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ORIGINAL ARTICLE

Paclitaxel-induced sensory peripheral neuropathy is associated with an *ABCB1* single nucleotide polymorphism and older age in Japanese

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Abstract
Purpose Whether age and inter-individual variability of pharmacogenetics are risk factors for paclitaxel-induced peripheral neuropathy (PIPN) is inconclusive. This study was conducted to evaluate the influence of previously investigated single nucleotide polymorphisms (SNPs) and age, using genotype data from a prospective study of paclitaxel-related toxicity in Japanese patients with breast cancer.
Methods Peripheral blood mononuclear cells from 127 Japanese women with breast cancer who received weekly adjuvant paclitaxel were used to genotypes *SLCO1B3* T334G (rs4149117), *CYP2C8* A1196G (rs10509681), *ABCB1* C1236T (rs1128503), *ABCB1* G2677T/A (rs2032582), and *ABCB1* C3435T (rs1045642). Genotypic and clinical factors were investigated for associations with PIPN.
Results Of the five SNPs evaluated, no SNPs were significantly associated with grade 2 or higher PIPN. However, *ABCB1* 1236 TT showed a trend to associate with grade 2 or higher PIPN compared to *ABCB1* CT/CC (odds ratio 2.1, 95% CI 0.991–4.548, $p = 0.051$). In subgroup analysis, patients ≥60 years old with an *ABCB1* 1236 TT had a higher incidence of ≥grade 2 PIPN compared to patients with CT or CC genotype ($p = 0.027$). On multivariable analysis, age ≥60 years and the *ABCB1* 1236 TT showed a significant association with ≥grade 2 PIPN ($p = 0.005$ and $p = 0.034$, respectively).
Conclusions *ABCB1* 1236 TT genotype and older age might be a predictor of PIPN, which diminishes quality of life of cancer survivors.

Keywords Paclitaxel-induced peripheral neuropathy · Older age · *SLCO1B3* · *CYP2C8* · *ABCB1*

Introduction

Paclitaxel is a key chemotherapeutic agent in the treatment of early-stage and metastatic breast cancer [1, 2]. Paclitaxel-induced peripheral neuropathy (PIPN) predominantly

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presents with sensory symptoms such as numbness, tingling, and burning pain in a stocking and glove distribution, without motor symptoms. PIPN may limit the number of paclitaxel doses and may significantly diminish quality of life because it may persist and intensify after completion of chemotherapy. Approximately 50% of patients who developed PIPN recover within 4–6 months, although severe neuropathy may persist for years [3, 4]. The incidence of PIPN depends on several factors: dosage per cycle, treatment schedule, duration of infusion, cumulative dosage, concomitant platinum administration [5], and co-morbidities such as diabetes [6–9]. In particular, drug exposure is a primary driver of toxicity [10]. Paclitaxel is transported into hepatocytes by solute carrier organic anion transporter family member 1B3 (SLCO1B3) [11], an influx transporter, and is metabolized by cytochrome P450 2C8 (CYP2C8) and cytochrome P450 3A4 (CYP3A4) in the liver [12, 13]. ATP-binding cassette subfamily B member 1 (ABCB1) [14], an efflux transporter, ultimately disposes the metabolite into the bile canaliculi (Fig. 1). Therefore, whether single nucleotide polymorphisms (SNPs) in the genes of these proteins involved in the transport and metabolism of paclitaxel could explain the variability in toxicity has been investigated [15–20].

SLCO1B3 is a polymorphic gene with major SNPs in exon 3 (T334G) and exon 6 (G699A), which are in complete linkage disequilibrium. These SNPs result in a change from serine to alanine at amino acid 112 (S112A) and methionine to isoleucine at amino acid 233 (M233I), respectively [21]. Polymorphic variants in *SLCO1B3* exhibit differences in their transport characteristics for several substrates [22], although conflicting data exist regarding the relationship between *SLCO1B3* and pharmacokinetics. Smith et al. had reported that *SLCO1B3* polymorphisms were not associated with changes in the pharmacokinetics of paclitaxel [23], while van de Steegl et al. had reported that human *SLCO1B3* polymorphisms affected the pharmacokinetics of paclitaxel in mice [24]. One of the promising candidates as a risk factor for PIPN is *CYP2C8*3*. A significant relationship between grade 2 or higher neuropathy and the *CYP2C8*3* allele has been reported in both European-American and African-American patient cohorts [15]. The *CYP2C8*3* variant (rs11572080 and rs10509681) also leads to decreased paclitaxel metabolism [25] and increased drug exposure [18]. SNPs in *ABCB1* (*p*-glycoprotein, MDR1) have also been associated with neuropathy, since the ABCB1 protein is primarily responsible for excreting agents from the nervous system and back into the systemic circulation. *ABCB1* 3435 TT variant had significantly higher risk of grade ≥2 neurotoxicity compared to TC and CC genotype [20]. On the other hand, there is a report that *ABCB1* 3435 TT variant does not explain the

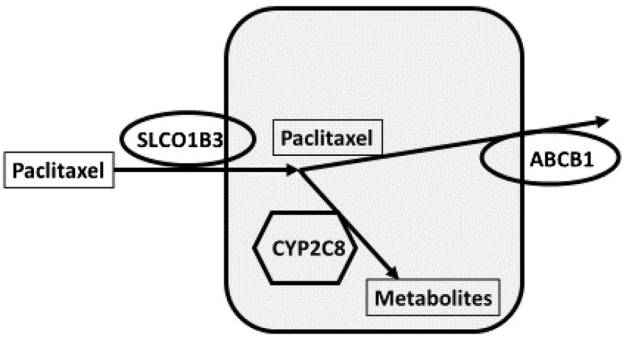

Fig. 1 Transport and metabolism of paclitaxel. Paclitaxel is transported into hepatocytes by SLCO1B3, an influx transporter, and is metabolized by CYP2C8 and CYP3A4 in the liver. ABCB1, an efflux transporter, ultimately disposes the metabolite into the bile canaliculi. *SLCO1B3* solute carrier organic anion transporter 1B3, *CYP2C8* cytochrome P4502C8, *CYP3A4* cytochrome P450 3A4, *ABCB1* ATP-binding cassette subfamily B1

substantial inter-individual variability in paclitaxel pharmacokinetics [26]. For the genetic polymorphism in *ABCB1* 2677G>T/A (rs2032582), a trend of a protective effect for sensory neuropathy was observed in GG wild-type carriers who received paclitaxel and carboplatin [27]. Moreover, *ABCB1* 1236 polymorphism associated with pharmacokinetics and toxicity in Japanese patients has been reported [28, 29]; however, there are negative reports also regarding associations of *ABCB1* 1236 and 2677G>T/A with pharmacokinetics and toxicity.

More recently, although genome-wide association studies related to PIPN included variants in *TUBB2A*, *FZD3, FGD4, XKR*, *EPHA5,* and *EPHA6* for a possible association with neurotoxicity [30–33], few results have been replicated in large, independent validation studies. Moreover, pharmacoethnicity in PIPN is reported [34]. However, associations between PIPN and genetic alterations in drug-metabolizing enzymes and transporters have not yet been clearly demonstrated in Asian people. While older age is considered a risk factor for treatment-related toxicity due to age-related changes in drug metabolism, comorbid conditions, and the frequent use of concomitant medications, no definitive associations between PIPN and age have been found [35, 36]. However, PIPN severity was associated with older age in Japanese patients treated with paclitaxel in our previous study [3]. We hypothesized that combination assessment of age and SNPs related to drug exposure would identify the high-risk patients for PIPN. Therefore, we retrospectively evaluated the impact of previously investigated candidate polymorphisms of genes and age on the development of PIPN using genotype data from a prospective study of Japanese breast cancer patients who received paclitaxel as adjuvant therapy.

Materials and methods

Patients

Japanese women with histologically confirmed breast cancer receiving neoadjuvant and/or adjuvant paclitaxel-containing regimens were enrolled in a prospective observational study to evaluate paclitaxel-related toxicity and explore the variants of genes associated with PIPN using the genome-wide association study (GWAS) (UMIN000005294). Eligible patients for this study were required to meet the following criteria: no previous chemotherapy, no history of diabetes, and no preexisting grade 1 or higher neuropathy. All patients provided written informed consent for adjuvant treatment and DNA collection for genetic analysis. The study was conducted in accordance with the Declaration of Helsinki and approved by the local institutional review board (protocol number 2013-199).

Treatment

Patients were pretreated with 4 cycles of cyclophosphamide (600 mg/m^2) and doxorubicin (60 mg/m^2) (AC) or cyclophosphamide (500 mg/m^2) with epirubicin (100 mg/m^2) and 5-fluorouracil (500 mg/m^2) (CEF) every 3 weeks. Paclitaxel (80 mg/m^2) was subsequently administered weekly as a 1-h infusion for 12 weeks. Patients who were positive for human epidermal growth factor receptor 2 (HER2) by immunohistochemistry or gene amplification (in situ hybridization) received trastuzumab concurrently with paclitaxel (weekly or every 3 weeks).

PIPN evaluation

Neuropathy was prospectively evaluated at baseline before paclitaxel treatment, at week 7, within 3 weeks after the final dose, and 1 year after the last dose of paclitaxel, based on the National Cancer Institute Common Terminology Criteria for Adverse Events 4.0 [37]. We decided four assessment points for PIPN assessment, based on our previous study, which showed that median time to onset of PIPN was 28 days. Moreover, 40% of patients showed persistent PIPN at 1 year after completion of treatment [3].

Genotyping

A 10-mL blood sample was collected from each patient at enrollment. Genotyping was performed for eligible patients who had sufficient DNA in the sample. DNA was extracted, and the concentration was fixed at 10 ng/μL. Blinded genotyping was performed using the i-densy™ genetic testing platform (ARKRAY, Inc., Kyoto, Japan) and the quenching probe system (QP-system) based on the principles of mutant detection. The i-densy™ automatically performs polymerase chain reaction (PCR), and mutant detection using extracted DNA within 60 min as previously described [38]. We used quenching probes (QProbe, Nippon Steel Kankyo Engineering Co., Ltd., Tokyo, Japan).

The SNPs that we analyzed were *SLCO1B3* T334G (rs4149117), *CYP2C8* A1196G (rs10509681), and *ABCB1* C1236T (rs1128503), G2677T/A (rs2032582), and C3435T (rs1045642). The genotypes were categorized as wild type, heterozygous, or homozygous variant. For *ABCB1* G2677T/A, each patient was classified as having *ABCB1* homozygous (TT) variant, heterozygous (GT or AT), or homozygous (GG) wild type. QP-system cannot distinguish between GT and AT as haplotype of *ABCB1* G2677T/A. The primers are shown in Supplementary Table 1. The fluorescent pigments that were used are TAMRA, PACIFIC BLUE, and BODIPY FL.

Genotyping was performed blinded to neuropathy data. For quality control, cutoff value for exclusion was set at 0.95 for call rate by SNP and patient. Hardy–Weinberg equilibrium (HWE) was also assessed to detect possible genotyping issues.

Statistical analysis

The primary objective was to evaluate the association between the grade of PIPN, age, and the variants of *SLCO1B3*, *CYP2C8,* and *ABCB1*. The *SLCO1B3*, *CYP2C8,* and *ABCB1* genotype frequencies were assessed for concordance with expectations under the HWE with the threshold for significant deviation from theoretical distribution being set at $p = 0.05$, using the Chi-square test and Fisher's exact test (degree of freedom = 1). All analyses were performed using the highest grade of treatment-related sensory peripheral neuropathy. Patients in whom paclitaxel was discontinued due to adverse events, except neuropathy, were excluded from the analyses. The univariate association between genotype and severity of PIPN on genotypic or recessive model was assessed using Chi-square test. For the tri-allelic SNP G2677T/A in *ABCB1*, patients carrying an A allele were analyzed as a T allele because of QP-system treating the A allele as a T allele. Multivariable logistic regression analysis was used to identify the risk factors for grade 2 or higher maximum PIPN at any time after the administration of paclitaxel. Pre-treatment regimen (AC vs. CEF), body surface area (BSA) (<1.5 vs. ≥1.5 m^2), and age (<60 vs. ≥60 years) were included as clinical covariates. We pre-planned to dichotomize age at 60 years and compare PIPN, referring to our previous study that showed significant association between age ≥60 years and duration of PIPN [3]. Moreover, we

Table 1 Patient characteristics

	All patients ($n = 127$)
Age (years)	
Median (range)	50 (25–75)
Body surface area (m^2)	
Median (range)	1.51 (1.20–1.91)
ABCB1 C1236T	
Wild (CC)/hetero (CT)/variant (TT)	20 (16%)/65 (51%)/42 (33%)
*ABCB*1 G2677A/T	
Wild (GG)/hetero (GT)/variant (TT)	52 (41%)/61 (48%)/14 (11%)
ABCB1 C3435T	48 (38%)/58 (46%)/21 (16%)
Wild (CC)/hetero (CT)/variant (TT)	
*SLCO1*B3 T334G	
Wild (TT)/hetero (TG)/variant (GG)	9 (7%)/44 (35%)/74 (58%)
CYP2C8 1196A>G	
Wild (TT)/hetero (CT)/variant (CC)	127 (100%)/0/0
Maximum PN	
Grade 0/1/2/3	2/59/56/10 (2%/46%/44%/8%)
Cumulative paclitaxel dose (mg/m^2) median (range)	933 (560–960)
Treatment prior to paclitaxel	
AC	65 (51%)
CEF	62 (49%)
Treatment concurrent with paclitaxel	
Trastuzumab (yes vs. no)	29 (23%) vs. 98 (77%)
Treatment setting	
Neoadjuvant	62 (49%)
Adjuvant	65 (51%)
Full-dose administration of paclitaxel (960 mg/m^2 over 12 weeks)	108 (85%)
Paclitaxel dose reduction	4 (3%)
Termination of paclitaxel due to PIPN	11 (9%)
Dose omission due to other reasons	4 (3%)

AC cyclophosphamide and doxorubicin, *CEF* cyclophosphamide, doxorubicin, and 5-fluorouracil, *PIPN* paclitaxel-induced peripheral neuropathy

pre-planned to dichotomize BSA by 1.5 and compare PIPN, referring to the administration method of S-1 therapy for Japanese cancer patients [39]. A two-sided P value of <0.05 was considered statistically significant, and all analyses were performed using SAS software (version 9.2; SAS Institute, Cary, NC, USA).

Results

Patient characteristics

One hundred and sixty-two of 197 Japanese women enrolled between February 2011 and October 2013 at two study sites were analyzed. Thirty-five patients were excluded from the analysis including patients treated with docetaxel ($n = 20$), patients lost to follow-up ($n = 9$), patients in whom paclitaxel was discontinued due to adverse events other than peripheral neuropathy ($n = 3$), and patients with a history of prior paclitaxel usage ($n = 3$). Patient characteristics are listed in Table 1. The median age was 50 years (range 25–75 years), and 33 patients were ≥60 years old (26%).

Distribution of the *SLCO1B3*, *CYP2C8*, and *ABCB1* genotypes

Genotyping call rates by SNP and patient were estimated. It was found that the both call rates (by SNP and patient) were >0.95, and all the SNPs and samples were included in analyses. G2677T/A genotypes were confirmed to be in HWE ($\chi^2 = 0.475$, $p = 0.491$ for *SLCO1B3* T334G, $\chi^2 = 0.388$, $p = 0.533$ for *ABCB1* C1236T, $\chi^2 = 0.239$, $p = 0.625$ for *ABCB1* C3435T, and $\chi^2 = 0.385$, $p = 0.535$ for *ABCB1* G2677T/A). The genotype distributions were all in HWE except *CYP2C8* A1196G, for which genotypes

of all of the patients were homozygous for the major allele, and thus, statistical analyses were not conducted. Minor allele frequencies (MAF) were 0.244 for *SLCO1B3* T334G, 0.413 for *ABCB1* C1236T, 0.394 for *ABCB1* C3435T, and 0.350 for *ABCB1* G2677T/A.

Age and grade of PIPN

Among the 127 patients who were treated with weekly paclitaxel (median cumulative dose 933 mg/m^2, range 560–960 mg/m^2), 66 (52%) patients experienced grade 2 or higher PIPN. Grade 2 or higher PIPN was significantly associated with an age ≥60 years compared to age <60 years [odds ratio 3.30, 95% confidence interval (CI) 1.39–7.86, $p = 0.006$].

Association between SNPs and PIPN

None of the four SNPs were significantly associated with grade 2 or higher PIPN in the genotypic model (Table 2). However, *ABCB1* 1236 TT showed a trend to associate with grade 2 or higher PIPN compared to ABCB1 CT/CC in the recessive model. (odds ratio 2.1, 95% CI 0.991–4.548, $p = 0.051$) (Supplementary Table 2). For patients who were ≥60 years old, *ABCB1* 1236 TT was significantly associated with PIPN ($p = 0.027$). In contrast, no association was observed for *ABCB1* 1236 TT among patients who were <60 years old (Table 3).

Multivariable analyses

The clinically relevant covariates [SNPs, age, pre-treatment regimen (CEF vs. AC), and body surface area (<1.5 vs. ≥1.5 m^2)] were included in logistic regression analysis. The age of 60 years (odds ratio 3.652, 95% CI 1.468–9.085, $p = 0.005$) and *ABCB1* 1236 TT (odds ratio 2.404, 95% CI 1.067–5.419, $p = 0.034$) were identified as independent risk factors associated with grade 2 or higher PIPN. The grade of PIPN in patients with the *SLCO1B3* 334 TT tended to be higher than in those with *SLCO1B3* 334 GG or GT ($p = 0.052$) (Table 4).

Discussion

We retrospectively evaluated the influence of candidate genes with functions in either transport or metabolism of paclitaxel and PIPN and age on the development of PIPN for breast cancer patients treated with paclitaxel, using prospectively collected data. Multivariable analysis revealed that the *ABCB1* 1236 TT variant and patient age of 60 years were significantly associated with grade 2 or higher PIPN. In addition, there was a trend for *SLCO1B3* 334 TT to be associated with an increased risk of PIPN. To the best of our knowledge, the present study is the first study for Japanese patients to demonstrate that older age and SNPs are associated with an increased severity of PIPN.

Table 2 The association between gene variant and the occurrence of PIPN ($n = 127$)

Gene variant	dbSNP ID	Genotype	PIPN		*p* value
			Grade 0–1 (*n*)	Grade 2–3 (*n*)	
SLCO1B3 T334G	rs4149117	Wild (TT)	2% (2)	5% (7)	0.255
		Hetero (TG)	17% (21)	18% (23)	
		Variant (GG)	30% (38)	28% (36)	
ABCB1 C1236T	rs1128503	Wild (CC)	9% (11)	7% (9)	0.148
		Hetero (CT)	28% (35)	23% (30)	
		Variant (TT)	12% (15)	21% (27)	
ABCB1 G2677T[a]	rs2032582	Wild (GG)	21% (26)	21% (26)	0.888
		Hetero (GT)	22% (29)	25% (32)	
		Variant (TT)	5% (6)	6% (8)	
ABCB1 C3435T	rs1045642	Wild (CC)	19% (24)	19% (24)	0.939
		Hetero (CT)	21% (27)	24% (31)	
		Variant (TT)	8% (10)	9% (11)	
ABCB1 C1236T, G2677T/A, C3435T		All-wild (1236CC/2677GG/3435CC)	7% (10)	5% (6)	0.444
		Hetero	35% (45)	43% (54)	
		All-variant (1236TT/2677TT/3435TT)	5% (6)	5% (6)	

PIPN paclitaxel-induced peripheral neuropathy

[a] *ABCB1* G2677A was excluded because QP-system could not distinguish between GT and AT as haplotype of *ABCB1* G2677T/A

Table 3 The association of PIPN with gene variants and age

Gene variant	Genotype	Age <60 years ($n = 94$)		Age ≥60 years ($n = 33$)	
		PIPN Grades 0–1/2–3 (n)	p value	PIPN Grades 0–1/2–3 (n)	p value
SLCO1B3 T334G	Wild (TT)	2%/5% (2/5)	0.106	0/6% (0/2)	0.077
	Hetero (TG)	16%/18% (15/17)		18%/18% (6/6)	
	Variant (GG)	38%/21% (35/20)		9%/49% (3/16)	
ABCB1 C1236T	Wild (CC)	10%/7% (9/7)	0.769	6%/6% (2/2)	0.027
	Hetero (CT)	30%/21% (28/20)		21%/30% (7/10)	
	Variant (TT)	16%/16% (15/15)		0/37% (0/12)	
ABCB1 G2677T[a]	Wild (GG)	21%/19% (20/18)	0.894	18%/24% (6/8)	0.180
	Hetero (GT)	28%/20% (26/19)		9%/40% (3/13)	
	Variant (TT)	7%/5% (6/5)		0/9% (0/3)	
ABCB1 C3435T	Wild (CC)	19%/16% (18/15)	0.942	18%/27% (6/9)	0.278
	Hetero (CT)	25%/19% (24/18)		9%/40% (3/13)	
	Variant (TT)	11%/10% (10/9)		0/6% (0/2)	
ABCB1 C1236T, G2677T/A, C3435T	All-wild	9%/5% (8/5)	0.825	6%/3% (2/1)	0.205
	Hetero	40%/35% (38/33)		21%/64% (7/21)	
	All-variant	7%/4% (6/4)		0/6% (0/2)	

PIPN paclitaxel-induced peripheral neuropathy, *CI* confidence interval

[a] *ABCB1* G2677A was excluded because QP-system could not distinguish between GT and AT as haplotype of *ABCB1* G2677T/A

Table 4 Multivariate analysis of factors that were associated with grade 2 or higher PIPN

Variables	Odds ratio	95% CI	p value
Pre-treatment regimen			
AC vs. CEF	1.289	0.610–2.725	0.506
Body surface area (m^2)			
<1.5 vs. ≥1.5	1.575	0.733–3.384	0.245
Age (years)			
<60 vs. ≥60	3.652	1.468–9.085	0.005
ABCB1 1236 C>T			
CC or CT vs. TT	2.404	1.067–5.419	0.034
SLCO1B3 334 T>G			
GG or GT vs. TT	5.379	0.987–29.320	0.052

PIPN paclitaxel-induced peripheral neuropathy, *CI* confidence interval, *AC* cyclophosphamide and doxorubicin, *CEF* cyclophosphamide, doxorubicin, and 5-fluorouracil

Our findings indicate that age ≥60 years was the most significant risk factor for PIPN. Prior studies have given conflicting results regarding the pharmacokinetics of paclitaxel in elderly patients [40]. Multiple factors may contribute to a decrease in drug clearance in the liver of older individuals [41]. Liver size and hepatic blood flow are 25–35% lower in older individuals compared to younger adults. Older individuals also exhibit decreased bile flow [42]. Moreover, the specific cytochrome P450 (CYP) contents of the liver decrease with aging [43].

In addition to age, candidate genes in the pharmacokinetic and pharmacodynamic pathways for paclitaxel appear to play a role in the development of PIPN. *ABCB1* 1236 TT and *SLCO1B3* TT were identified as risk factors for PIPN in our study. However, *ABCB1* variants have been reported to be associated with both increased and decreased risks of PIPN previously [19, 44]. Moreover, there is no report of the association between a *SLCO1B3* genotype and PIPN although it is associated with clinical effect and toxicity except for PIPN. Most previous pharmacogenetic studies were conducted in a small number of patients with different tumor types undergoing a variety of treatment regimens, and differences in the paclitaxel dosing schedule may partially explain the conflicting results. *CYP2C8*3* variants have been most frequently reported as being positively associated with an increased risk of neurotoxicity [15]. However, no patients had *CYP2C8*3* in the present study. The *CYP2C8*3* variant occurs primarily in Caucasian individuals with a frequency of approximately 0.13, while most Japanese individuals do not have the *CYP2C8*3* variant [45]. Considering these ethnic differences in SNP distribution, it is reasonable to identify the risk factors, except for *CYP2C8*3,* in Japanese population.

There are some limitations in this study. First, QP-system is designed not to distinguish between 2677G and 2677A. However, because the heterozygous genotype can be specified and frequency of 2677A is low, its

influence is considered small. Moreover, we consider that QP-system is potentially convenient in clinic because of its fast turnaround time. Second, in whole analysis, the current study had 90% power to detect the differences between groups using Chi-squared test at a two-sided α error of 0.05. In subgroup analysis ($n = 33$; patients aged $\geq$60 years), it had 67% power at a two-sided α error of 0.2. Therefore, it is underpowered in the subgroup population. Additionally, no adjustments were made for multiplicity of inferences.

In conclusion, PIPN was associated with age $\geq$60 years and *ABCB1* 1236 TT in Japanese female breast cancer patients who received paclitaxel as adjuvant treatment for primary breast cancer. Optimal dosing of paclitaxel in elderly patients warrants further investigation to mitigate the risk of PIPN. Although our data are not yet sufficiently conclusive to clinically recommend genetic tests to predict neurotoxicity, we believe that combination assessment of older age and *ABCB1* 1236 variant may help to identify high-risk patients for PIPN.

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Compliance with ethical standards

Conflict of interest YF reports grants from Taiho Pharmaceutical Co. Ltd, grants from Takeda Pharmaceutical Company Ltd, grants from Takeda Bio Development Center Ltd, grants and other from Chugai Pharmaceutical Co Ltd, other from Astra Zeneca KK, other from Eisai Co Ltd, other from Daiichi Sankyo Co Ltd, other from Sanofi-Aventis KK, grants and other from Eli Lilly Japan KK, other from Yakult Honsha Co Ltd, other from NEC Corporation, outside the submitted work. CS reports grants from Eli Lilly Japan KK and Pfizer KK. KH is currently an employee at Chugai Pharmaceutical Europe. The other authors have no conflicts of interest to declare.

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional research committee and with the 1964 Declaration of Helsinki.

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