RESEARCH ARTICLE

Impact of *CYP2D6* Polymorphisms on Tamoxifen Responses of Women with Breast Cancer: A Microarray-based Study in Thailand

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Abstract

This study was designed to investigate the frequency of *CYP2D6* polymorphisms and evaluate the association between genetic polymorphisms of *CYP2D6* and tamoxifen therapeutic outcome in Thai breast cancer patients. We recruited 48 breast cancer patients who received adjuvant tamoxifen for evaluating *CYP2D6* genetic polymorphisms using microarray-based technology. Associations between genotypes-phenotypes and disease free survival were analyzed. Median follow up time was 5.6 years. The mean age of the subjects was 50 years. The 3 common allelic frequencies were 43.8% (10*), 36.5 (**1*) and 10.4% (**2*) which are related to extensive metabolizer (EM) and intermediate metabolizer (IM) with 70.8% and 29.2 %, respectively. No association between *CYP2D6* genotypes and DFS was demonstrated. Nevertheless, exploratory analysis showed statistically significant shorter DFS in the IM group of post-menopause patients (HR, 6.85; 95%CI, 1.48-31.69; *P*=0.005). Furthermore, we observed statistically significant shorter DFS of homozygous *CYP2D6*10* when compared with heterozygous *CYP2D6*10* and other genotypes (*P*=0.005). *CYP2D6*10* was the most common genotype in our subjects. Post-menopause patients with homozygous *CYP2D6*10* and IM have shorter DFS. To confirm this relationship, larger samples and comprehensively designed trials in Thailand are required.**

Keywords: Breast cancer - *CYP2D6* polymorphisms - tamoxifen - pharmacogenetics - microarray - Thailand

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Introduction

Tamoxifen, selective estrogen receptor modulators (SERM) is the most commonly prescribed drug for the treatment and prevention of recurrence for patients with estrogen and/or progesterone receptor positive disease (EBCTCG, 2005). Although it has been documented being safe and effective, one third of patients does not respond leading to disease relapse and eventually die (Higgins and Stearns, 2009). Two major anti-estrogen metabolites, 4-hydroxy-N-desmethyltamoxifen (endoxifen) and 4-hydroxytamoxifen are 30-100 times more potent than itself (Lim et al., 2006). Endoxifen, the greatest potent anti-estrogen, is converted from tamoxifen by sequential biotranformation involving CYP3A4/5 mediated N-demethylation of tamoxifen to form N-desmethyltamoxifen (NDM) and *CYP2D6* which is rate-limiting enzyme catalysed 4-hydroxylation of NDM to form endoxifen (Desta et al., 2004; Hoskins et al., 2009). The steady-state plasma concentrations of tamoxifen and its active metabolites have been shown to influence to therapeutic outcome that may be partly indicated by the pharmacogenetic relation of *CYP2D6* (Stearns et al., 2003; Borges et al., 2006; Lim et al., 2007; Sirachainan et al., 2012).

Approximately 100 *CYP2D6* genetic variants have been identified, which manifest in the population in 4 distinct phenotypes, extensive (normal activity), intermediate (reduced activity), poor (no activity), and ultra-rapid (high activity) metabolism. Patients receiving tamoxifen who either carry genetic variants associated with reduce or none *CYP2D6* activity have significantly lower level of endoxifen (Lim et al., 2011). Caucasians have the highest frequency of *CYP2D6*4*, poor metabolizer (PM), with frequency of 12%-23% while only 4%-6% has been found in Asian. Instead, *CYP2D6*5*, poor metabolizer, and *CYP2D6*10*, intermediate metabolizer (IM), alleles have been reported to be more prevalent in Asian populations, with frequencies of approximately 5% and more than 40%, respectively (Lim et al., 2006). Several studies performed primarily in Caucasian women (Nowell et al., 2005; Wegman et al., 2005; 2007; Goetz et

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al., 2007; 2011; Schroth et al., 2007; 2009; 2010) and a relatively few studies in Asian women (Lim et al., 2007) (Kiyotani et al., 2008; Xu et al., 2008) have suggested that *CYP2D6* PM or IM allelic status is associated with poorer outcomes in prevention, adjuvant and metastatic settings. However, whether *CYP2D6*5,*10* genotypes influences clinical effect in Asian populations including Thailand is still unclear (Toyama et al., 2009; Pechatanan, 2011; Sirachainan et al., 2012). The lack of a comprehensive assessment of the undiscovered *CYP2D6* deficiency variants might explain these controversial data. The AmpliChip CYP450 Test provides a comprehensive panel of all globally relevant *CYP2D6* alleles with accurate phenotype prediction and is suitable for applications within the context of tamoxifen outcome prediction.

The study to determine *CYP2D6* genotype and tamoxifen efficacy in Thai populations has never been reported. The objectives of the present study were to study the pharmacogenetics of *CYP2D6* polymorphisms and evaluated the association between genotypes and efficacy of tamoxifen in Thai patients who received adjuvant tamoxifen treatment of breast cancer.

Materials and Methods

Patients

We retrospectively identified 48 breast cancer patients in Ramathibodi Hospital between 1997 and 2008 who met our inclusion criteria including histological diagnosis of breast cancer with estrogen and/or progesterone receptor positive receiving tamoxifen as an adjuvant treatment of breast cancer and age at diagnosis ≥18 years old. Exclusion criteria included coincident or previous other malignancy. Patient's data were collected from medical records. Age at diagnosis of breast cancer, menstruation status, type of surgery, date of surgery, ER/PgR status, Her-2 status, histologic grading tumor, surgery margin status, lymphovascular involvement status, T stage of tumor, nodal involvement, number of nodes dissection, start and stop date of chemotherapy either neoadjuvant or adjuvant setting, start and stop date of adjuvant radiotherapy, start and stop date of tamoxifen and date and site of the first disease relapse were recorded. Because information on co-medication of patients receiving SSRIs (selective serotonin reuptake inhibitors) was incomplete, it was not included in the analyses. Blood samples were collected 5 ml in EDTA tube and stored at -20°C until isolation of genomic DNA for genotyping analysis. The study was approved by Ramathibodi's Ethic committee. All patients were informed and consent.

Genotyping and Definition of Phenotypes

We obtained EDTA whole blood from 48 patients and DNA was isolated by the salting out procedure. We used a microarray hybridization method (AmpliChip CYP450 GeneChip®, Roche) for the detection of different polymorphisms in the Cytochrome P450 2D6 gene. Primers and amplification conditions for the PCR reactions were provided by the manufacturer and protocols were performed following the test instructions. The *CYP2D6* pharmacogenetic analysis for defining genotype-phenotype relationships was based on known biochemical and pharmacological effects that described in AmpliChip CYP450 Test handbook.

End points and statistical Analyses of Associations

We tested for an association between *CYP2D6* polymorphisms and their influences to tamoxifen efficacy in adjuvant treatment of breast cancer and disease free survival (DFS) as a primary endpoint. Disease free survival was defined as the time from surgery to the occurrence of breast event, (local, regional, or distant occurrence or contralateral breast cancer) or death from any cause. Patients who were alive without a breast recurrence were censored at the date of their last disease evaluation. The distribution of disease-free survival was estimated overall using Kaplan-Meier method. Statistical significance of a relationship between outcome and each of the genetic polymorphisms was assessed by log-rank test. Cox regression was used to adjust for prognostic clinical factors and to test for an independent contribution of genetic factors to disease free survival. The result was considered to be statistically significant when bilateral *P* values ≤0.05. Statistical tests were run using STATA software version 10.1

Results

Patients' characteristics

The clinical data of 48 breast cancer Thai patients was demonstrated in Table 1. The mean age of the subjects was 50±11 years and DFS of EM and IM group were about 73 and 57 months respectively. The overall patient baseline characteristics were similar including menstrual status in which there were 30 pre- and 18 post-menopause patients. All patients were estrogen-receptor positive except one patient had estrogen-receptor negative but had progesterone receptor positive. Twenty four (50%)

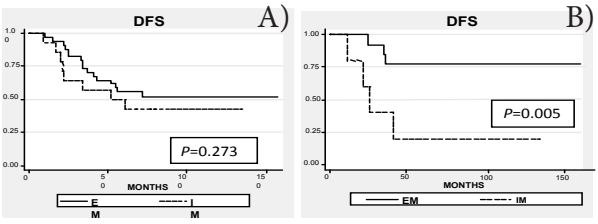

Figure 1. Kaplan-Meier probabilities of disease- free survival of patients as a function of predicted *CYP2D6* phenotypes (EM vs IM phenotypes). A) All patients, B) Postmenopausal patients

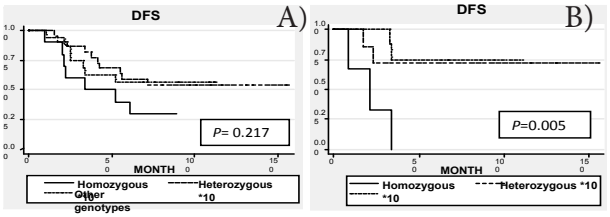

Figure 2. Kaplan-Meier probabilities of disease- free survival for patients with the *CYP2D6*10* genotype (Comparison among Homozygous *CYP2D6*10*, Heterozygous *CYP2D6*10* and other genotypes). A) All patients, B) Postmenopausal patients

patients had positive axillary lymph nodes. Most patients were treated with a modified radical mastectomy. The regimen of adjuvant chemotherapy composed of CMF, Adriamycin based and Adriamycin-Taxane based regimens. Three patients of the study did not receive adjuvant chemotherapy despite being eligible for treatment because they had positive axillary lymph nodes (N1).

CYP2D6 genotype and predicted phenotype profiles

Among 48 patients, we found homozygous for *CYP2D6*1/*1* genotype, 18.8% (9/48). Twenty-seven percent (13/48) of the patients carried the heterozygous *CYP2D6*1/*10* genotype. The homozygous of *CYP2D6*10/*10* genotype was found as 20.8% (10/48) while heterozygous for *CYP2D6*5/*10* genotype were 3 (6.2%) patients. We also found the rare SNPs as followings: one heterozygous *CYP2D6*35* allele, one heterozygous *CYP2D6*36* and two heterozygous *CYP2D6*41* patients, indicating allele frequencies were 1%, 1% and 2%, respectively. We found heterozygous *CYP2D6*4* in 1 patient (2 %), and characterized by 1846G>A mutation. The allele frequency of *CYP2D6*4* was 1% (Table 2). The phenotype frequencies of EM and IM were 70.8% and 29.2 %, respectively (Table 2). Nevertheless, no homozygous PM allele and multiple copies alleles were observed in this study. There were 12 (25%) EM patients with two functional alleles and 11 (22.9 %) IM patients with two reduced functional alleles. Twenty two (45.8%) patients had heterozygous EM. The overall patient baseline characteristics were similar including *CYP2D6* phenotypes (data not shown).

Table 1. Patients baseline characteristics according to *CYP2D6* predicted phenotype

Characteristics	EM (n=34) No.	%	IM (n=14) No.	%	*P*-value
Age at diagnosis: yr					0.341
≤50 yrs	15	44.12	9	64.29	
>50 yrs	19	55.88	5	35.71	
Age;					0.840
median (range): yr	51	(28-72)	47	(36-72)	
Disease free survival ; mean (sd); months					0.233
	73.03	(42.42)	57.13	(38.83)	
Menstrual					1.000
pre -menopause	21	61.76	9	64.29	
post -menopause	13	38.24	5	35.71	
Tumor size; cm;					0.699
≤2	7	20.59	2	14.29	
2.1-5	22	64.71	11	78.58	
>5	5	14.70	1	7.13	
Lymph node status; no;					0.420
0	18	52.94	6	42.86	
1-3	6	17.65	5	35.71	
≥4	10	29.41	3	21.43	
Grading					0.413
1	4	11.76	0	0.00	
2	13	38.24	8	57.14	
3	7	20.59	2	14.29	
Unknown	10	29.41	4	28.57	
LVI; no;					1.000
Positive	11	32.35	5	35.72	
Negative	16	47.06	8	57.14	
Unknown	7	20.59	1	7.14	
Progesterone receptor; no;					1.000
Positive	13	38.24	7	50.00	
Negative	6	17.65	4	28.58	
Unknown	15	44.11	3	21.43	
Her2neu; no;					0.423
Positive	0	0.00	1	7.14	
Negative	15	44.12	10	71.43	
Unknown	19	55.88	3	21.43	
Chemotherapy; no;					0.591
No chemotherapy	3	8.82	0	0.00	
CMF	15	44.12	9	64.29	
Adriamycin-based	14	41.18	4	28.58	
Adriamycin-Taxane based	2	5.88	1	7.13	
Radiation; no;					0.317
Yes	15	44.12	4	28.58	
No	19	55.88	10	71.42	

CYP2D6 genotype-phenotype and clinical outcome

Forty-eight patients were evaluated for DFS. Patients were grouped according to their *CYP2D6* phenotypes to two groups; EM and IM group. There was no significant correlation between clinicopathological parameters in both groups as shown in Table 1. No statistically significant difference were found in DFS between both groups (*P*=0.273) (Figure 1A).

The patients were analyzed according to have or have not the *CYP2D6*10* allele for hypothesis testing. Thus patients were grouped into homozygous *CYP2D6*10*, heterozygous *CYP2D6*10* and the other genotypes or grouped into homozygous EM, heterozygous EM (5 of 6 heterozygous *CYP2D6*10*) and IM (3 homozygous *CYP2D6*10* and 2 heterozygous *CYP2D6*10*) patients. All baseline characteristics well balance. The disease free survival when grouped into homozygous *CYP2D6*10*,

Table 2. Genotypes for *CYP2D6* and Predicted Phenotypes in Each Groups

CYP2D6 genotypes	N=48	Predicted *CYP2D6* phenotype	Phenotype frequencies (%)
**1/*1*	9	EM	18.8
**1/*2*	1	EM	2.1
**1/*5*	1	EM	2.1
**1/*10*	13	EM	27.0
**1/*36*	1	EM	2.1
**1/*41*	1	EM	2.1
**2/*2*	2	EM	4.2
**2/*4*	1	EM	2.1
**2/*10*	4	EM	8.3
**10/*35*	1	EM	2.1
**10/*5*	3	IM	6.2
**10/*10*	10	IM	20.8
**10/*41*	1	IM	2.1

Table 3. Hazard Ratio in Post-menopausae Subgroup

Variables	Hazard ratio (95%CI)		*P*-value
Predicted phenotypes			
EM	1	(ref)	
IM	6.85	(1.48-31.69)	0.005
*CYP2D6*10* genotypes			
Other genotype	1	(ref)	
Heterozygous *CYP2D6*10*	1.35	(0.19- 9.62)	0.817
Homozygous *CYP2D6*10*	10.52	(1.56-70.79)	0.005

heterozygous *CYP2D6*10* and other genotypes showed 34 months in homozygous *CYP2D6*10*, those of heterozygous *CYP2D6*10* and the other genotypes were not reach (*P*=0.217) (Figure 2A).

In the univariate Cox proportional hazard analysis, there was no significant correlation between clinicopathological parameters and DFS. An exploratory analysis of DFS in post-menopause patients according to EM (13/34) or IM (5/14) phenotypes, the result showed statistically significant of shorter DFS in IM phenotype patients (HR, 6.85; 95%CI, 1.48–31.69; *P*=0.005) (Figure 1B, Table 3) Furthermore, we observed statistically significant shorter DFS of homozygous *CYP2D6*10* (3/10) when compared between heterozygous *CYP2D6*10* (7/22) and other genotypes (8/16) (*P*=0.005).(Figure 2B, Table 3). On the other hand, an exploratory analysis of DFS in pre-menopause patients showed the no different DFS among groups (data not shown).

Discussion

It is well documented that post-menopausal breast cancer patients who are ER positive would get most benefit from receiving tamoxifen as adjuvant treatment compared to one pre-menopause. The higher endogenous estrogen level might limit the tamoxifen efficacy in premenopausal patients via competitive binding to ER (EBCTCG, 1992). However, our study suggested the clinical outcome variation among Thai postmenopausal patients who received adjuvant tamoxifen.

The comprehensive coverage of all globally relevant *CYP2D6* alleles in Thai patients has been performed by using AmpliChip CYP450 Test. The *CYP2D6*10* genotype was found to be highly prevalent in Thai populations. Even though, the results showed no association between *CYP2D6* genotypes or predicted phenotypes (EM, IM) and DFS. Nevertheless, an exploratory analysis in post-menopausal patients showed statistically significant inferior DFS in these who carries of homozygous *CYP2D6*10* genotype or carries of IM phenotype. Our results may indicated to these subgroup of patients had the tendency of shorter DFS by an increase of the number of *CYP2D6*10* alleles which was consistent with previous study in Asian population (Kiyotani et al., 2008; Xu et al., 2008).

The evidence from in vitro study, *CYP2D6*.10 (the enzyme product of the IM allele *CYP2D6*10*) produces an unstable enzyme with shorter half-life and has 1/40th lower rate of conversion of N-desmethyltamoxifen to endoxifen than *CYP2D6*1* (the product of the EM allele, *CYP2D6*1*) (Johansson et al., 1994). Nevertheless, it has been indicated that *CYP2D6*10/*10* genotypes influence the tamoxifen biotransformation with significantly lower concentrations of endoxifen (Lim et al., 2011). Furthermore, the recent clinical trial has been suggested that doubling the standard dose of tamoxifen, from 20-40 mg/day can raise endoxifen concentrations in IM patients (Irvin et al., 2011). Therefore, the pharmacogenetic relation of *CYP2D6*10/*10* or IM metabolizer and endoxifen level might be the reason that underpinned for the different clinical outcome in our findings.

The previous studies have been suggested that some clinico-pathologic characteristics such as T-stage and nodal involvement seemed to be related with the *CYP2D6*10* (Li et al., 2006) and PM metabolizer (Park et al., 2011) in Asian population. However, we did not find any genotype or phenotype-diseases state relation that may due to the small sample size and confounding factors even more no PM patient was found in this study. Therefore, further analysis using a large number of registered patients, especially post-menopausal patients, and well experimental design are required for verification of our results.

In future perspective, post-menopausal Thai women with high risk disease who have EM phenotype or do not carry *CYP2D6*10* allele may be considered adjuvant hormonal treatment tamoxifen instead of aromatase inhibitor. The prospective studies are also needed to figure out the role of tamoxifen and its metabolites, which would answer key questions about the critical threshold for endoxifen concentrations and tamoxifen efficacy as well as the association between *CYP2D6* polymorphisms and tumor progression.

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