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Mini-Review

Pharmacokinetics and pharmacogenomics of selective estrogen receptor modulators in breast cancer patients

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ABSTRACT

Many factors affect an individual's response to a drug, and large inter-ethnic, intra-ethnic, and even intra-individual variations exist. These variations may affect both the therapeutic response to a drug, and the side effects that the patient experiences. It is very desirable to be able to predict these variations in response or to ensure that these variations are as small as possible. Using pharmacokinetic and pharmacodynamic information may increase the accuracy of response prediction. The clinical benefit obtained from adjuvant treatment with tamoxifen might be reduced in patients who have either a particular *Cytochrome P450* (*CYP*) *2D6* genetic polymorphism or who are taking paroxetine, a strong inhibitor of CYP2D6. In this review, we summarize current knowledge in the field of pharmacogenomics and pharmacokinetics as it relates to selective estrogen receptor modulators, focusing particularly on clinical data.

KEYWORDS: pharmacokinetics, tamoxifen, CYP2D6, pharmacogenomics, pharmacodynamics, toremifene

INTRODUCTION

When genetic variation affecting drug response was believed to be relatively uncommon and thus found exclusively in a minority of patients, pharmacogenomic approaches were used only in rare cases of severe adverse events. However, in recent years, several pharmacogenomic studies have demonstrated a link between genetic variation and the efficacy of drugs. Genes harbor sequence variations at single nucleotides, called single nucleotide polymorphisms (SNPs). In humans, SNPs occur every 300 to 1000 bases along the genome, making the estimated total number of SNPs 3,200,000 in an entire genome. Clearly, polymorphisms in genes encoding drug-metabolizing enzymes and transporters are not exclusive to a minority of patients.

1. Polymorphisms in genes encoding tamoxifen-metabolizing enzymes and levels of active tamoxifen metabolites

Tamoxifen (Tam) is one of the standard drugs in the treatment of recurrent and advanced breast cancer and in postoperative adjuvant endocrine therapy. Figure 1 shows the main metabolic pathway of Tam. Tam is a prodrug, and 4-hydroxytamoxifen (4-OH-Tam) and endoxifen, converted from Tam mainly by CYP2D6, are active metabolites. Compared to the parent compound, both 4-OH-Tam and endoxifen are 30 to 100 times more potent in binding to the estrogen (E) receptor and in inhibiting cell proliferation in an E-dependent manner [1]. In steady state conditions, the blood concentration of *N*-desmethyl Tam is the highest, and thus the concentration of its metabolite, endoxifen, is 5 to 10 times higher than that of 4-OH-Tam. On the basis of these findings, blood endoxifen concentrations

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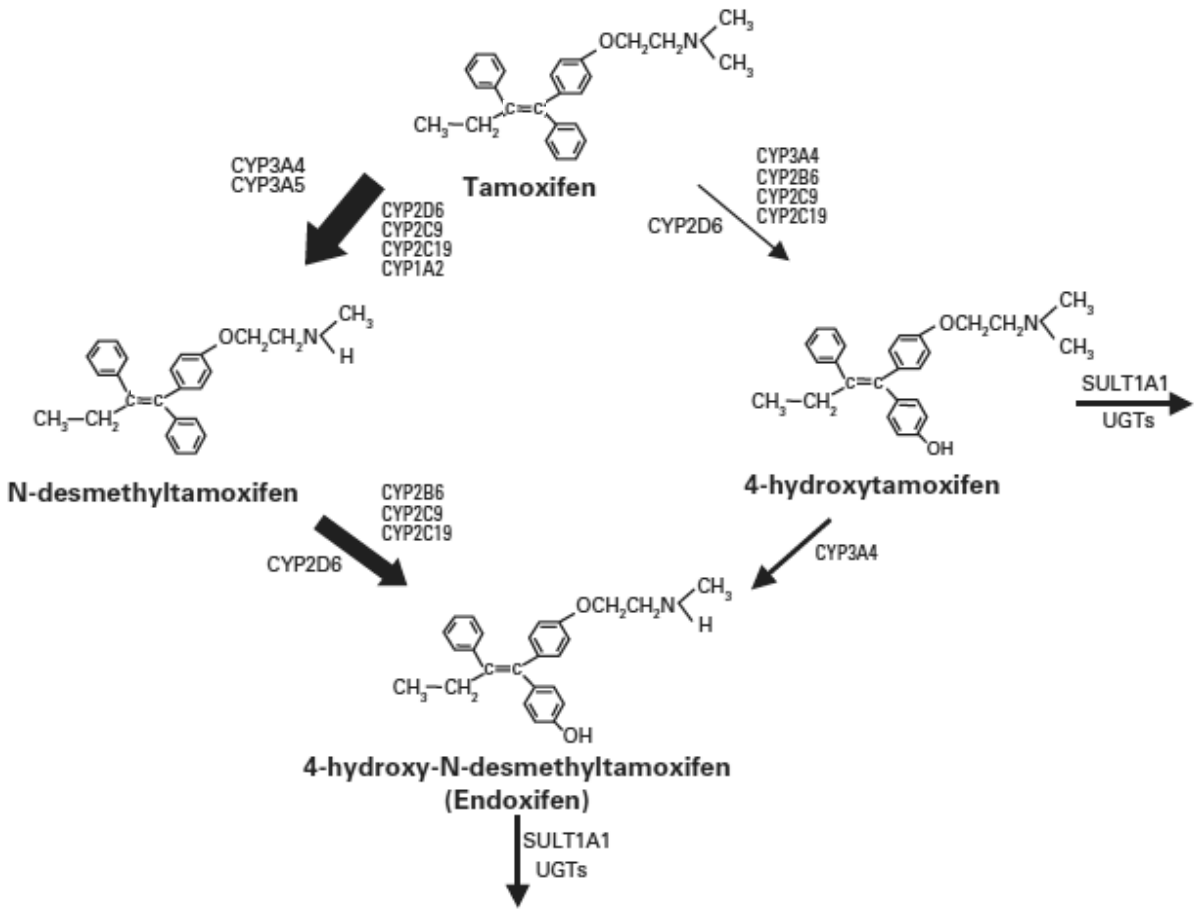

Figure 1. The main metabolic pathway of tamoxifen: Figure modified from [2, 3].

have served as an indicator of CYP2D activity to assess its association with the beneficial effects and adverse events caused by Tam [2].

Several polymorphisms in *CYP2D6* were shown to be associated with the blood concentration of endoxifen. Allelic variants *CYP2D6*3, CYP2D6*4, CYP2D6*5* and *CYP2D6*6* encode proteins with little enzymatic activity [3]. The frequencies of these non-functional alleles are about 20-30% in Europe (Caucasian population), while only 7% in Japan [4]. The steady-state blood concentrations of endoxifen during Tam treatment are 75% lower in patients with homozygous genotypes for these non-functional *CYP2D6* alleles, and 45% lower in those with heterozygous genotypes than in those with the wild-type *CYP2D6* genotype [3] (Figure 2A). On the other hand, allelic variants *CYP2D6*9* and *CYP2D6*10*, encoding unstable enzymes with reduced activity, are found relatively frequently in the Asian population [4] (allele frequency of 40%). The steady-state blood concentrations of endoxifen during Tam treatment were 60-70% lower in patients homozygous for these unstable *CYP2D6* alleles, and slightly lower in those with heterozygous genotypes than in those with the wild-type *CYP2D6* genotype [5] (Figure 2B). Meanwhile, several metabolic enzymes affect the pharmacodynamics of endoxifen (see above), and a variety of concomitant drugs influence the blood concentrations of endoxifen (see below). Therefore, it is difficult to estimate the blood concentration of endoxifen solely on the basis of the *CYP2D6* genotypes.

2. Other enzymes involved in Tam metabolism

Several enzymes such as other cytochrome P450s (CYPs), SULT1A1 and UDP-glucuronosyltransferases (UGTs) are involved

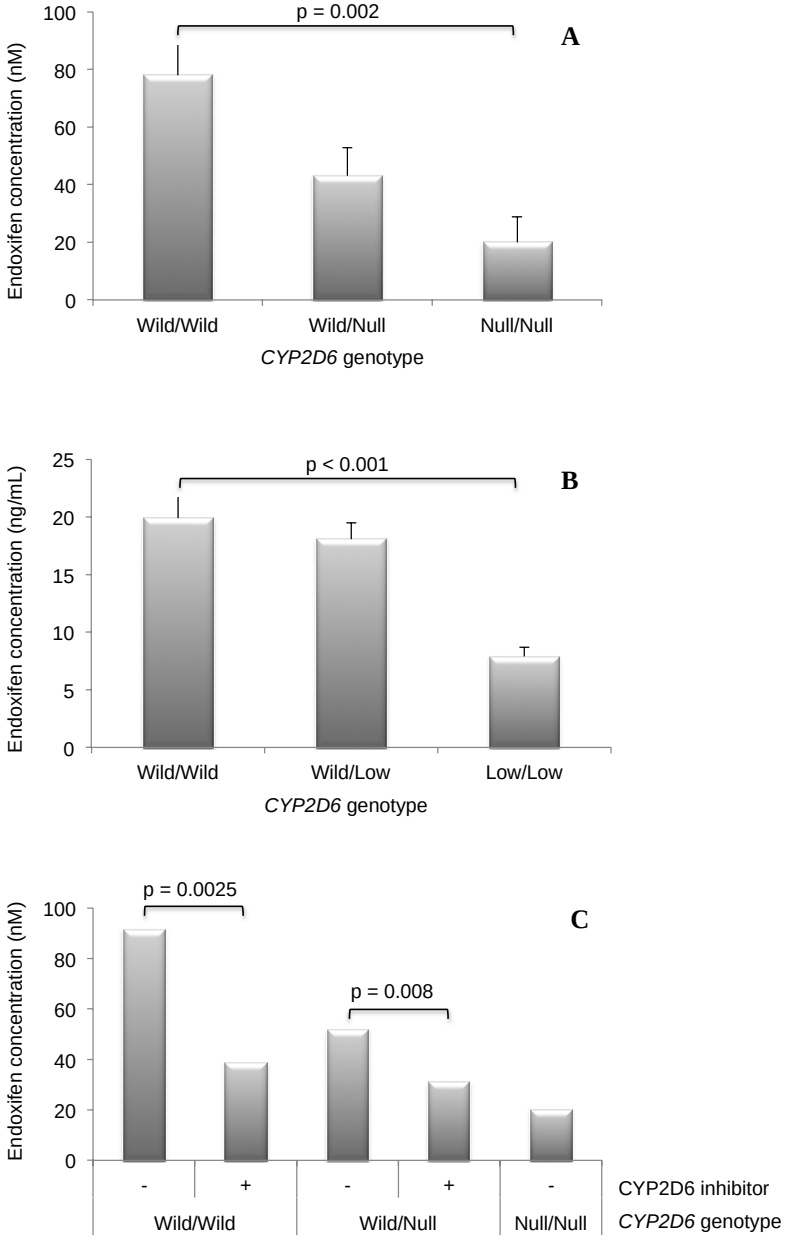

Figure 2. Endoxifen concentrations in breast cancer patients treated with tamoxifen, according to *CYP2D6* genotype. (A) Wild-type versus null genotype [3]. (B) Wild-type versus low genotype [5]. (C) Wild-type versus null genotype with or without CYP2D6 inhibitor [3].

in endoxifen metabolism (Figure 1), and polymorphisms in genes encoding these enzymes are implicated in the pharmacokinetics of tamoxifen and its metabolites [6]. Patients with the homozygote of *CYP2C19* high enzyme activity promoter variant **17* may have a higher concentration of endoxifen [7] and carriers of **17*, whether homozygous or heterozygous, are reported to have a more favorable clinical outcome than carriers of other alleles [8]. Although results from recent studies indicate that the SULT1 genotype may influence the outcome of tamoxifen treatment, a pharmacology study showed that the SULT1 genotype or copy number did not influence the concentration of tamoxifen and its active metabolites [9]. The functional

polymorphisms in UGT2B7 and potentially UGT1A8 may be important in inter-individual variability in Tam metabolism and response to Tam therapy [10].

Two SNPs in the adenosine triphosphate-binding cassette transporter (ABC) C2 (also known as multidrug resistance-associated protein 2 [MRP2]) were found to be significantly associated with recurrence-free survival of patients receiving adjuvant tamoxifen monotherapy. Interestingly, these SNPs do not seem to affect the concentration of Tam and its active metabolites, and it has been suggested that ABCC2 might regulate local exposure of endoxifen to breast cancer cells [11].

3. Concomitant drugs and blood concentrations of Tam metabolites

Blood concentrations of endoxifen vary greatly even among patients with the wild-type *CYP2D6* genotype. Concomitant use of CYP2D6 inhibitors such as paroxetine, sertraline, amiodarone and metoclopramide during Tam treatment leads to a decrease of more than 50% in blood endoxifen concentration [3] (Figure 2C). In particular, when the strong CYP2D6 inhibitor paroxetine is co-administered with Tam, blood endoxifen concentrations in patients with the wild-type *CYP2D6* genotype become as low as those in patients with a homozygous non-functional *CYP2D6* genotype [3]. This indicates that not only genetic factors but also environmental factors (e.g. use of concomitant drugs) have a great impact on drug metabolism. Table 1 shows the major CYP2D6 inhibitors. It is recommended that the use of strong CYP2D6 inhibitors be avoided, and weak to moderate inhibitors be replaced during Tam treatment by alternative drugs expected to have little inhibitory effect, as suggested in Table 1 [12].

4. CYPD6 activity in Tam metabolism and adverse events

Among the adverse events associated with Tam therapy, hot flashes are the most influential in determining whether the treatment should be continued. Hot flashes appear to be rare in patients with genotypes associated with severely impaired CYP2D6 activity, suggesting a link between adverse events and blood concentrations of the active metabolites of Tam [2]. It has also been shown that compliance with Tam treatment becomes poorer as the CYP2D6 activity score, determined by *CYP2D6* genotypes and the use of concomitant drugs, increases.

5. Relationship between therapeutic effects of Tam and *CYP2D6* polymorphisms

The relationship between polymorphisms in *CYP2D6* and therapeutic effects of Tam has been studied, but the results are contradictory and inconclusive. There are several possible explanations for the variation in findings between studies: (1) frequencies of non-functional and reduced-function *CYP2D6* alleles in Asian countries are very different from those in European countries, resulting in inconsistencies in the effects of Tam treatment depending on the place of study; (2) systems used for classification and scoring of *CYP2D6* polymorphisms are inconsistent; (3) many enzymes, in addition to CYP2D6, are involved in Tam metabolism, and thus it is impossible to explain differences in the pharmacokinetics of endoxifen solely by polymorphisms in *CYP2D6*; (4) concomitant use of CYP2D6 inhibitors may have a greater impact on the blood concentration of endoxifen than polymorphisms in *CYP2D6*; and (5) it is possible that compliance with Tam therapy is poor in patients with a high blood endoxifen concentration, thereby reducing the therapeutic effects. If these issues are not addressed, conducting similar studies, no matter how many, will not determine the influence of polymorphisms in *CYP2D6* on the therapeutic effects of Tam. Instead, direct determination of drug concentrations, as is common practice for anticonvulsants and immunosuppressants, is considered a more suitable approach in the future. A recent study showed that increasing the oral dose of Tam from 20 mg to 40 mg did not increase blood endoxifen levels in some patients who were *CYP2D6* poor metabolizers [13]. Meanwhile, the Japan Breast Cancer Research Group is currently conducting a clinical trial in which patients who have been on 20 mg oral Tam are screened for failure to attain a sufficient endoxifen concentration, and

Table 1. Medications showing possible interaction with tamoxifen: Table modified from [7].

Class	**Moderate ~ Potent Inhibitors**	**Weak ~ Moderate Inhibitors**	**Little *In Vivo* Inhibition**
SSRI/SNRI	Paroxetine Fluoxetin Bupropion Duloxetine	Sertraline Citalopram Fluvoxamine	Venlafaxine Desvenlafaxine Reboxetine Escitalopram Mirtazapine
Tricyclic antidepressants		Clomipramine Doxepine Desipramine Imipramine Amitriptyline Nortriptyrine	
Antipsychotics	Thioridazine Perphenazine Pimozide	Chlorpromazine Fluphenazine Haloperidol	Thiothixene Clozapine Risperidone Clozapine Olanzapine Ziprasidone Quetiapin
Cardiac medications	Quinidine Ticlopidine	Amiodarone Nicardipine Verapamil Amlodipine Felodipine Nifedipin	Diltiazem
Anti-infectives	Terbinafine Quinidine	Ritonavir Halofantrine Chloroquine	Indinavir Saquinavir Nelfinavir Delavirdine Nevirapine Efaviren
H_2 blockers		Cimetidine	Ranitidine
H_1 Blockers		Clemastine Tripelennamine Promethazine Hydroxyzine Diphenylpyralin	Chlorpheniramine Cetirizine Loratadine
Miscellaneous	Cinacalcet	Celecoxib	Gabapentin

in those patients, Tam is replaced with toremifene (TOR, initial dose 40 mg, escalated dose 120 mg), in order to investigate differences in blood concentrations of the active metabolites of TOR between the 40-mg and 120-mg regimens in individual patients.

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