original article

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Association of the *ABCB1* gene polymorphisms 2677G>T/A and 3435C>T with clinical outcomes of paclitaxel monotherapy in metastatic breast cancer patients

H. Chang[1,2,3], S. Y. Rha[1,2,3,4], H.-C. Jeung[1,2,3], C.-K. Im[1,2,3], J. B. Ahn[1,2,3], W. S. Kwon[2,4], N. C. Yoo[1,2,3], J. K. Roh[1,2,3,4] & H. C. Chung[1,2,3,4]*

[1]*Department of Internal Medicine;* [2]*Cancer Metastasis Research Center;* [3]*Medical Oncology, Yonsei Cancer Center;* [4]*Brain Korea 21 Project for Medical Science, Yonsei University College of Medicine, Seoul, Korea*

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Background: *ABCB1* is responsible for multidrug resistance, the principal mechanism by which many cancers develop resistance to chemotherapeutic drugs. There is a controversy whether *ABCB1* gene polymorphisms correlate with survival and response in cancer patients treated with chemotherapy. We evaluated the association between clinical outcome (safety and efficacy) of paclitaxel monotherapy in metastatic breast cancer patients with *ABCB1* gene polymorphisms 2677G>T/A or 3435C>T.

Patients and methods: Patients with metastatic breast cancer were treated with 175 mg/m^2 paclitaxel per 3-week cycle. Peripheral blood mononuclear cells from patients were used to genotype *ABCB1* 2677G>T/A and 3435C>T polymorphisms. Genotypes were investigated for their association with tumor response, survival, toxicity, and chemoresistance.

Results: *ABCB1* 3435 CT showed a significantly lower disease control rate than the CC genotype ($P = 0.025$). *ABCB1* 3435 CT was correlated with shorter overall survival (OS) in Cox regression analysis ($P = 0.026$). The 2677 GG genotype showed a significant association with chemoresistance to paclitaxel and anthracycline ($P = 0.04$ and 0.04, respectively). None of the *ABCB1* genotypes correlated with toxicity.

Conclusions: *ABCB1* genotypes may be a predictor of paclitaxel activity as well as a prognostic factor in metastatic breast cancer patients.

Key words: *ABCB1* polymorphism, breast neoplasms, paclitaxel, tumor response

original article

background

Paclitaxel is an effective agent in the treatment of metastatic breast cancer. It seems particularly promising because it has elicited impressive response rates as second- and third-line therapy [1]. Paclitaxel has been reported to elicit a response rate of 20%–62% as a first-line therapy and 4%–32% in previously treated patients [2]. Chemotherapy resistance is a major obstacle to successful treatment and several potential mechanisms have been reported to account for resistance to paclitaxel. These are decreased sensitivity to apoptosis-inducing stimuli, alterations in tubulin binding and microtubule dynamics, and overexpression of the transporter protein P-glycoprotein (P-gp) [3].

In searching for an answer to the multidrug resistance phenotype, many studies have been focused on the *ABCB1* gene. It encodes P-gp, a transmembrane protein that acts as an energy-dependent drug efflux pump for chemotherapeutic drugs commonly used in metastatic breast cancer, including doxorubicin and taxanes [4]. More than 50 single-nucleotide polymorphisms (SNPs) and three insertion/deletion polymorphisms have been reported in the *ABCB1* gene and some of these variants affect the expression and function of P-gp [5, 6]. Hoffmeyer et al. found that *ABCB1* gene polymorphism could affect P-gp function. They indicated that a synonymous SNP in exon 26, 3435C>T, correlated with the level of P-gp expression in the intestine. Individuals homozygous for this SNP had lower P-gp expression and showed higher plasma levels of the P-gp substrate digoxin [7]. Tanabe et al. [8] also found a nonsignificant trend for placental P-gp expression in relation to polymorphisms at position 2677 (GG>G/mut>mut/mut). SNP of *ABCB1* may increase the efflux of antineoplastic agents from cancer cells or increase

*Correspondence to: Dr H. C. Chung, Medical Oncology, Yonsei Cancer Center, Cancer Metastasis Research Center, Department of Internal Medicine, Yonsei University College of Medicine, 134, Shinchon-Dong, Seodaemoon-gu, 120-752, Seoul, Korea. Tel: +82-2-2228-8132; Fax: +82-2-393-3652; E-mail: unchung8@yuhs.ac

elimination from the body, resulting in lower plasma concentrations, thereby influencing their therapeutic efficacy.

On the basis of this information, we carried out an association study between clinical outcome of paclitaxel monotherapy (efficacy and safety) and the *ABCB1* gene polymorphisms 2677G>T/A and 3435C>T in metastatic breast cancer patients.

patients and methods

patients

Women with histologically confirmed breast cancer were eligible for enrollment. They were required to be nonpregnant (≥18 years of age), have an Eastern Cooperative Oncology Group performance status of 0–2, and a life expectancy of >12 weeks. Prior chemotherapy was permitted if completed at least 4 weeks before entry into the study. Prior taxane therapies were not allowed, but prior hormonal therapy, immunotherapy, and localized radiotherapy were permitted.

All patients were required to have clinically or radiographically measurable disease and to have adequate renal, hepatic, and bone marrow function defined as follows: serum creatinine ≤1.5 × upper normal limit (UNL), total bilirubin ≤ 1.5 × UNL, absolute neutrophil count ≥ 1.5×10^9/l, platelet count ≥ 100×10^9/l, AST and ALT ≤ 3.0 × UNL, and alkaline phosphates ≤ 3.0 × UNL. Pretreatment evaluation was carried out within 4 weeks of therapy initiation and included full history, physical examination, blood cell count, biochemical screening profile, chest X-ray, and appropriate computed tomography imaging for disease assessment.

Patients were ineligible if they had a history of neoplasm other than breast cancer (excepting nonmelanomatous skin cancer or curatively treated cervical carcinoma *in situ*), a history of ventricular arrhythmias or congestive heart failure, preexisting motor or sensory neuropathy greater than grade 1, or any other underlying medical condition that would hinder study participation. Pregnant or lactating patients and those with child-bearing potential who did not implement adequate contraceptive measures were also ineligible.

definition of anthracycline and paclitaxel sensitivity

Anthracycline-refractory disease referred to recurrent disease during anthracycline-containing adjuvant therapy or disease that never responded and progressed during palliative anthracycline chemotherapy. Anthracycline-resistant disease was defined as disease that relapsed within 12 months after anthracycline adjuvant therapy, disease that initially responded but progressed with therapy, or disease that progressed within 6 months after stopping palliative anthracycline therapy. An anthracycline-sensitive disease referred to a disease that relapsed 12 months after anthracycline adjuvant therapy or a disease that progressed 6 months after stopping palliative anthracycline therapy [9]. Generally, paclitaxel treatment was done after anthracycline failure and thus, paclitaxel-resistant disease was defined as a disease that progressed while receiving paclitaxel or within 3 months of the last administration of paclitaxel. A paclitaxel-sensitive disease was defined as a disease that progressed 3 months after the last paclitaxel chemotherapy cycle [10].

treatment

Paclitaxel (175 mg/m^2) was administered over 3 h every 3 weeks. Premedications consisted of diphenhydramine, H_2 blocker, and dexamethasone. Treatment continued until disease progression or occurrence of prohibitive toxicity. In the event of grade 3–4 hematologic toxicity, treatment was delayed until recovery. For all non-hematologic grade 3 toxic effects, treatment was held until toxicity recovered to grade 1.

response and toxicity assessment

Tumor response measurements were made according to the Response Evaluation Criteria in Solid Tumors every two cycles and all responses had to be confirmed by a second measurement after an additional 4 weeks. Complete blood cell counts and toxicity assessments were carried out weekly, and performance status and serum chemistry were assessed before each cycle. Toxicity was evaluated according to National Cancer Institute Common Toxicity Criteria (version 3.0).

genotyping

Peripheral blood mononuclear cells were isolated from blood using Ficoll-Paque (Pharmacia, Uppsals, Sweden) following the manufacturer's instructions. Genomic DNA (gDNA) from lymphocytes was extracted with the LaboPass™ Blood kit (Genotein Biotech, Seoul, Korea). Extracted gDNA was amplified by PCR using an Eppendorf Mastercycler Gradient (Brinkmann Instruments, Inc., New York, USA). PCR cycling was done with an initial denaturation at 95°C for 2 min followed by 30 cycles of denaturation at 94°C for 30 s, annealing at 57°C for 20 s, and extension at 72°C for 30 s. Forward (F) and reverse (R) primers were designed on the basis of target gene sequences obtained from GenBank: *ABCB*1 2677G>T/A: 5′-ATTGCAATAGCAGGAGTTGT-3′(F), 5′-CTGGCTTTGCTACTTTCTGT-3′(R) and 3435C>T: 5′-ACAATTATGACCTTGTTGGG-3′(F), 5′-TTCTCTTCACTTCTGGGAGA-3′(R). Sequencing of PCR products was carried out according to the manufacturer's instructions using the CEQ 8000 Dye Terminator Kit (CEQ™ 8000, Beckman Coulter, Inc., Fullerton, CA, USA). Sequence data were analyzed and compared using the GeneDoc system (www.psc.edu/biomed/genedoc) and FinchTV software.

statistical methods

The haplotype frequency of *ABCB*1 was estimated by the expectation-maximization algorithm, PHASE version 2.0 (http://www.stat.washington.edu/stephens/software.html). The significance of the differences in genotypes between chemoresistant and sensitive patients was calculated using a Fisher's exact test. Progression-free survival (PFS) was defined as the time interval between the date of the first administration of paclitaxel and the date of disease progression or the date of death as a result of any cause. For PFS analyses, patients were censored at the time of last clinical contact if they were lost to follow-up, did not experience disease progression, or died before the cut-off date for the analyses. Patients were also censored on the date they received any subsequent anticancer therapy. Overall survival (OS) was calculated from the date of the first administration of paclitaxel to the date of death or the date of last contact (censored observation). The Kaplan–Meier method was used to estimate the distribution of time to events. Cox regression analysis was applied to determine the contribution of polymorphisms and other factors to survival rate. The following characteristics were included for the Cox regression analysis of prognostic factors: age, performance status, hormone receptor status, number of previous regimens, prior history of anthracycline treatment, anthracycline resistance, number of metastatic sites, response to paclitaxel, and *ABCB1* 2677G>T/A and 3435C>T genotypes. A logistic regression model was used to calculate the odds ratio and the corresponding 95% confidence interval (CI).

results

patient characteristics

Characteristics of 121 patients treated from September 1998 to August 2005 are listed in Table 1. The majority (85%) of patients had received prior anthracycline chemotherapy, either

as adjuvant treatment (54 patients) or as therapy for metastatic disease (49 patients). There were 9 anthracycline-refractory patients, 40 anthracycline-resistant patients, and 54 anthracycline-sensitive patients.

ABCB1 genotype was examined in 108 patients (89.3%), whose gDNA could be extracted from peripheral blood cells. Frequencies of the *ABCB1* 2677 GG, GT, GA, TT, TA, and AA genotypes were 21.3%, 27.8%, 16.7%, 14.8%, 14.0%, and 3.3%, respectively. Frequencies of the *ABCB1* 3435 CC, CT, and TT genotypes were 50.9%, 10.2%, and 38.9%, respectively. Frequencies of the 2677G–3435C, 2677G–3435T, 2677T–3435C, 2677T–3435T, 2677A–3435C, and 2677A–3435T haplotypes were 24.5%, 19.0%, 20.4%, 11.6%, 10.6%, and 13.9%, respectively.

association with tumor response and disease control rate

The median number of treatment cycles was 6 (range 1–16), with a total of 713 cycles. The median relative dose intensity of paclitaxel was 0.89 (range 0.29–1.00). Of the 121 patients enrolled, 113 were fully eligible for response evaluation. Eight patients were unevaluable because of treatment refusal (two patients) and treatment discontinuation before the first scheduled response evaluation (six patients). There were five complete responses and 24 partial responses, for an overall response rate of 25.6%.

The *ABCB1* 3435 genotypes were associated with disease control rate (50% in CT, 84.9% in CC and 77.5% in TT: CT versus CC, $P = 0.025$). The disease control rate of paclitaxel was also affected by a patient's sensitivity to anthracycline (anthracycline refractory versus sensitive; 50.0% versus 84.3%, $P = 0.04$, anthracycline-resistant versus sensitive; 63.9% versus 84.3%, $P = 0.04$). In contrast, the *ABCB1* 2677 genotype and haplotypes did not correlate with response rate or disease control rate (Table 2).

association with survival

The median time to progression and median OS was 5.7 months (95% CI = 4.6–6.8) and 18.1 months (95% CI = 12.5–23.8), respectively.

There was no difference in PFS among *ABCB1* 3435 genotypes. In multivariate analysis for PFS, response to paclitaxel and anthracycline resistance was independent prognostic factors [response to paclitaxel hazard ratio (HR) = 1.81, 95% CI = 1.02–3.21, $P = 0.042$; anthracycline refractory HR = 3.49, 95% CI = 1.35–9.06, $P = 0.01$]. In contrast, patients with the *ABCB1* 3435 CT genotype showed a tendency towards shorter OS than patients with the CC genotype (13.6 versus 18.5 months, $P = 0.06$). In multivariate analysis for OS, the *ABCB1* 3435 genotype was an independent prognostic factor. The HR of the 3435 CT genotype was 3.51 (95% CI = 1.16–3.51, $P = 0.026$). Response to paclitaxel, anthracycline-resistance, the number of metastatic sites, and age also were

Table 1. Patient characteristics

Characteristic	Number of patients	%
Number of enrolled patients	121	
Age (years), median (range)	49 (32–71)	
Eastern Cooperative Oncology Group performance status		
0	19	15.7
1	58	47.9
2	44	36.4
Dominant site of disease		
Soft tissue	15	12.4
Osseous	16	13.2
Visceral	90	74.4
Number of metastasis site		
1	37	30.6
2	54	44.6
3+	30	24.8
Hormone receptor status		
Positive	80	66.1
Negative	23	19.0
Unknown	18	14.9
Prior chemotherapy		
Adjuvant therapy only	68	56.2
Palliative therapy only	25	20.7
Both adjuvant and palliative	26	21.5
No prior therapy	2	1.6
Prior chemotherapy with anthracycline ($n = 103$)		
Adjuvant therapy	54	52.4
Palliative therapy	49	47.6

Table 2. Comparison of response and disease control rates according to clinical and pathologic characteristics and genotypes

Characteristic	RR (%)	*P* value	DCR (%)	*P* value
Paclitaxel treatment				
First line	24/66 (36.3)	0.002	54/66 (81.8)	>0.05
Second line	5/47 (10.6)		32/47 (68.1)	
Prior history of anthracycline				
No	9/18 (50.0)	0.017	16/18 (88.9)	>0.05
Yes	20/95 (21.0)		70/95 (73.7)	
Resistance to anthracycline				
Refractory	0/8 (0)	<0.001	4/8 (50.0)	0.024
Resistant	2/36 (5.5)		23/36 (63.9)	
Sensitive	18/51 (35.2)		43/51 (84.3)	
ABCB1 2677 G>T/A				
GG	5/23 (21.7)	>0.05	17/23 (73.9)	>0.05
GT + GA	15/44 (34.0)		36/44 (81.8)	
TT + TA + AA	8/36 (22.2)		28/36 (77.8)	
ABCB1 3435C>T				
CC	12/53 (22.6)	>0.05	45/53 (84.9)	0.04
CT	4/10 (40.0)		5/10 (50.0)	
TT	12/40 (30.0)		31/40 (77.5)	
ABCB1 haplotypes				
2677G–3435C	13/51 (25.4)	>0.05	40/51 (78.4)	>0.05
Others	43/155 (27.7)		122/155 (78.7)	

CR, complete response; PR, partial response; SD, stable disease; RR, response rate (CR + PR); DCR, disease control rate (CR + PR + SD).

independent prognostic factors (response to paclitaxel HR = 2.48, 95% CI = 1.05–5.83, $P = 0.037$; anthracycline resistant HR = 5.03, 95% CI = 2.30–10.9, $P < 0.001$, the number of metastatic sites HR= 2.09, 95% CI = 1.01–4.31, $P = 0.045$; age, HR= 3.14, 95% CI = 1.31–7.50, $P = 0.01$).

Neither the *ABCB1* 2677G>T/A genotype nor the *ABCB1* 2677/3435 haplotypes correlated with PFS or OS.

association between *ABCB1* genotypes and chemotherapy resistance

The distribution of *ABCB1* 2677G>T/A and 3435C>T genotypes according to chemotherapy sensitivity is shown in Table 3. The 2677 GG genotype was more frequent in paclitaxel-resistant patients than other 2677 genotypes (GG versus GT + GA, $P = 0.028$; GG versus others, $P = 0.04$). Other factors associated with paclitaxel sensitivity were anthracycline-resistance, previous treatment, and the number of metastatic sites (anthracycline-resistant versus sensitive, 11.1% versus 45.0%, $P = 0.001$; paclitaxel first-line versus second-line, 39.3% versus 19.1%, $P = 0.02$; one metastatic site versus multiple metastatic sites, 47.0% versus 24.0%, $P = 0.02$). The 2677 GG genotype was also more frequent in anthracycline-refractory patients than other 2677 genotypes ($P = 0.04$). Polymorphisms of *ABCB1* 3435C>T or *ABCB1* 2677/3435 haplotypes did not correlate with resistance to anthracycline or paclitaxel.

association with toxicity

Toxicity evaluation was available for all patients. Grade 3 or 4 neutropenia occurred in 36 patients (29.7%). Grade 3 anemia was observed in three patients (2.4%), and five patients experienced grades 3 and 4 thrombocytopenia (4.1%). Grade 3 neuropathy was encountered in 12 patients (9.9%), and no patient experienced grade 4 neuropathy. Grade 3 arthralgia/myalgia occurred in 5.8% of patients. Other grade 3 non-hematologic toxic effects were quite uncommon, occurring in no >2% of patients. Grade 4 non-hematologic toxicity was limited to one patient who experienced a severe infection.

No association was observed between the frequency of grade 3–4 hematologic or non-hematologic toxicity and *ABCB1* 2677G>T/A, 3435C>T genotypes or their haplotypes.

discussion

We evaluated the association between clinical outcome (efficacy and safety) of paclitaxel monotherapy (175 mg/m^2 every 3 weeks) and *ABCB1* 2677G>T/A or 3435C>T polymorphisms in patients with metastatic breast cancer, including patients who were treated with <6 cycles of chemotherapy. If we select patients with >6 cycles of treatment, it could be too selective in a clinical setting in predicting the patient's clinical outcome before treatment. We observed that *ABCB1* 3435 genotypes were significantly associated with disease control rate and this was also shown in patients who were treated with ≤6 cycles of paclitaxel (data not shown). As most of the metastatic breast cancer patients during the period of our study received paclitaxel-based combination chemotherapy with gemcitabine or other agents in clinical trials, the number of patients treated with paclitaxel monotherapy was fairly small.

Some studies have shown that selection of cells for resistance to either paclitaxel or doxorubicin can result in cross-resistance to both drugs [11, 12]. Moreover, less than one-half of breast cancer patients respond to paclitaxel after failing anthracycline chemotherapy [13]. Meta-analysis revealed a significant difference in the time to progression between women who had received prior anthracycline treatment and those who had not [14]. In our study, anthracycline-sensitive patients were more sensitive to paclitaxel than anthracycline-resistant patients. *In vitro* studies have shown that resistance to anthracycline may imply resistance to paclitaxel [15, 16]. A cDNA microarray study reported that approximately one-third of genes that changed expression after paclitaxel selection exhibited similar changes in expression after doxorubicin selection (and vice versa) [17]. In our study, resistance to both anthracycline and paclitaxel correlated with the *ABCB1* 2677 GG genotype, and this result indicates one possible explanation for cross-resistance to anthracycline and paclitaxel in the treatment of metastatic breast cancer. Guo et al. [15] reported that cells selected for resistance to doxorubicin and paclitaxel showed dramatically higher levels of *ABCB1* mRNA than those of wild-type cells. Kars et al. [18] reported that cell lines resistant to paclitaxel or doxorubicin expressed both P-gp and *ABCB1* genes. These findings may help to individualize paclitaxel- and anthracycline-based

Table 3. Paclitaxel and anthracycline resistance according to ABCB1 2677 and 3435 genotypes

	2677			3435		
	GG	GT + GA	TT + TA + AA	CC	CT	TT
Paclitaxel ($n = 103$)						
Sensitive (%)[a,b]	3 (9.4)	18 (56.3)	11 (34.3)	15 (46.9)	4 (12.5)	13 (40.6)
Resistant (%)[a,b]	20 (28.2)	27 (38.0)	24 (33.8)	38 (53.5)	7 (9.8)	26 (36.7)
Anthracycline ($n = 91$)						
Sensitive (%)[c]	6 (12.5)	22 (45.8)	20 (41.7)	24 (50.0)	4 (8.3)	20 (41.7)
Resistant (%)	6 (17.7)	18 (52.9)	10 (29.4)	19 (55.9)	3 (8.8)	12 (35.3)
Refractory (%)[c]	4 (44.5)	3 (33.3)	2 (22.2)	4 (44.5)	2 (22.2)	3 (33.3)

[a] $P = 0.028$ for 2677 GG versus GT + GA, $P > 0.05$ for 3435C>T.

[b] $P = 0.04$ for 2677 GG versus GT + GA or TT + TA + AA.

[c] $P = 0.04$ for 2677 GG versus GT + GA or TT + TA + AA, $P > 0.05$ for 3435C>T.

chemotherapy in patients with breast cancer. For example, patients with chemoresistant *ABCB1* genotypes might be initially treated with new agents that evade the mechanism of *ABCB1*, such as epothilones and capecitabine [19]. Alternatively, an *ABCB1* modulator or a hammerhead ribozymes against the *ABCB1* gene and *ABCB1*-targeted antisense oligonucleotides might be used to increase the therapeutic benefits in patients with an *ABCB1* genotype such as 2677 GG [20, 21].

P-gp expression and *ABCB1* 3435C>T polymorphism has been previously identified as an independent factor for disease-free survival and the response rate to chemotherapy in breast cancer [22–24]. We found that breast cancer patients with heterozygous expression of the *ABCB1* 3435C>T gene had lower disease control rates and a tendency towards shorter OS than homozygous patients. Several studies have reported higher bioavailability of *ABCB1* substrates in carriers of T allele at 3435C>T locus, attributed to lower functional activity of the protein. 3435C>T polymorphism is associated with a certain changes in P-gp expression, although in transfection studies of cells, no differences in either mRNA or protein levels were observed [25]. Illmer et al. [26] reported that acute myeloid leukemia patients with heterozygous variant had increased survival than homozygotes (3435 CC, $P < 0.01$; 3435 TT, $P = 0.05$). Similar results on genotype-survival relation were obtained in one previous study that showed a tendency to higher survival rate in heterozygotes of *ABCB1* 2677G>T/A than homozygotes ($P = 0.02$) [27]. *ABCB1* 3435 CT, heterozygous variant could have a greater effect on P-gp by changing the timing of cotranslational folding and resulted in altered function, than homozygous genotypes. This contradictory result may indicate that SNPs of the *ABCB1* gene should be analyzed according to complete haplotypes. Given the modest sample size of patient analyzed, this finding should be considered exploratory in nature. A study with a larger sample size must be carried out to make definite conclusions.

Paclitaxel treatment in our study was continued until cancer progression or patient's refusal from toxicity. After discontinuation of paclitaxel, we changed to other regimen in 61.9% of the patients and, the remaining patients did not get any more treatment (data not shown). The continuous treatment with paclitaxel may up-regulate the pump which affects efficacy or toxicity of the subsequent treatment. On the other hand, we speculated that *ABCB1* could have a prognostic role as well as a predictive value. Some studies reported that the alteration of *ABCB1* expression could be associated with a decreased activity of natural killer and CD8+ cells, which are involved in the regulation of immune response and in the killing of tumor cells [28]. Evidence indicated that cell lines expressing high levels of P-gp were less sensitive to caspase-mediated apoptosis induced by a wide range of death stimuli [29]. Nordgard et al. [30] reported that *ABCB1* was associated with a chance of acquiring a mutation in the TP53 gene. Taken together, we thought that the effect of *ABCB1* genotype on the survival probability of breast cancer patients could be related with P-gp action, and not just with drug efflux function. Further investigations should be made to address the relationship between *ABCB1* genotype and clinical outcome.

Taken together, our results reveal an association of the *ABCB1* polymorphism with chemoresistance and the survival of metastatic breast cancer patients. In our study, two patients with a haplotype of 2677 GG and 3435 CT showed significantly lower disease control rate and shorter OS and PFS (data not shown). A controlled, prospective trial of adjuvant chemotherapy with taxane, doxorubicin, and cyclophosphamide or doxorubin and cyclophosphamide followed by taxane in breast cancer patients on the basis of the *ABCB1* genotype is warranted. In conclusion, an association was found between chemotherapy resistance (both anthracycline and paclitaxel) and the *ABCB1* 2677 GG genotype. Patients with the *ABCB1* 3435 CT genotype showed lower disease control rate and shorter OS in response to paclitaxel monotherapy. These results indicate that *ABCB1* genotypes could be used to predict chemotherapeutic resistance and may be a prognostic factor for OS in patients receiving paclitaxel for metastatic breast cancer.

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