count $\geq 1.5 \times 10^9$/L, platelet count $\geq 100 \times 10^9$/L), hepatic function (serum aspartate aminotransferase and alanine aminotransferase ≤ 2.5 upper limit of normal [UNL] and serum bilirubin ≤ 2 mg/dL) and renal function (serum creatinine ≤ 1.5 mg/dL). Treatment consisted of four cycles of adriamycin 60 mg/m^2 and cyclophosphamide 600 mg/m^2 on day 1 every 3 weeks, followed by 4 cycles of docetaxel 100 mg/m^2 on day 1 every 3 weeks as adjuvant chemotherapy. Toxicity was graded according to National Cancer Institute Common Toxicity Criteria (version 3.0). Complete blood counts were checked on day 8 and 15 of the first cycle of docetaxel chemotherapy. Menopause was defined as cessation of menstruation for at least 12 months.

We performed a retrospective cohort study utilizing genomic DNA derived from blood samples collected during study period in a total of 218 Korean breast cancer patients. The protocol was approved by the institutional review board, and all patients provided written informed consent and participated in the pharmacogenetic analysis.

Genotyping assay

Genomic DNA was isolated from about 3 mL peripheral blood using a Qiagen DNA extraction kit (Qiagen, Hilden, Germany). The genotyping of CYP3A5 (6986A>G; rs776746) was screened using the TaqMan fluorogenic 5′ nuclease assay (ABI, Foster City, CA, USA). The final volume of polymerase chain reaction (PCR) was 5 μL, containing 10 ng of genomic DNA and 2.5 μL TaqMan Universal PCR Master Mix, with 0.13 μL of 40× Assay Mix (Assay ID C___2684958_10). Thermal cycle conditions were as follows: 50°C for 2 min to activate the uracil N-glycosylase and to prevent carry-over contamination, 95°C for 10 min to activate the DNA polymerase, followed by 45 cycles of 95°C for 15 s and 60°C for 1 min. All PCR were performed using 384-well plates by a Dual 384-Well GeneAmp PCR System 9700 (ABI, Foster City, CA, USA), and the endpoint fluorescent readings were performed on an ABI PRISM 7900 HT Sequence Detection System (ABI, Foster City, CA, USA). Duplicate samples and negative controls were included to ensure accuracy of genotyping. The following polymorphisms were analyzed with SNaPshot assay: ABCB1(3435C>T, 2677G>T/A, 1236C>T; rs1045642, rs2032582, rs1128503), ABCC2 (−24C>T, 1249G>A, 3972C>T; rs717620, rs2273697, rs3740066) and SLCO1B3 (334T>G, 699G>A; rs4149117, rs7311358). The SNaPshot assay was performed according to the manufacturer's instructions (ABI PRISM SNaPShot Multiplex kit, Foster City, CA, USA). Analysis was carried out using Genemapper software (version 4.0; Applied Biosystems). Briefly, the genomic DNA flanking the interested SNP was amplified with PCR with Forward and Reverse primer pairs and standard PCR reagents in 10 microliter reaction volume, containing 10 ng of genomic DNA, 0.5 pM of each oligonucleotide primer, 1 microliter of 10× PCR buffer, 250 μM dNTP(2.5 mM each) and 0.25 unit i-StarTaq DNA Polymerase(5 unit/μL) (iNtRON Biotechnology, Sungnam, Kyungki-Do, Korea). Table 1 shows the primer sets and T_m used for the SNaPshot assay. Genotyping was carried out by researchers blinded to clinical outcome and toxicity data.

Statistical analysis

Chi-square test and Fisher's exact test were used to analyze associations between adverse events and genotypes. Data analyses were performed using the Statistical Software Package for Social Sciences (SPSS version 14.0; Chicago, IL).

Table 1 Primer sets and T_m for SNaPshot assay

	T_m (°C)
ABCB1 3435C>T (rs1045642)	55
Forward: TGTTTGACTGCAGCATTGC	
Reverse: TTTATTTGAAGAGAGACTTACATTAGGC	
SNP Primer: TGTTGGCCTCCTTTGCTGCCCTCAC	
ABCB1 2677G>T/A (rs2032582)	55
Forward: TTGTTGAAATGAAAATGTTGTCTG	
Reverse: AAAATAACACTGATTRGAATA CTTTACTCTACT	
SNP Primer: GAAAGATAAGAAAGAACTAGAAGGT	
ABCB1 1236C>T (rs1128503)	60
Forward: CAGGAAACAGCTATGACCTATTC GAAGAGTGGGCACAA	
Reverse: TGTAAAACGACGGCCAGTTCCATC AACACTGACctgga	
SNP Primer: GCCCACTCTGCACCTTCAGGTTCAG	
ABCC2 −24C>T (rs717620)	60
Forward: CAGGAAACAGCTATGAC Cactggtgagtctccctgtcc	
Reverse: TGTAAAACGACGGCCAG Taaggcaattttgcgactagc	
SNP Primer: GCATGATTCCTGGA CTGCGTCTGGAAY	
ABCC2 1249G>A (rs2273697)	55
Forward: TTTGTCCATGGGTCCTAATTT	
Reverse: ATGAAGTTGGTCACATCCATG	
SNP Primer: GACATCAGGTTCACTGTTTCTCCAA	
ABCC2 3972C>T (rs3740066)	55
Forward: TACCGACCTGAGCTGGATC	
Reverse: CATCCAGGCCTTCCTTCA	
SNP Primer: CTCCACCTACCTTCTCCATGCTACC	
SLCO1B3 334T>G (rs4149117)	55
Forward: TTGCTTGTGATTGTATTTGT	
Reverse: AAAAGGTAACTGCCCACT	
SNP Primer: TTATGGGAACTGGAAGTATTTTGACA	
SLCO1B3 699G>A (rs7311358)	55
Forward: GCATGTTAAATGAAAACCAA	
Reverse: GAATGGTGTCCTGCACTT	
SNP Primer: GCACTGGGATCTCTGTTTGCTAAAAT	

Table 2 Characteristics of patients

Total ($N = 218$)	No. of patients	(%)
Age* (years)	44	(26–65)
Weight* (kg)	59	(41–85.9)
Height* (cm)	157.7	(143.2–170.8)
Pathologic T stage		
T0	1	(0.5)
T1	77	(35.3)
T2	119	(54.6)
T3	19	(8.7)
T4	2	(0.9)
Pathologic N stage		
N1	116	(53.2)
N2	69	(31.7)
N3	33	(15.1)
Estrogen receptor		
Positive	158	(72.5)
Negative	60	(27.5)
Progesterone receptor		
Positive	154	(70.6)
Negative	64	(29.4)
HER-2		
Positive	74	(33.9)
Negative	144	(66.1)

* Age, weight and height are expressed in means (range)

Results

Clinical characteristics

Patient characteristics are shown in Table 2. The median age of the patients was 44 years (range, 26–65 years). Hormone receptor was expressed in 172 (78.9%) of 218 cases; estrogen receptor 72.5% and progesterone receptor 70.6%. HER-2/neu overexpression was observed in 33.9% of patients. Menstrual status was confirmed in 163 of 218 patients (74.8%). Among the confirmed patients, 50.9% (83/163) were pre-menopausal at time of surgery; however, only 11.7% (19/163) continued menstruation when adjuvant treatment for docetaxel was initiated.

Relationship between polymorphisms of CYP3A5, ABCB1, ABCC2 and SLCO1B3 and docetaxel-related toxicities

In general, treatment was well tolerated. Most of the patients completed 4 cycles of docetaxel regardless of genotype, and mean dose intensity was 24.43 ± 7.88 mg/m^2/week, which is 73% of the planned regimen of 100 mg/m^2 every 3 weeks (Table 3). The most frequently occurring toxicities were myalgia, nail changes, hand-foot skin changes, edema/fluid retention and neutropenia of all grades. The incidence of grade 3 non-hematologic toxicities was observed in the following incidence: myalgia, 15%; hand-foot skin changes, 4%; nail changes, 1%; and edema/fluid retention, 1%. Of the 94 incidences, 40.4% (38/98) were grade 3 and 59.6% (56/98) were grade 4 neutropenia.

The relationship of toxicities of all grades and polymorphisms of CYP3A5, ABCB1, ABCC2 and SLCO1B3 is shown in Table 4. Of the toxicities, only neutropenia

Table 3 Mean dose intensity of docetaxel according to genotype

SNP	Genotypes	No.	No. of patients who completed 4 cycles (%)	Dose intensity (mg/m^2/week)
CYP3A5 6986 A>G	*1/*1	122	110 (90)	24.72 ± 7.94
	*1/*3	82	71 (87)	24.10 ± 7.94
	*3/*3	13	11 (85)	23.48 ± 6.73
ABCB1 1236 C>T	*1/*1	40	39 (98)	25.87 ± 3.53
	*1/*8	106	93 (88)	24.16 ± 8.43
	*8/*8	72	61 (85)	24.01 ± 8.08
ABCB1 3435 C>T	*1/*1	97	90 (93)	25.28 ± 3.96
	*1/*6	98	84 (86)	23.63 ± 8.16
	*6/*6	21	18 (86)	24.98 ± 8.31
ABCB1 2677 G>T(A)	G/G	48	43 (90)	24.31 ± 7.49
	G/T(A)	98	85 (87)	23.96 ± 8.40
	T(A)/T(A)	62	55 (89)	25.14 ± 7.40
ABCC2 −24 C>T	C/C	118	107 (91)	24.85 ± 6.94
	C/T	83	72 (87)	23.97 ± 8.87
	T/T	15	13 (87)	23.85 ± 8.25
ABCC2 1249 G>A	G/G	183	161 (88)	24.01 ± 7.83
	G/A	35	32 (91)	26.62 ± 7.67
	A/A	0	–	–
ABCC2 3972 C>T	C/C	117	106 (91)	24.98 ± 6.81
	C/T	85	73 (86)	23.79 ± 9.05
	T/T	14	12 (86)	23.61 ± 8.49
ABCC2 rs12762549	G/G	90	81 (90)	24.86 ± 7.24
	G/C	97	86 (89)	24.43 ± 8.02
	C/C	31	26 (84)	23.16 ± 8.93
SLCO1B3 334T>G	T/T	16	13 (81)	22.58 ± 8.75
	T/G	83	73 (88)	24.26 ± 8.17
	G/G	118	105 (89)	24.78 ± 7.51
SLCO1B3 699G>A	G/G	16	14 (88)	22.58 ± 8.75
	G/A	82	72 (88)	24.23 ± 8.21
	A/A	119	106 (89)	24.79 ± 7.48
SLCO1B3 rs11045585	G/G	3	3 (100)	27.85 ± 3.65
	G/A	56	48 (86)	23.40 ± 8.02
	A/A	157	140 (89)	24.70 ± 7.87

showed a significant association with genotypes, which included ABCB1 3435 C>T. The relative risk (95% confidence interval) for neutropenia of ABCB1 3435 T/T genotype was 1.689 (1.183–2.416) compared with wild type ($P = 0.015$) (Table 5). Allele frequencies for CYP3A5 6986 G and ABCB1 3435 T revealed a trend for neutropenia ($P = 0.107$ and 0.068). There was no association between genotype and other toxicities. Additionally, patients were analyzed according to menopausal status at initiation of adjuvant chemotherapy. While pre-menopausal patients did not show a significant association between neutropenia and ABCB1 3435 T/T genotype, post-menopausal patients did show significance ($P = 0.048$, Table 5).

Discussion

This study evaluated the influence of pharmacogenetics on docetaxel toxicities in homogenously treated Korean population with early breast cancer. In our study, ABCB1 3435 T/T was significantly associated with docetaxel-related neutropenia and allele frequencies for CYP3A5 6986 G and ABCB1 3435 T revealed a trend for neutropenia. The results are consistent with previous reports that have identified ABCB1 and CYP3A5 as important factors in the effects of docetaxel [9–11].

Despite its activity in various entities, docetaxel is challenging to prescribe because of severe toxicities in selected

Table 4 Relationship between toxicities of all grades after docetaxel adjuvant therapy and genotypes

SNP	Genotypes	No.	N (%)				
			Neutropenia	Myalgia	Nail changes	Hand-foot skin changes	Edema/fluid retention
CYP3A5 6986 A>G	G/G	122	49 (40.2)	110 (90.2)	91 (74.6)	79 (64.8)	67 (54.9)
	G/A	82	42 (51.2)	76 (92.7)	57 (69.5)	53 (64.6)	46 (56.1)
	A/A	13	7 (53.8)	11 (84.6)	9 (69.2)	7 (53.8)	7 (53.8)
ABCB1 1236 C>T	C/C	40	17 (42.5)	36 (90.0)	23 (57.5)	25 (62.5)	19 (47.5)
	C/T	106	51 (48.1)	96 (90.6)	79 (74.5)	65 (61.3)	56 (52.8)
	T/T	72	31 (43.1)	66 (91.7)	55 (76.4)	50 (69.4)	46 (63.9)
ABCB1 3435 C>T	C/C	97	41 (42.3)	89 (91.8)	65 (67.0)	66 (68.0)	49 (50.5)
	C/T	98	43 (43.9)	89 (90.8)	75 (76.5)	60 (61.2)	56 (57.1)
	T/T	21	15 (71.4)	19 (90.5)	17 (81.0)	13 (61.9)	15 (71.4)
ABCB1 2677 G>T(A)	G/G	48	20 (41.7)	43 (89.6)	32 (66.7)	32 (66.7)	21 (43.8)
	G/T(A)	98	45 (45.9)	89 (90.8)	71 (72.4)	67 (68.4)	52 (53.1)
	T(A)/T(A)	62	29 (46.8)	57 (91.9)	47 (75.8)	37 (59.7)	44 (71.0)
ABCC2 −24 C>T	C/C	118	54 (45.8)	110 (93.2)	83 (70.3)	84 (71.2)	65 (55.1)
	C/T	83	38 (45.8)	72 (86.7)	61 (73.5)	44 (53.0)	44 (53.0)
	T/T	15	7 (46.7)	14 (93.3)	12 (80.0)	10 (66.7)	10 (66.7)
ABCC2 1249 G>A	G/G	183	80 (43.7)	165 (90.2)	134 (73.2)	115 (62.8)	99 (54.1)
	G/A	35	19 (54.3)	33 (94.3)	23 (65.7)	25 (71.4)	22 (62.9)
	A/A	0	0 (−)	0 (−)	0 (−)	0 (−)	0 (−)
ABCC2 3972 C>T	C/C	117	55 (47.0)	110 (94.0)	85 (72.6)	84 (71.8)	66 (56.4)
	C/T	85	36 (42.4)	73 (85.9)	59 (69.4)	46 (54.1)	45 (52.9)
	T/T	14	8 (57.1)	13 (92.9)	11 (78.6)	10 (71.4)	8 (57.1)
ABCC2 rs12762549	G/G	90	41 (45.6)	82 (91.1)	69 (76.7)	58 (64.4)	50 (55.6)
	G/C	97	45 (46.4)	88 (90.7)	68 (70.1)	58 (59.8)	51 (52.6)
	C/C	31	13 (41.9)	28 (90.3)	20 (64.5)	23 (74.2)	20 (64.5)
SLC01B3 334T>G	T/T	118	53 (44.9)	108 (91.5)	84 (71.2)	76 (64.4)	63 (53.4)
	T/G	83	39 (47.0)	75 (90.4)	61 (73.5)	53 (63.9)	46 (55.4)
	G/G	16	7 (43.8)	14 (87.5)	12 (75.0)	10 (62.5)	11 (68.8)
SLC01B3 699G>A	G/G	16	7 (43.8)	14 (87.5)	12 (75.0)	10 (62.5)	11 (68.8)
	G/A	82	38 (46.3)	74 (90.2)	60 (73.2)	52 (63.4)	45 (54.9)
	A/A	119	53 (44.5)	109 (91.6)	84 (70.6)	77 (64.7)	64 (53.8)
SLC01B3 rs11045585	G/G	3	0 (0)	3 (100)	2 (66.7)	2 (66.7)	2 (66.7)
	G/A	56	26 (46.4)	52 (92.9)	37 (66.1)	37 (66.1)	29 (51.8)
	A/A	157	72 (45.9)	141 (89.8)	116 (73.9)	100 (63.7)	90 (57.3)

patients. Various attempts to identify factors that account for this inter-individual variability have been done with pharmacokinetics and pharmacogenetics. After a variety of dose and schedules for monotherapy were evaluated, 100 mg/m^2 every 3 weeks became the standard schedule in many phase II studies [1]. However, as the optimal dose to balance efficacy and toxicity has not been fully evaluated with this capricious agent, clinicians prescribe docetaxel at a range from 60 to 100 mg/m^2. Moreover, in metastatic breast cancer, three doses of docetaxel (60, 75 or 100 mg/m^2) have been compared in a randomized phase III study [12]. In that study, 100 mg/m^2 was correlated with higher tumor response, but no significant improvement in the time to disease progression or overall survival was achieved. Moreover, an exploratory analysis of a randomized adjuvant trial in breast cancer has also shown that 80 mg/m^2 was not inferior to 100 mg/m^2 every 3 weeks [13]. Similar reports have been also done in the usage of docetaxel in different entities [12, 14]. In our study, the average dose intensity of docetaxel was 24.43 ± 7.88 mg/m^2/week, which approximates 75 mg/m^2 every 3 weeks. This contrasts from a retrospective Denmark study on docetaxel toxicity, which has reported that 1,055 of 1,143 patients completed 3 cycles of epirubicin (90 mg/m^2) and cyclophosphamide (600 mg/m^2) followed by three

Table 5 Estimated relative risk and 95% confidence interval of ABCB1 3435 C>T, menopausal status and neutropenia

	Neutropenia		RR (95% CI)	*P* value
	(+)	(−)		
ABCB1 3435 C>T				
Genotypes				
C/C	41	56	1.00	
C/T	43	55	1.04 (0.75–1.43)	0.82
T/T	15	6	1.69 (1.18–2.42)	0.015
Alleles				
C	125	167	1.00	
T	73	67	1.22 (0.99–1.50)	0.068
Pre-menopause				
ABCB1 3435 C>T				
Genotypes				
C/C	18	22		
C/T	16	18	1.05 (0.64–1.72)	0.859
T/T	5	3	1.39 (0.73–2.62)	0.454
Alleles				
C	52	62		
T	26	24	1.14 (0.82–1.59)	0.451
Post-menopause				
ABCB1 3435 C>T				
Genotypes				
C/C	15	21		
C/T	16	22	1.01 (0.59–1.73)	0.970
T/T	7	2	1.87 (1.11–3.14)	0.048
Alleles				
C	46	64		
T	30	26	1.28 (0.92–1.78)	0.151

cycles of docetaxel (100 mg/m^2) given intravenously every third week [15]. The relatively low-dose intensity and high incidence of toxicities in our report may be related to ethnic differences. The susceptibility of East Asians to taxane treatments has been explained by differences in drug-metabolizing genetic makeup; however, more investigation is required into identifying the exact culprit [5, 16].

Difficulties in identifying the optimal dosage may be related to the variability in pharmacokinetics. This has undergone extensive evaluation, especially as the population pharmacokinetic modeling methods were established during clinical drug development. Recently, Engels et al. have tried therapeutic drug monitoring that applied the modeling methods and successfully narrowed the pharmacokinetic variability of docetaxel with limited sampling [17]. However, pharmacokinetics may be only one component of the pharmacodynamics of docetaxel. This has been demonstrated by a study that investigated the high incidence of neutropenia in elderly patients with non-small cell lung cancer. In that study, despite lower tolerability to docetaxel, elderly did not show differences in pharmacokinetic parameters. Moreover, the influences of drug-metabolizing enzymes on pharmacokinetics may be limited by evaluating plasma concentrations alone [18].

Pharmacogenetic analysis on the metabolic pathway of docetaxel has been performed in hopes of identifying predicting factors related to docetaxel-related toxicities. Recently, Baker et al. have evaluated the functional and genetic pathway of docetaxel elimination in 92 cancer patients. In that study, 17 variants of SLCO1B3, CYP3A4, CYP3A5, ABCB1 and ABCC2 were functionally analyzed by the clearance of docetaxel and midazolam [9]. They reported that the simultaneous presence of CYP3A4*1B and CYP3A5*1A alleles was associated with an increase in docetaxel clearance. However, the clinical outcome was not reported with the pharmacogenetic and pharmacokinetic data. Recently, a Japanese case–control pharmacogenetic study, which investigated CYP3A4, CYP3A5, ABCB1, ABCC2, SLCO1B3, NR1/2 and NR1/3, concluded that rs12762549 in ABCC2 G and rs11045585 in SLCO1B3 G alleles were significantly associated with significant neutropenia [19]. Unfortunately, the clinical characteristics including diagnosis, demographics or pre-treatment chemotherapy were not assessable. On the other hand, a Taiwanese study evaluated CYP3A4, CYP3A5 and ABCB1 in the adjuvant treatment of docetaxel, epirubicin and cyclophosphamide in breast cancer patients; CYP3A5*3/*3, ABCB1 2677 G/G genotypes showed events of febrile neutropenia and ABCB1 3435 C/C more leucopenia [10]. In this study, however, pharmacogenetic influences of the combined regimen were evaluated. As our study, which evaluated a similar East Asian population of breast cancer patients in the adjuvant setting, evaluated the pharmacogenetics effects in the single treatment of docetaxel, the relationship between pharmacogenetics and toxicities of docetaxel was hoped to be more clarified.

In our study, which also evaluated dose intensity in this homogenous patient population, ABCB1 3435 T/T was significantly associated with docetaxel-related neutropenia not ABCB1 3435 C/C. The TT genotype of ABCB1 3435 C>T has been reported to be associated with increased drug levels and decreased intestinal ABCB1/P-gp expression including tacrolimus and digoxin [20, 21]. In addition, a recent neoadjuvant study has suggested that CC genotype has lower exposure of docetaxel in pre-menopausal breast cancer patients. These findings are consistent with our data and suggest an association between ABCB1 3435 T allele, increased docetaxel exposure and increased risk of neutropenia [11]. However, the hormonal influence of estrogen was not evident in our data. Hormonal status, however, is hard to evaluate without biochemical evidence including serum LH, FSH or estradiol levels. As the patients in our

study received sequential chemotherapy, menstrual status can change during treatment despite the fact that 12 months has not passed since last menstruation. This effect could have influenced our data.

Our study prospectively evaluated adverse events and performed SNP analysis ad hoc. Although our study is limited by the fact that it did not evaluate serum concentrations of docetaxel or its metabolites and was not fully balanced between various genotypes, it supports the pharmacogenetic-pharmacokinetic-toxicity relationship. Data related to efficacy and quality of life are presently under analysis, which will further improve our understanding of the complex pharmacology of docetaxel. We believe that future studies should include pharmacokinetic analysis and genotype-driven trial approaches to fully validate the predictive value of this genotype.

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