

Role of Cytochrome P450 Polymorphisms on Breast Cancer Treatment

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Abstract

Pharmacogenetics is one of the key factors that is responsible for biological signaling variations that can lead to various diseases. Being led by genetic mutations, breast cancer is affected at higher level due to pharmacogenetic variations. Chemotherapeutic drug is mainly bio transformed in the liver by cytochrome P450 (CYP) enzyme. CY450 isoforms and polymorphisms direct inter individual and interethnic variability in pharmacokinetics and pharmacodynamics of drugs. This further leads to alteration in cancer prognosis. This paper discusses clinically used drugs in breast cancer treatment where interethnic differences in drug safety and efficacy are known to exist. Best known anticancer drug for estrogen receptor-positive breast cancer is Tamoxifen and its efficacy depends predominantly on genetic variants of CYP2D6. Other polymorphisms of CYP3A4, CYP3A5, and sulfotransferase1A1 (SULT1A1) also provide important information about mechanism of tamoxifen activity and resistance. Many chemotherapeutics like anthracyclines have also showed association with polymorphism of genes (CBR3, ABCB1, glutathione-related transporter genes, oxidative stress-related genes) and clinical outcomes. Many chemotherapeutic drug including taxanes, gemcitabine, capecitabine/5-fluorouracil, vinorelbine, methotrexate, and cyclophosphamide are being studies for the association of genetic variations with their bioactivity.

Keywords: CYP450 enzymes; Polymorphisms; Cancer; Genetic variations

Introduction

The cytochrome P450 (CYP) is the group of enzymes present predominantly in the liver and at lower levels in the other organs [1-3]. It encodes enzymes involved in metabolism of pharmaceuticals, foreign chemicals and pollutants. Initially it was thought to be restricted to understand detoxification of unknown chemicals in the body [4,5]. But later advancements in the field triggered its necessity in understanding critically important life processes. This led to the identification of mutations in a number of CYP genes are responsible for errors of metabolism and further contribute to several important relevant diseases or unwanted effects during drug treatment [6-8]. Few CYP enzymes are also responsible for transformation of pro drugs in cancer to their activated forms [7]. Enzyme expression or enzyme diminished depends on the number of alleles present though the exact location of corresponding allele is yet to be identified [9]. By activation or inactivation of carcinogens as well as anticancer drugs, CYP has critical role in identifying the causes of cancer and also treatment of it [10]. The most important enzymes for drug metabolism are CYP2C9*, CYP2C19, CYP2D6 and CYP3A4, whereas the most important isoforms responsible for the biotransformation of chemicals and especially for the metabolic activation of pre-carcinogens are CYP1A, CYP1A2, CYP1B1, CYP2A6, CYP2E1 and CYP3A4 [11]. By understanding these polymorphisms, it is easier to estimate interindividual and interethnic variability in drug pharmacokinetics and pharmacodynamics [12].

Breast cancer is a major cause of death not only in the USA but worldwide [13]. Occurrence of cancer is majorly due to genetic susceptibility or inheritance [14]. At the same time, the etiology of the

majority of breast cancers is unclear [14]. Breast cancer is highly heterogeneous which is calling for individual therapy these days [15-18]. The condition get worsened by important gene mutations [19-22], aggressiveness [23], metastasis [24] and resistance [25,26]. Estrogen receptor (ER) positive tumors have characteristics of luminal cell types and responsive to endocrine treatment [27,28]. Chemotherapy, radiotherapy and treatment with natural compounds are being research interests in treating cancer with high pharmacological activity and low minimal toxicity [29-31].

Selection of CYP enzyme activity against a particular drug does not depend upon its levels in the body. In other words, low level CYPs can be more responsible for drug metabolism. Most CYP enzymes are highly present in centrilobular area of the liver [32]. The same area of the liver is very susceptible to damage by drug toxic concentrations in the liver as they are also the substrates for the CYPs. Chemotherapeutic drugs are known for their significant adverse effects and hence can affect levels and activity of other CYPs in this area [32]. Hence several natural compounds are being tested in the research studies [33,34]. They are showing promising results and need further development [35]. Natural compounds are also subjected to chemical reactions to synthesize semi-synthetic derivatives with low toxicity and more in vivo anticancer activity [36]. Nano formulations and sustained release formulations can hold great hope in drug development [37-40]. Most CYPs involved in the biotransformation of xenobiotics are inducible. But, CYP2D6 is not the same due to its multiple gene copies are responsible for increased detoxifying potential of the enzyme. Induction and inhibition mediated by cancer targeting drugs alter CYPs transcriptional, translational and posttranslational activities [41].

Impact on breast cancer treatments

There are different types of systemic treatments for breast cancer like hormonal interventions, chemotherapy and novel agents. Efficacy of the treatments in each and very cancer type depends not only on dose and schedule but also on functional targets, drug metabolizing enzymes and transporters. The genetic alterations have positive response and/or potential adverse effects.

Tamoxifen

Tamoxifen is a selective estrogen-receptor modulator indicated for mainline and adjuvant treatment of breast cancer in women. Being a pro drug, Tamoxifen has to metabolize to its active metabolite, endoxifen, through CYP2D6 enzyme [42]. When metabolized by CYP3A4/5, Tamoxifen transforms into N-desmethyltamoxifen. This metabolite accounts for around 90% of primary tamoxifen oxidation. Both N-desmethyl- tamoxifen (via CYP2D6) and 4-hydroxy-tamoxifen (via CYP3A4/5) are secondarily metabolized to 4-hydroxy-N-desmethyl- tamoxifen (endoxifen). Other than endoxifen, 4-hydroxy-tamoxifen also has similar anticancer activity in the body. But later studies suggest that endoxifen [43,44] is more important than 4-OH tamoxifen due to its inter-individual variability in expression. Second stage of metabolism of Tamoxifen is mediated by sulfotransferases such as sulfotransferase1A1 (SULT1A1), or glucuronidation by the UDP glucuronosyltransferases (UGT). As many of the tamoxifen-metabolizing enzymes are polymorphic, genetic variations may account for interindividual or interethnic differences in tamoxifen-related outcomes. More than 80 allelic variants have been described in CYP2D6, that have higher, lower or absence of enzymatic activity. The nonfunctional variants CYP2D6*3 (2637delA), CYP2D6*4 (1934G>A), CYP2D6*5 and CYP2D6*6 (1795delT) result in formation of lower or no endoxifen concentrations compared with wild-type variants of enzymes [45]. Up to 10% of Caucasians are poor metabolizers, with the CYP2D6*4 allele being the predominant allele [46]. In contrast, expression of CYP2D6*4 variant is extremely low in Asians or Black Africans. At the same time, ultra-rapid forms of CYP2D6 are rare in Caucasians and Asians but are common in Ethiopians and Saudi Arabians [19].

As the activity of Tamoxifen is determined by CYP2D6 variations, the drugs which alter the activity of the enzyme should be studied when giving Tamoxifen treatment to patients. Potent CYP2D6 inhibitors include antidepressants such as fluoxetine and paroxetine, whereas moderate/weak inhibitors include cimetidine, amiodarone, ticlopidine, and haloperidol. Different genetic variants other than CYP2D6 have also been studied, which also involves with tamoxifen metabolism. Among them, CYP3A5*3 (6986A>G), a genetic variant of CYP3A5 have less activity with no association of tamoxifen metabolism [47,48]. The enzymes involved with inactivation and elimination of both tamoxifen and its metabolites through sulfate or glucuronide conjugation may also have significant genetic variation.

Aromatase Inhibitors (AIs)

Aromatase (CYP19A1) is the main enzyme implicated in estrogen biosynthesis. Polymorphisms in CYP19A1 can affect both aromatase expression and activity leading to changes in the estrogen levels. As few types of breast cancer are estrogen-dependent, CYP19A1 is important factor in its occurrence and treatment. AIs have proven efficacy in both advanced and early postmenopausal hormone receptor-positive breast cancers. Interestingly, the Arg39 variant is present in 6.7% Han

Chinese Americans but is very rare in the other three ethnic groups, whereas the Cys264 variants present Han Chinese Americans and African-Americans (11.7% and 22.5%) than Caucasian Americans or Mexican Americans (2.5% and 5%). Letrozole is the AI used in breast cancer therapy [49]. Presence of a SNP in the 3'-untranslated region (3'-UTR) of the CYP19 aromatase gene is associated with improved treatment efficacy in patients with hormone receptor-positive metastatic breast cancer treated with the aromatase inhibitor, letrozole.

Anthracyclines

Doxorubicin and epirubicin are the chemotherapeutic drugs which belong to the Anthracyclines group. They showed prominent interindividual variations in pharmacokinetics (PK) and pharmacodynamics (PD) parameters after administering. The variation is also due to the patient ethnic variations when comparing Chinese and Asian populations [50].

In the liver, doxorubicin and epirubicin are transformed to the corresponding C-13 alcohol metabolites doxorubicinol and epirubicinol in phase I reactions. These phase I are carried by carbonyl reductases (CBR1 and CBR3) and aldoketoreductases (AKR1A1 and AKR1C2). After metabolic transformation, respective alcohol metabolites exert weak antitumor activity but more cardio toxicity in patients. SNPs of CBR1 and CBR3 enzymes alter PK and PD of doxorubicin. It was found that CBR3 11A variant was more common in Chinese than Caucasians (57% versus 36%) and responsible for more doxorubicin-induced myelosuppression in Chinese [51].

Taxanes

Taxanes show anticancer activity by increasing stabilization of microtubule network after binding to the same. Hence used in several cancer types including lung, breast, gastric, ovarian and prostate cancer. However, it has major side effect by myelosuppression and peripheral neuropathy. Paclitaxel and docetaxel are examples of Taxane group of chemotherapeutic agents. They both bind to P-glycoprotein on biliary canalicular membrane and bind to tubulin residues to stabilize microtubules. Paclitaxel is metabolized by CYP3A4 to a minor active metabolite and by CYP2C8 to a major inactive metabolite 6-8-hydroxypaclitaxel. Some polymorphisms of CYP2C8 have been identified such as CYP2C8*3, CYP2C8*4, and CYP2C8*2. CYP2C8*3 and CYP2C8*4 were found to be associated with diminished catalytic activity of the conversion of the parent drug to 6-hydroxytaxol compared to the wild type genotype [52].

ABCB1 genotype and haplotypes correlate with taxane PK and toxicities, there have been many others that have not shown any correlation. Docetaxel clearance is approximately 40% lower while drug exposure is approximately 25% higher in Asians compared to Caucasians [53].

Capecitabine and 5-FU

Capecitabine is used in treatment of solid tumors which required to be metabolized to active form, 5-Fluoro uracil (5-FU). Further, 5-Fluorouracil is reduced to the inactive metabolite dehydro-fluorouracil via dihydropyrimidine dehydrogenase (DPD) enzyme during second phase of metabolizing in liver. Tumors with low expression of DPD mRNA and activity are associated with improved response to fluorouracil and improved survival [54]. Over 20 functional mutations have been reported in the DPD gene. Thus, the clinical significance of each and every mutations is unknown. Thymidylate (dTMP) which is

incorporated in DNA, produce from deoxyuridylate (dUMP) by thymidylate synthetase (TS). TS is the target of 5-FU and responsible for cellular expression of several genes. TS gene is associated with differential activity leading to worse response due over expression of several tandem repeat sequences (TSER*2, TSER*3, TSER*4, and TSER*9) in its structure [54,55].

Trastuzumab and lapatinib

HER-2 overexpressing breast cancer is clinically targeted by combination of trastuzumab and lapatinib. Trastuzumab is the anti-HER2 monoclonal antibody and lapatinib is the tyrosine kinase inhibitor. The dual action of drug showed encouraging results in the neoadjuvant setting. No genetic variant yet found to influence trastuzumab metabolism, efficacy, or toxicity so far. However, binding of trastuzumab to its target at the extracellular domain of ERBB2 may influence individual drug responses. CYP2C19, CYP3A4/5, P-glycoprotein, and BCRP are involved in the metabolism and transport of lapatinib, and polymorphisms in genes encoding these proteins may affect lapatinib disposition [56].

Conclusion

CYPs have important roles in activation and inactivation of both precarcinogens and of anticancer drugs. Interindividual variability in the efficacy and toxicity of drug therapy is associated with polymorphisms in genes encoding drug-metabolizing enzymes, transporters, or drug targets. Pharmacogenetics is the source to identify individuals that are more susceptible to certain type of toxicity or variation from conventional doses of cancer chemotherapeutic agents. Several potential candidate genes and polymorphisms have been studied and most of them need further investigation and are difficult to draw a clear conclusion and correlation between genotype and pharmacological effects. More work is required to compare drug efficacy and toxicity across different ethnic groups, where host-genotype interactions may be significant.

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