Pharmacogenomics and Personalized Medicine

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ORIGINAL RESEARCH

Association of *CYP3A4/5*, *ABCB1* and *ABCC2* polymorphisms and clinical outcomes of Thai breast cancer patients treated with tamoxifen

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This article was published in the following Dove Press journal:
Pharmacogenomics and Personalized Medicine
23 August 2013
Number of times this article has been viewed

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Background: Pharmacogenetic study of cytochrome P450 (CYP) gene *CYP2D6* and tamoxifen outcomes remain controversial. Apart from CYP2D6, other drug-metabolizing enzymes and transporters also play a role in tamoxifen metabolic pathways. The aim of this study is to investigate the impact of *CYP3A4/5, ABCB1*, and *ABCC2* polymorphisms on the risk of recurrence in Thai patients who received tamoxifen adjuvant therapy.

Methods: Patients with early-stage breast cancer who received tamoxifen adjuvant therapy were recruited in this study. All six single-nucleotide polymorphisms (SNPs), including *CYP3A4*1B* (–392 A>G)/**18*(878 T>C), *CYP3A5*3*(6986 G>A), *ABCB1* 3435 C>T, *ABCC2*1C* (–24 C>T), and *ABCC2* 68231 A>G, were genotyped using real-time polymerase chain reaction assays. The impacts of genetic variants on disease-free survival (DFS) were analyzed using the Kaplan–Meier method and Cox regression analysis.

Results: The *ABCB1* 3435 C>T was found to have the highest allele frequency among other variants; however, *CYP3A4*1B/*18* could not be found in this study. Patients with heterozygous *ABCB1* 3435 CT genotype showed significantly shorter DFS than those with homozygous 3435 CC genotype ($P = 0.041$). In contrast, patients who carried homozygous 3435 TT genotype showed no difference in DFS from wild-type 3435 CC patients. Cox regression analysis showed that the relative risk of recurrence was increased by five times ($P = 0.043$; hazard ratio = 5.11; 95% confidence interval: 1.05–24.74) in those patients carrying *ABCB1* 3435 CT genotype compared to those with *ABCB1* 3435 CC.

Conclusion: *ABCB1* 3435 C>T is likely to have a clinically significant impact on recurrence risk in Thai patients with breast cancer who receive tamoxifen adjuvant therapy.

Keywords: breast cancer, *CYP3A4/5*, drug transporters, pharmacogenetics, disease-free survival, tamoxifen

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Introduction

Tamoxifen, a selective estrogen receptor modulator (SERM), is the standard prescribed drug for the treatment of breast cancer in patients with estrogen and/or progesterone receptor positive disease.[1] Tamoxifen is extensively metabolized by cytochrome P450 (CYP) enzyme 2D6 in the liver to produce pharmacologically active metabolites such as endoxifen and 4-hydroxytamoxifen.[2] It is well documented that *CYP2D6* polymorphisms play an important role in tamoxifen effectiveness;[3] however, some findings have been inconsistent.[4–7] To date, there is no consensus whether *CYP2D6* genotyping is definitely essential before receiving the drug regimen. In addition to CYP2D6, tamoxifen could be metabolized by other metabolizing enzymes such as CYP3A4/5.[8] Recently, it was reported that drug transporters such

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as ABCB1 are involved in the transport of endoxifen and 4-hydroxytamoxifen, active metabolites of tamoxifen.[9] Furthermore, overexpression of ABCC2, an efflux transporter, has been reported in tamoxifen-resistant breast cancer.[10] Therefore, genetic variants of these metabolizing enzymes and drug transporters are likely to be associated in variable degree with clinical outcome observed in patients treated with tamoxifen. The impact of *CYP3A4/5*, *ABCB1*, and *ABCC2* polymorphisms on tamoxifen effectiveness in Thai populations has not yet been reported. In this study, genetic variants of *CYP3A4*1B* (–392 A>G)/**18*(878 T>C), *CYP3A5*3*(6986 G>A), *ABCB1* 3435 C>T, *ABCC2*1C* (–24 C>T), and *ABCC2* 68231 A>G in Thai patients with early-stage breast cancer were investigated. The risk of recurrence within 3 years among Thai women after receiving tamoxifen adjuvant therapy was evaluated.

Materials and methods

Patients

This study was retrospectively conducted in 30 breast cancer patients who visited Ramathibodi Hospital, Bangkok, Thailand, during the time between February 1997 and January 2008. All patients were estrogen and/or progesterone receptor positive and received tamoxifen as an adjuvant treatment for breast cancer. All patients had previously been treated with cyclophosphamide/methotrexate/5-fluorouracil (CMF) chemotherapy prior to tamoxifen treatment. The prognostic clinical factors known to affect the clinical outcome, such as age, tumor size, and lymph node status were matched between recurrence and nonrecurrence groups. Exclusion criteria included concurrent medications that induce or inhibit CYP2D6, CYP3A, and efflux transporters. Patients' data were collected from medical records. The clinical data included in this study are given in Table 1. All analyzed patients had uniform diagnostic, management, and follow-up protocols. Blood samples were collected (5 mL) in an ethylenediaminetetraacetic acid (EDTA) tube and stored at –20°C until isolation of genomic DNA for genotype analysis. The study was approved by Ramathibodi Hospital's ethics committee. All patients gave informed consent.

Genotyping

The criteria for candidate single-nucleotide polymorphism (SNP) selection in this study are that *CYP3A4*1B*/*18*[11] and *CYP3A5*3*[12,13] have been reported to be involved in variable metabolism of CYP3A4/5 substrates. *ABCB1* 3435 C>T is the common SNP associated with altered P-glycoprotein (P-gp) expression and/or function.[14,15] It has been reported that ABCC2 was overexpressed in tamoxifen-resistant breast cancer cells.[10] Thus, the possibility of active metabolites being pumped out from breast cancer cells by ABCC2 was suggested.[10] *ABCC2* 68231 A>G (**1A*, –1774delG linkage disequilibrium)[16] and *ABCC2*1C* (–24 C>T)[16,17] have been reported to be associated with decreased *ABCC2* promoter activity. All polymorphisms, except *CYP3A4*1B*/*18*, have been shown by HapMap (http://hapmap.ncbi.nlm.nih.gov/) to have minor allele frequency (≥5%) in a Han Chinese population.

In brief, genomic DNA was isolated from 5 mL venous blood stored in an EDTA tube by the standard phenol–chloroform method. The genotype of each candidate SNP was determined using TaqMan® drug metabolism genotyping assays (Applied Biosystems®; Life Technologies, Carlsbad, CA, USA) as follows: *CYP3A4*1B* (5'-flanking region –392 A>G, reference sequence [rs]2740574) (assay ID: AHPAJVY); *CYP3A4*18*(c.878 T>C, rs28371759) (assay ID: C_27859823_20); *CYP3A5*3*(g.6986 G>A, rs776746) (assay ID: C_26201809_30); *ABCB1* (c.3435 C>T, rs1045642) (assay ID: C_7586657_20); *ABCC2*1C* (5'-flanking region –24 C>T, rs717620) (assay ID: C_2814642_10); and *ABCC2* (g.68231 A>G, rs3740065) (assay ID: C_22271640_10). The genotyping experiments were carried out using allele-specific Taqman® MGB probe 5' nuclease assay with real-time PCR (polymerase chain reaction) Viia™ 7 system (Applied Biosystems®; Life Technologies). Each 20 µL PCR mixture contained 4 µL of genomic DNA (5 ng/µL), 10 µL of Taqman® Genotyping Mastermix, 1 µL of allele-specific Taqman® MGB probe and sequence-specific primer kit, 5 µL of DNase-free H_2O. The thermal cycler program was set up as follows: at 95°C for 10 minutes, repeated 50 cycles at 92°C for 15 seconds and 60°C for 90 seconds. The Allelic Discrimination Plot was analyzed by Viia™ 7 software (Applied Biosystems®; Life Technologies).

Statistical analysis

The association between genetic variants and their influences to disease-free survival (DFS) was examined. DFS time was defined as the period from surgery to the date at first disease recurrence (local, regional, or contralateral breast cancer or distant recurrence). Patients who survived without any recurrence during tamoxifen treatment for 3 years were grouped as the nonrecurrence group, whereas patients who relapsed within 3 years were grouped as the recurrence group. The overall distribution of DFS was estimated using the Kaplan–Meier method. Statistical significance of a relationship between outcome and each of the genetic polymorphisms was assessed by log-rank test. Independent contribution of genetic factors to DFS was evaluated by Cox regression analysis.

Table 1 Baseline characteristics of patients with and without recurrence (N = 30)

Characteristics	Recurrence (n = 10)		Nonrecurrence (n = 20)		*P*-value[a]
Age at diagnosis, years					
Mean (range)	48.30 (30–72)		48.45 (28–74)		
Disease-free survival, years					
Mean (standard deviation)	1.73 (0.74)		6.61 (1.73)		
	Number	**%**	**Number**	**%**	
Menstrual status					0.760
Premenopause	8	80	15	75	
Postmenopause	2	20	5	25	
Tumor size, cm					0.187
≤2	0	0	5	25	
2.1–5	7	70	12	60	
>5	3	30	3	15	
Lymph node status					0.549
0	4	40	6	30	
1–3	4	40	6	30	
≥4	2	20	8	40	
Tumor grading					0.985
1	1	10	3	15	
2	6	60	11	55	
3	1	10	2	10	
Unknown	2	20	4	20	
Lymphovascular invasion					0.948
Positive	2	20	6	30	
Negative	3	30	9	45	
Unknown	5	50	5	25	
Estrogen receptor					0.333
Positive	9	90	20	100	
Negative	1	10	0	0	
Progesterone receptor					0.055
Positive	7	70	7	35	
Negative	3	30	5	25	
Unknown	0	0	8	40	
HER2					0.184
Positive	1	10	0	0	
Negative	7	70	11	55	
Unknown	2	20	9	45	
Radiation					0.196
Yes	3	30	9	45	
No	7	70	11	55	

Note: [a]Fisher's exact test.
Abbreviations: N, total number; n, group number; HER2, human epidermal growth factor receptor 2.

The result was considered to be statistically significant at bilateral *P*-values ≤ 0.05. Statistical tests were performed using Stata software (version 12; StataCorp LP, College Station, TX, USA).

Results

Patient characteristics

All patients were estrogen receptor positive except one patient, who was estrogen receptor negative but progesterone receptor positive. There were no statistically significant differences between baseline characteristics of the two groups. The patient characteristics are listed in Table 1. Ten patients had either local or distant recurrence of within during 3 years of tamoxifen treatment. The mean DFS time of the recurrence group was 1.73 ± 0.74 years. The nonrecurrence had an average DFS time of 6.61 ± 1.73 years.

CYP3A4/5, ABCB1 and *ABCC2* genotype and allele frequency

ABCB1 3435 T was found to have the highest allele frequency among the variants. However, *CYP3A4*1B/*18* variants could not be investigated in all patients. *CYP3A5*3, ABCB1* 3435 C>T, *ABCC2*1C*, and *ABCC2* 68231 A>G allele frequency were found to be within Hardy–Weinberg equilibrium. The frequency of *CYP3A5*1/*1*,**1/*3* and **3/*3* genotypes were 63% (n = 19), 33% (n = 10) and 4% (n = 1), respectively. The frequency of *ABCB1* 3435 CC, CT and TT genotypes were 43% (n = 13), 40% (n = 12) and 17% (n = 5), respectively.

Table 2 Genotype and allele frequency of *CYP3A5, ABCB1*, and *ABCC2*

Genetic polymorphisms	Patients, n	Genotype frequency	Allele frequency
*CYP3A5*3* 6986 G>A			
**1/*1*	19	0.63	G = 0.80
**1/*3*	10	0.33	
**3/*3*	1	0.04	A = 0.20
ABCB1 3435 C>T			
CC	13	0.43	C = 0.67
CT	12	0.40	
TT	5	0.17	T = 0.33
*ABCC2*1C* –24 C>T			
**1/*1*	17	0.57	C = 0.78
**1/*1C*	13	0.43	T = 0.22
ABCC2 68231 A>G			
AA	14	0.47	A = 0.73
AG	16	0.53	G = 0.27

The frequency of *ABCC2*1/*1* and **1/*1C* genotypes were 57% (n = 17) and 43% (n = 13), respectively. The frequency of *ABCC2* 68231 AA and AG genotypes were 47% (n = 14) and 53% (n = 16), respectively. Genotype and allele frequency of *CYP3A5*, *ABCB1*, and *ABCC2* are shown in Table 2.

CYP3A5, ABCB1 and *ABCC2* genetic variants and clinical outcomes

Genetic polymorphisms of all patients were evaluated for DFS association. Kaplan–Meier analysis showed that patients with heterozygous *ABCB1* 3435 CT genotype had significantly shorter DFS than those with homozygous 3435 CC genotype ($P = 0.041$) (Figure 1A). In contrast, homozygous 3435 TT genotype did not show different clinical outcomes than in wild-type 3435 CC patients (data not shown). Furthermore, patients with 3435 CT genotype also had significantly shorter DFS than others (CC+TT genotypes), as shown in Figure 1B ($P = 0.011$). No statistical association between *CYP3A5*3, ABCC2*1C*, and *ABCC2* 68231 A>G with clinical outcome was observed.

Cox regression analysis revealed that 3435 CT was associated with increased recurrence risk compared to 3435 CC ($P = 0.043$; hazard ratio [HR] = 5.11; 95% confidence interval [CI]: 1.05–24.74) and 3435 CC+TT genotypes ($P = 0.023$; HR = 4.83; 95% CI: 1.24–18.8) (Table 3).

Discussion

Intermediate and poor metabolizer-related *CYP2D6* genotypes have been associated with unfavorable outcomes in estrogen positive breast cancer patients who received tamoxifen adjuvant therapy.[18–22] However, several studies with large sample sizes have shown contradictory results.[4–7] In Asian (including Thai) studies, *CYP2D6**10, which is the most common variant, has been associated with short DFS.[20,23–25] However, it could not be indicated as a recurrent predictive marker in tamoxifen treatment.[23–26] It has been suggested that genetic polymorphisms of other CYPs and drug transporters are involved in the variable effectiveness of tamoxifen.[21,27] In this study, we evaluated the additional genetic variants associated with tamoxifen effectiveness in Thai patients with early-stage breast cancer.

*CYP3A4*1B/18* could not be found in our limited sample size due to the fact that the frequency of both alleles is only

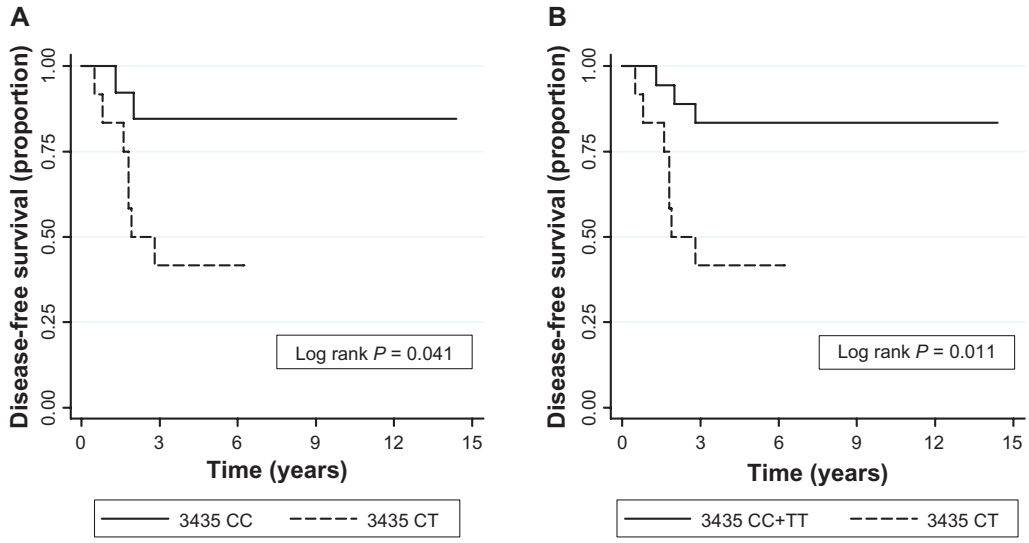

Figure 1 Kaplan–Meier estimates of disease-free survival of patients with 3435 *ABCB1* genotype.
Notes: (**A**) Analysis model 1 (CT compared with CC). (**B**) Analysis model 2 (CT compared with CC+CT).

Table 3 HRs in breast cancer patients treated with tamoxifen

ABCB1 genotype	HR	95% CI	*P*-value
(Analysis model 1)			
CC	1.0 (ref)		
CT	5.11	1.05–24.74	0.043
(Analysis model 2)			
CC+TT	1.0 (ref)		
CT	4.83	1.24–18.80	0.023

Abbreviations: CI, confidence interval; HR, hazard ratio.

around 1% in the Asian population;[28] however, the allele frequency of *CYP3A5*3* (non-function variant) was observed to be comparable to that in other reports.[29,30] Several studies, including one by our group, investigated the association of *CYP3A5* genotype with tamoxifen clinical outcomes; no significant association was observed.[27,31–35] It has been demonstrated that *CYP3A5*3/*3* does not affect endoxifen level in vitro and in vivo.[30,36] Moreover, tamoxifen can be metabolized by other CYP enzymes such as CYP3A4 and CYP2C19 in the liver or by CYPs that are expressed in breast cancer cells.[2,37,38]

Research in Japanese women has suggested that the A allele of *ABCC2* 68231 A>G is at risk for recurrence after 5 years of tamoxifen treatment but not *ABCC2*1C* (–24 C>T) and *ABCB1* 3435 C>T.[21] In contrast, we found that neither *ABCC2* 68231 A>G nor *ABCC2*1C* (–24 C>T) appear to influence tamoxifen adjuvant treatment. However, we found an association between *ABCB1* 3435 C>T and impact on recurrence risk in patients with 3435 CT genotype, which occurred more than in those with 3435 CC. Surprisingly, homozygous 3435 TT is not associated with the risk of recurrence whilst heterozygous 3435 CT is. This can be explained from evidence that 3435 C>T polymorphism is associated with certain changes in P-gp expression.[14] No difference in P-gp messenger (m)RNA and protein levels was observed in non-tumor cells with either 3435 CT or TT polymorphism.[15] However, a previous study in humans found that liver tumors with 3435 CT genotype expressed higher levels of P-gp protein compared to CC and TT genotype.[39] The increased P-gp protein expression limits drug penetration into intratumor cells. Furthermore, *ABCB1* 3435 CT genotype has previously been identified as an independent factor for DFS in breast and other cancers.[40–42] However, this correlation needs to be verified based on an individual's complete haplotype of the *ABCB1* gene. Although in our study the sample size is not large, the association can still be observed. Therefore, our findings are interesting and warrant further investigation in a larger sample.

Conclusion

The findings of this study suggest that *ABCB1* is a potential predictive marker of tamoxifen therapy outcomes.

Author contributions

All authors contributed to the interpretation of the results and read and approved the final manuscript.

Acknowledgment

This research project was financially supported by the Faculty of Science and Faculty of Medicine, Ramathibodi Hospital, Mahidol University. Additional support for this work has been provided by the Ramathibodi Cancer Center, Ramathibodi Hospital, Bangkok, Thailand.

Disclosure

The authors report no conflicts of interest in this work.

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