Association of CYP3A4/5, ABCB1 and ABCC2 polymorphisms and clinical outcomes of Thai breast cancer patients treated with 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. Tamoxifen is extensively metabolized by cytochrome P450 (CYP) enzyme 2D6 in the liver to produce pharmacologically active metabolites such as endoxifen and 4-hydroxytamoxifen. It is well documented that CYP2D6 polymorphisms play an important role in tamoxifen effectiveness; however, some findings have been inconsistent. 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. Recently, it was reported that drug transporters such
as ABCB1 are involved in the transport of endoxifen and 4-hydroxytamoxifen, active metabolites of tamoxifen. Furthermore, overexpression of ABCC2, an efflux transporter, has been reported in tamoxifen-resistant breast cancer. 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 \textit{CYP3A4/5}, \textit{ABCB1}, and \textit{ABCC2} polymorphisms on tamoxifen effectiveness in Thai populations has not yet been reported. In this study, genetic variants of \textit{CYP3A4*1B} (−392 A>G)/*18(878 T>C), \textit{CYP3A5*3}(6986 G>A), \textit{ABCB1} 3435 C>T, \textit{ABCC2*1C} (−24 C>T), and \textit{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 \textit{CYP3A4*1B/18} \cite{11} and \textit{CYP3A5*3} \cite{12,13} have been reported to be involved in variable metabolism of \textit{CYP3A4/5} substrates. \textit{ABCB1} 3435 C>T is the common SNP associated with altered P-glycoprotein (P-gp) expression and/or function. \cite{14,15} It has been reported that \textit{ABCC2} was overexpressed in tamoxifen-resistant breast cancer cells. \cite{16} Thus, the possibility of active metabolites being pumped out from breast cancer cells by \textit{ABCC2} was suggested. \cite{17} \textit{ABCC2} 68231 A>G (*1A, −1774delG linkage disequilibrium) \cite{18} and \textit{ABCC2*1C} (−24 C>T) \cite{17,19} have been reported to be associated with decreased \textit{ABCC2} promoter activity. All polymorphisms, except \textit{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: \textit{CYP3A4*1B} (5′-flanking region −392 A>G, reference sequence [rs]2740574) ( assay ID: AHPAJVY); \textit{CYP3A4*18} (c.878 T>C, rs28371759) ( assay ID: C_27859823_20); \textit{CYP3A4*3} (g.6986 G>A, rs776746) ( assay ID: C_26201809_30); \textit{ABCB1} (c.3435 C>T, rs1045642) ( assay ID: C_7586657_20); \textit{ABCC2*1C} (5′-flanking region −24 C>T, rs717620) ( assay ID: C_2814642_10); and \textit{ABCC2} (g.68231 A>G, rs3740605) ( 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 H2O. 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.
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 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.

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

| Characteristics                     | Recurrence (n = 10) | Nonrecurrence (n = 20) | P-value* |
|-------------------------------------|---------------------|------------------------|----------|
| Age at diagnosis, years             | 48.30 (30–72)       | 48.45 (28–74)          |          |
| Disease-free survival, years        | 1.73 (0.74)         | 6.61 (1.73)            |          |
| Menstrual status                    |                     |                        |          |
| Premenopause                        | 8                   | 15                     | 75       |
| Postmenopause                       | 2                   | 5                      | 25       |
| Tumor size, cm                      |                     |                        |          |
| ≤ 2                                 | 0                   | 5                      | 25       |
| 2.1–5                               | 7                   | 12                     | 60       |
| > 5                                 | 3                   | 3                      | 15       |
| Lymph node status                   |                     |                        |          |
| 0                                   | 4                   | 6                      | 30       |
| 1–3                                 | 4                   | 6                      | 30       |
| ≥4                                  | 2                   | 8                      | 40       |
| Tumor grading                       |                     |                        |          |
| 1                                   | 1                   | 3                      | 15       |
| 2                                   | 6                   | 11                     | 55       |
| 3                                   | 1                   | 2                      | 10       |
| Unknown                             | 2                   | 4                      | 20       |
| Lymphovascular invasion             |                     |                        |          |
| Positive                            | 2                   | 6                      | 30       |
| Negative                            | 3                   | 9                      | 45       |
| Unknown                             | 5                   | 5                      | 25       |
| Estrogen receptor                   |                     |                        |          |
| Positive                            | 9                   | 20                     | 100      |
| Negative                            | 1                   | 0                      | 0        |
| Progesterone receptor               |                     |                        |          |
| Positive                            | 7                   | 7                      | 35       |
| Negative                            | 3                   | 5                      | 25       |
| Unknown                             | 0                   | 8                      | 40       |
| HER2                                |                     |                        |          |
| Positive                            | 1                   | 0                      | 0        |
| Negative                            | 7                   | 11                     | 55       |
| Unknown                             | 2                   | 9                      | 45       |

**Table 1 Continued**

| Characteristics                     | Recurrence (n = 10) | Nonrecurrence (n = 20) | P-value* |
|-------------------------------------|---------------------|------------------------|----------|
| Radiation                           |                     |                        |          |
| Yes                                 | 3                   | 9                      | 45       |
| No                                  | 7                   | 11                     | 55       |

Note: *Fisher’s exact test.

Abbreviations: N, total number; n, group number; HER2, human epidermal growth factor receptor 2.

**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.
The frequency of \textit{ABCC2*1/*1} and \textit{ABCC2*1/*1C} genotypes were 57\% (n = 17) and 43\% (n = 13), respectively. The frequency of \textit{ABCC2} 68231 AA and AG genotypes were 47\% (n = 14) and 53\% (n = 16), respectively. Genotype and allele frequency of \textit{CYP3A5}, \textit{ABCB1}, and \textit{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 \textit{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 \textit{CYP3A5*3}, \textit{ABCC2*1C}, and \textit{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 \textit{CYP2D6} genotypes have been associated with unfavorable outcomes in estrogen positive breast cancer patients who received tamoxifen adjuvant therapy.\textsuperscript{18–22} However, several studies with large sample sizes have shown contradictory results.\textsuperscript{4–7} In Asian (including Thai) studies, \textit{CYP2D6*10}, which is the most common variant, has been associated with short DFS.\textsuperscript{20,23–25} However, it could not be indicated as a recurrent predictive marker in tamoxifen treatment.\textsuperscript{23–26} It has been suggested that genetic polymorphisms of other CYPs and drug transporters are involved in the variable effectiveness of tamoxifen.\textsuperscript{21,27} In this study, we evaluated the additional genetic variants associated with tamoxifen effectiveness in Thai patients with early-stage breast cancer.

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

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**Table 2** Genotype and allele frequency of \textit{CYP3A5}, \textit{ABCB1}, and \textit{ABCC2}

| Genetic polymorphisms | Patients, n | Genotype frequency | Allele frequency |
|------------------------|------------|--------------------|-----------------|
| \textit{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        |
| \textit{ABCB1 3435 C>T} |            |                    |                 |
| CC                     | 13         | 0.43               | C = 0.67        |
| CT                     | 12         | 0.40               |                 |
| TT                     | 5          | 0.17               | T = 0.33        |
| \textit{ABCC2*1C −24 C>T} |           |                    |                 |
| *1/*1                  | 17         | 0.57               | C = 0.78        |
| *1/*1C                 | 13         | 0.43               | T = 0.22        |
| \textit{ABCC2 68231 A>G} |            |                    |                 |
| AA                     | 14         | 0.47               | A = 0.73        |
| AG                     | 16         | 0.53               | G = 0.27        |

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**Figure 1** Kaplan–Meier estimates of disease-free survival of patients with 3435 \textit{ABCB1} genotype.

**Notes:** (A) Analysis model 1 (CT compared with CC). (B) Analysis model 2 (CT compared with CC+CT).
around 1% in the Asian population; however, the allele frequency of CYP3A5*2 (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.\(^{31-35}\) It has been demonstrated that CYP3A5*3/*3 does not affect endoxifen level in vitro and in vivo.\(^{30,38}\) 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.\(^{29}\) 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 ABBC1 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.

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#### Table 3 HRs in breast cancer patients treated with tamoxifen

| ABCC1 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.

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### Conclusion

The findings of this study suggest that ABCC1 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.

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### Disclosure

The authors report no conflicts of interest in this work.

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