

RESEARCH ARTICLE

CYP2D6 Genotype and Risk of Recurrence in Tamoxifen Treated Breast Cancer Patients

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Abstract

Background: Despite consistent pharmacogenetic effects of CYP2D6 on tamoxifen exposure, there is considerable controversy regarding the validity of CYP2D6 as a predictor of tamoxifen outcome. Understanding the current state of evidence in this area and its limitations is important for the care of patients who require endocrine therapy for breast cancer. **Materials and Methods:** A total of 101 patients with breast cancer who received tamoxifen therapy for at least 3 years, were genotyped for common alleles of the CYP2D6 gene by nested-PCR and restriction fragment length polymorphism PCR. Patients were classified as extensive or poor metabolizers (PM) based on CYP2D6*4 alleles in 3 different groups according to the menopause, Her2-neu status, and stage 3. **Results:** The mean age of the patients with the disease recurrence was 50.8 ± 6.4 and in non recurrent patients was 48.2 ± 6.8 . In this study 63.3% (n=64) patients were extensive metabolizers and 36.6% (n=37) were poor metabolizers. Sixty four of the 101 patients (63.3%) were Her2-neu positive. For tamoxifen-treated patients, no statistically significant difference in rate of recurrence observed between CYP2D6 metabolic variants in stage 3 and post-menopausal patients. However, there was a significant association between CYP2D6 genotype and recurrence in tamoxifen-treated Her2-neu positive patients. Compared with other women with breast cancer, those with Her2-neu positive breast cancer and extensive metabolizer alleles had a decreased likelihood of recurrence. **Conclusions:** This study for the first time demonstrated significant effects of CYP2D6 extensive metabolizer alleles on risk of recurrence in Her2-neu positive breast cancer patients receiving adjuvant tamoxifen therapy. Therefore, CYP2D6 metabolism, as measured by genetic variation, can be a predictor of breast cancer outcome in Her2-neu positive women receiving tamoxifen.

Keywords: Breast cancer - tamoxifen - recurrent - menopause - CYP2D6

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Introduction

Breast cancer is the most common cause of mortality among women accounting for 23% all cancers (Forat-yazdi et al., 2015). In recent years, the mortality rate from breast cancer has increased rapidly in all countries (Shiryazdi et al., 2015). Tamoxifen is currently used for the prevention and treatment of estrogen receptor (ER)-positive breast cancer in premenopausal women, and although aromatase inhibitors (AIs) are generally preferable for post-menopausal patients, some women do not tolerate these drugs (Motamedi et al., 2012; Darakhshan et al., 2013). However, about 25% of patients with early breast cancer who receive adjuvant tamoxifen relapse and eventually die from the disease (Meiyanto et al., 2012; Dueñas et al., 2014). Tamoxifen is also used for breast cancer prevention in women older than 35 years with a calculated Gail Model 5-year risk of invasive breast cancer greater than 1.67%. Gail Model uses the patient's medical history, age, and family history to calculate risk

of breast cancer over the next 5 years and until age 90. The Gail Model risk calculators are easily accessible on the internet. Tamoxifen and its primary metabolite (N-desmethyl tamoxifen) are metabolized mostly by the gene product of cytochrome P450 2D6 (CYP2D6) to 4-hydroxytamoxifen and endoxifen (Lash et al., 2011).

The cytochrome P450 (CYP450) superfamily is a large and diverse group of enzymes, Metabolizes about 25% of prescribed drugs in the endoplasmic reticulum (Nelson et al., 2004). It is most polymorphic CYP enzyme with at least 75 different known variants and a series of sub variants (Jin et al., 2013). Notably, CYP450 enzymes show extensive structural differences due to genetic polymorphisms in the corresponding genes, thus giving rise to different enzymatic activities and leading to great intra- and inter-population differences in drug efficacy and adverse reactions. Based on the metabolic capacity of CYP2D6, the population can be divided into four metabolizer phenotypes: ultrafast (UM), extensive metabolizers (EM), intermediate metabolizers (IM) and

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poor metabolizers (PM) (Kirchheiner et al., 2007). Genetic diagnosis can be used to predict an individual's phenotype rather reliably, as demonstrated by the close relationship between the CYP2D6 genotype and phenotype. Assessing the CYP2D6 genotype also offers distinct advantages over the experimental determination of a CYP2D6 phenotype (Serin et al., 2012).

The new study suggests that CYP2D6 can predict ineffectiveness. The results show that after 5 years of taking tamoxifen, breast cancer patients with genetic alterations of CYP2D6 who are considered to be poor metabolizers of tamoxifen experienced disease recurrence or died at a rate that was 2.5 times higher than women with normal CYP2D6 enzyme activity (Hassan et al., 2011; Nelson, 2012).

Published treatment guidelines do not currently recommend CYP2D6 testing (Hayes et al., 2008), but the effects of drug metabolism are being studied as correlative questions in multiple ongoing clinical trials. Understanding the current state of evidence in this area and its limitations is important for the care of patients who require endocrine therapy for breast cancer.

Materials and Methods

Study population

Total of a 101 non-metastatic eligible breast cancer patients were prospectively recruited from the Shahid Sadoughi hospital Yazd, Iran. Pre- and postmenopausal patients with age range 30-60 years who received tamoxifen as standard adjuvant therapy at least for 3 years were included in this study. Local ethic committee reviewed and approved the study. Breast Cancer patients were divided into 3 different groups according to the Menopause, Stage 3, and Her2-neu+. Within groups, patients according to the recurrence of the disease divided in 2 groups.

The committee agreed that obtaining consent from the individual patient for the use of cancer tissues was not feasible as most of the patients in the "cases" group were already deceased. Also some of the patients in the "control" group had moved to different areas.

Genotyping of CYP2D6

We used to A-PCR to detect the known polymorphism of CYP2D6. Allele-specific primers were used for detection of variant and wild-type alleles in a multiplex PCR. The final reaction was carried out in a total volume of 25 µl PCRmix containing diluted first PCR product (1:100), 0.06 µM of common primer, forward and reverse primer: CYP2D6*4, 5'-TTGGAGTGGGTGGTGGATGGT-3', 5'-AGCCCGACTCCTCCTCAG-3'; 0.4 µM of wild-type primers, forward primer: CYP2D6*4, 5'-CGCATCTCCCACCCCG-3', 0.2 µM of variant primer, reverse primer: CYP2D6*4, 5'-TGGGGCGAAGGGGCGTGT-3'. The thermocycling conditions for this PCR were 95°C for 5 min (initial denaturation), followed by 35 cycles of 94°C for 1 min; 64°C for 30 s; 72°C for 1.5 min and a final extension of 72°C for 5 min. Eight microlitres of the PCR product was checked on 1% agarose gel and appropriately

diluted product and was used as the template in the second PCR.

Statistical analysis

Genotyping experiments were presented as allelic frequencies and Genotype distribution with those expected from Hardy-Weinberg Equilibrium (HWE) were made using chi square test, and Values of P (two - tailed) less than 0.005 were considered statistically significant.

Results

The mean age of the patients with the disease recurrence was 50.83±6.4 and in non recurrent patients was 48.2±6.8. In this study 63.3% (n=64) patients were extensive metabolizer and 36.6% (n=37) were poor metabolizer. Sixty four of 101 patients (63.3%) were Her2-neu positive. In the present study Grade III showed the highest frequency, 49 cases in stage III. Out of 101 cases, 61 cases were post menopause and 61 cases were Her2-neu+.

In this study 63.3% (n=64) patients were extensive metabolizer and 36.6% (n=37) were poor metabolizer. Breast carcinoma patients were assessed on the basis of clinical and pathological examinations. Tables 1 and 2 show the results of CYP2D6 genotypes, out of 20 postmenopausal tamoxifen treated cases with recurrent 4 cases were extensive metabolizers, 16 cases were poor metabolizers, and in non-recurrent postmenopausal cases out of 41 cases 18 cases were extensive metabolizers, 23 cases were poor metabolizers (p=0.09). In out of 23 recurrent tamoxifen treated cases in Stage 3 were extensive metabolizers, 15 cases were poor metabolizers, and in Stage 3 non-recurrent cases out of 26 cases 12 cases were extensive metabolizers, 14 cases were poor metabolizers. There was no statistically significant association between recurrence and stage 3 for any of the variation at the CYP2D6 locus in patients receiving tamoxifen (p=0.5). In recurrent Her2-neu positive cases out of 31 cases, 7 cases were extensive metabolizers, 24 cases were poor

Table 1. Association of Genotypes and Patients' Clinical Outcomes

	Extensive	Poor	Total	p-value
Menopause				
Recurrent	4(20)	16(80)	20(100)	0.09
Non-recurrent	18(43.9)	23(56.1)	41(100)	
Non-Menopause				0.9
Recurrent	9(37.5)	15(62.5)	24(100)	0.5
Non-recurrent	6(37.5)	10(62.5)	16(100)	
Stage II				
Recurrent	5(25.0)	15(75.0)	20(100)	0.5
Non-recurrent	10(35.7)	18(64.2)	28(100)	
Stage III				
Recurrent	8(34.7)	15(65.2)	23(100)	0.5
Non-recurrent	12(46.1)	14(53.9)	26(100)	
Her2-neu+				
Recurrent	7(22.5)	24(77.5)	31(100)	<0.001
Non-recurrent	22(66.7)	11(33.3)	33(100)	
Her2-neu-				
Recurrent	7(53.8)	6(46.2)	13(100)	0.07
Non-recurrent	11(45.8)	13(54.2)	24(100)	

Table 2. Cox Proportional Estimates of Hazard Ratios (HRs) of the Risk of Recurrence in Breast Cancer Patients with Tamoxifen

Variables	Univariate		Multivariate	
	p-value	Hazards ratio [95% CI]	p-value	Hazards ratio [95% CI]
CYP2D6 Metabolizes				
Extensive	0.32	4.2[0.24-12.43]	0.45	6.3[1.12-16.54]
Poor	0.44	2.1[0.45-4.32]		
Age	1	0.88[0.21-1.27]		
Menopausal status	0.87	0.91[0.42-1.33]		
Tumour size	0.54	1.3[0.68-3.14]	0.31	1.8[0.85-4.34]
Nodal status	0.43	0.92[0.44-1.65]		
Grade	0.45	1.11[0.67-2.14]		
HER2	0.07	2.1[0.98-13.12]		
Recurrence (Distance)	0.62	1.01[0.78-3.32]		

Menopausal status, post versus premenopausal; and nodal status, n1 versus n0; Her-2, positive versus negative; were analyzed as binary variables. The others were analyzed as ordinal variables. CI, confidence interval; ER, estrogen receptor status

metabolizers, and in non-recurrent Her2-neu positive cases out of 33 cases 22 cases were extensive metabolizers, 11 cases were poor metabolizers. Analysis revealed significant effect of CYP2D6 extensive metabolizer allele on risk of recurrence in Her2-neu positive breast cancer patients who received adjuvant tamoxifen therapy ($p < 0.001$).

Discussion

Clinical impact of CYP2D6*4 on breast cancer recurrence was the main subject of this study. There are numerous studies performed that provide conflict results to support or not this assumption (Zhou et al., 2012). Previous studies have shown that genetic polymorphism in CYP2D6 may predict the benefit of tamoxifen therapy with a significantly improved disease free survival in patients that were carriers of the CYP2D6*4 allele (Wegman et al., 2005; Wegman et al., 2007; Sukasem et al., 2012). However, other studies have shown no significant influence of polymorphisms upon clinical outcome. Studies involving the effect of concomitant use of CYP2D6 inhibitors and tamoxifen on breast cancer recurrence have also been conflicting (Phuong K). Patients possessing at least one CYP2D6*4 allele had a better survival and demonstrated a significantly decreased risk of recurrence (RR = 0.28, 95%CI = 0.11-0.74) when randomised to tamoxifen. The outcome among patients homozygous for CYP2D6*1 was approximately equal between tamoxifen treated and untreated cases (Wegman et al., 2005; Wegman et al., 2007)

In a previous report Wegman et al. observed that the patients with breast cancer randomized to treatment with and without tamoxifen, with genetic polymorphism in CYP2D6 and SULT1A1 may predict the benefit of tamoxifen therapy with a significantly improved disease free survival in patients that were carriers of the CYP2D6*4 allele and/or were homozygous for the SULT1A1*1 allele (Wegman et al., 2005). Following this study, Wegman et al. investigated different and larger cohort, which also included additional polymorphic enzymes that participate in the biotransformation and elimination of tamoxifen. Prognostic evaluation in the total population revealed a significantly better disease-free

survival in patients homozygous for CYP2D6*4 (Wegman et al., 2007).

In this study we investigated rate of recurrence in patients treated with tamoxifen according to the menopause, Her2-neu status and stage of the disease. By genotyping CYP2D6 in 101 breast cancer, we have demonstrated that Her2-neu positive Tamoxifen treated patients with extensive CYP2D6 alleles have a lower risk of breast cancer recurrence. Expression of human epidermal growth factor receptor 2 (HER2), which is associated with tumor aggressiveness, was observed in 7 recurrent cases with extensive metabolizer phenotype. Additionally, it has been suggested that overexpression of HER2 can be another mechanism of tamoxifen resistance, which is consistent with the lower efficacy of tamoxifen in ER+HER2+ patients (Dowsett et al., 2009). In general, the breast cancer patients who were positive for hormonal receptors status were advised to take hormonal therapy (tamoxifen), which is mainly metabolized by CYP2D6 enzyme. In contrast, Martins et al, in a study to determination of CYP2D6 *3, *4, and *10 frequency in women with breast cancer in Brazil, reported that only poor metabolizer patient presented with a tumor larger than 2 cm, with moderately differentiated histology, positive lymph nodes, and positive HER2 expression (Martins et al., 2014).

No association between the recurrence rate and the genotypes of CYP2D6, menopause, stage status was found among 3 years Tamoxifen treated patients. Okishiro et al., conducted a study to Genetic Polymorphisms of CYP2D6*10 and CYP2C19*2,*3 in Japanese breast cancer patients treated with adjuvant Tamoxifen. They demonstrated that none of these genotypes showed any significant association with various clinicopathologic parameters, including menopausal status, tumor size, lymph node status, ER, PgR, HER-2, histologic grade, and type of adjuvant therapy (Okishiro et al., 2009). In a study, Surekha et al., have found the frequency of IM genotype and pooled genotypes (PM and IM) were found to be increased in patients who were positive for estrogen receptor (47.8%), progesterone receptor (44.8%) and also HER2/neu (26.9%) status Surekha et al. Data from the correlation analysis of CYP2D6 vs. Grades of the disease showed that, the percentage of IM was increased from

Grade I to Grade III, where as in SULT1A1 gene, we observed that there is Slight increase of IM genotype from Grade I to Grade III. (Wegman et al., 2007). Park et al. found no significant association with any of the CYP2D6 genetic variants and prognostic factors, including tumor size, nodal status, Ki67, PR negativity, and HER2 positivity (Park et al., 2013).

The CYP2D6*4 allele has been postulated by researchers over the years to have many potential consequences, both positive and negative. The result of CYP2D6 is partly in contrast to Nowell et al., that noted that the CYP2D6*4 () variant seemed to be associated with a decreased risk of death or recurrence. Others have found contrary results (Nowell et al., 2005). In a recent study by Goetz et al., who investigated the CYP2D6*4 genotype in 180 postmenopausal breast cancer patients treated with tamoxifen, they demonstrated that patients homozygous for CYP2D6*4 had significantly worse relapse- and disease-free time but not overall survival (Goetz et al., 2005). It has been reported that tamoxifen-treated Caucasian patients who are heterozygous or homozygous homozygous for the CYP2D6*4 allele have a significantly increased risk of breast cancer recurrence, a shorter relapse-free period, and a lower event-free survival rate in comparison to carriers of functional alleles (Schorth et al., 2007; Schroth et al., 2009).

In this study the recurrence rate in patients with poor metabolizer allele was higher than extensive allele. In addition, we found that post-menopausal and stage III patients with extensive allele tended to have decreased rate of recurrence with tamoxifen for three years, although this was not statistically significant (Table 1). It was reported that pooled genotypes of PM and IM was more strongly associated with disease recurrence than EM genotype (Gonzalez-Santiago et al., 2007; Bijl et al., 2009; Abraham et al., 2010). For other gene SULT1A1*2, Nowell et al. demonstrated that patients with the genotype responsible for a low activity phenotype, sulfotransferase 1A1*2 (SULT1A1*2) was shown to have a significantly increased risk of disease recurrence compared to those with the wildtype alleles (Nowell et al. 2002). Morrow K et al., have not found a significant effect of CYP2D6 genotype on risk of recurrence in early stage breast cancer patients who received adjuvant tamoxifen therapy (Morrow et al., 2012).

It suggested that CYP2D6 is an independent predictor of therapeutic outcome in postmenopausal breast cancer patients receiving tamoxifen (Goetz et al., 2007). According to the available data, Brauch et al., postulated that the current evidence is sufficient to accept the CYP2D6-tamoxifen pharmacogenetic relationship in postmenopausal women (Brauch et al., 2008). The use of CYP2D6 testing in premenopausal women is more controversial because a standard alterative therapy is not available (Goetz et al., 2005). Wegman et al., have demonstrated that genotype of metabolic enzymes might be useful as a guide for adjuvant endocrine treatment of postmenopausal breast cancer patients. CYP2D6 testing has been proposed in postmenopausal women because poor metabolizers alternatively could be treated with an AI (Wegman et al). However, we have not found a significant

association between CYP2D6 genotype and recurrence in pre or post-menopause breast cancer patients who received adjuvant tamoxifen therapy. Thus, our results do not support the hypothesis that CYP2D6 genotype predicts clinical benefit of adjuvant tamoxifen treatment among postmenopausal breast cancer patients.

In conclusion, genetic variations in CYP2D6 may be associated with recurrence of breast cancer patients. The present study indicates that Her2-neu positive patients with extensive metabolizer CYP2D6 polymorphisms had shown less recurrent rate than others. Therefore, this study for first time demonstrated significant effect of CYP2D6 extensive metabolizer alleles on risk of recurrence in Her2-neu positive breast cancer patients who received adjuvant tamoxifen therapy. However, some results are in contradiction to prior hypotheses and the present sample size is relatively small. Findings therefore need to be confirmed in a larger cohort.

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