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REVIEW ARTICLE

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Cancer pharmacogenomics: achievements in basic research

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Abstract Pharmacogenomics is the study of how genetic inheritance influences the responses to drugs. Genetic polymorphisms in drug-metabolizing enzymes result in altered pharmacokinetics in therapeutic drugs. In recent years, there has been great progress in our knowledge of the effects of cytochrome P450 (CYP) polymorphisms on the pharmacokinetics of therapeutic drugs. CYP enzymes catalyze the activation or detoxification of several anticancer drugs. Anticancer drugs generally have a narrow therapeutic margin. Therefore, the interindividual variability in their efficacy and toxicity is a major problem in clinical practice. In this review, genetic polymorphisms of CYP enzymes and their clinical relevance in cancer chemotherapy are discussed.

Key words Drug-metabolizing enzymes · Cytochrome P450 · Interindividual variability · Genetic polymorphism · Chemotherapy

Introduction

Most medications exhibit large interindividual variability in their efficacy and toxicity, which is a major problem in clinical practice. These interindividual differences are due in part to genetic polymorphisms in genes encoding drug-metabolizing enzymes. For most drugs, oxidative metabolism by cytochrome P450 (CYP) is a common metabolic pathway.[1] Human CYP enzymes, particularly the CYP1, CYP2, and CYP3 families, play a role in the metabolism of drugs and environmental chemicals. Genetic polymorphisms have been described in all the main CYPs that contribute to the metabolism of drugs (http://www.imm.ki.se/CYPalleles/). There is accumulating evidence that CYP polymorphisms contribute significantly to interindividual variations in the capacity of individuals to metabolize drugs. The mutated alleles cause abolished, reduced, altered, or increased enzymatic activity, because of single nucleotide polymorphisms (SNPs), gene deletions, or gene duplications. When the therapeutic index is narrow, polymorphisms can be considered to be clinically significant.

Most anticancer drugs also exhibit significant interpatient variability in pharmacokinetics and toxicity. Anticancer drugs generally have a narrow therapeutic index. Some drugs are prodrugs and are biotransformed to active counterparts, and other drugs are detoxified by metabolic enzymes. Several CYP isoforms participate in the metabolic pathways. This review focuses on the role of genetic polymorphisms of CYP enzymes in cancer chemotherapy.

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CYP2A6 and tegafur

In the human CYP2A family, three genes, *CYP2A6*, *CYP2A7*, and *CYP2A13*, have been reported.[2] Among them, only the *CYP2A6* gene encodes an active protein, while the two other genes produce catalytically defective enzymes.[3,4] CYP2A6 is well known as a nicotine *C*-oxidase enzyme.[5] Pharmaceutical drugs that are metabolized by CYP2A6 include SM-12502 (a platelet-activating factor antagonist), valproic acid, and halothane.[6] As for anticancer drugs, CYP2A6 metabolizes tegafur, which has been used clinically for over 20 years. Tegafur is a prodrug and is bioactivated to 5-fluorouracil (5-FU) by CYP2A6.[7,8]

There is significant interindividual difference in CYP2A6 activity, and this is due to genetic polymorphisms. Several variant alleles have been reported to decrease or delete the enzymatic activity (http://www.imm.ki.se/CYPalleles/cyp2a6.htm). *CYP2A6*4*, the allele with the whole gene deleted, completely lacks the enzymatic activity.[9,10] It should be noted that the frequency of the *CYP2A6*4* allele is high in Orientals, with a frequency of

approximately 15%–20% of the population.[6] Alleles possessing an SNP, such as *CYP2A6*2*,[3] *CYP2A6*5*,[11] *CYP2A6*6*,[12] *CYP2A6*7*,[13] *CYP2A6*10*,[14] *CYP2A6*11*,[15] and *CYP2A6*17*[16] have been reported to show decreased enzymatic activity in vitro and/or in vivo. The *CYP2A6*9* allele with an SNP in the TATA box shows decreased transcriptional activity and decreased enzymatic activity in vitro and in vivo.[17,18] A *CYP2A7/CYP2A6* hybrid allele (*CYP2A6*12*) carrying an unequal crossover in intron 2 has been reported to show decreased enzymatic activity in vivo.[19] The *CYP2A6*1X2* allele has a duplication of the *CYP2A6* gene.[20]

There is accumulating evidence that individuals who are homozygous or heterozygous for certain variant alleles are poor metabolizers of CYP2A6.[6,10,21–23] Such evidence suggests the possibility that the pharmacokinetics of tegafur may also be affected by *CYP2A6* genetic polymorphisms. In fact, the *CYP2A6*11* allele which leads to decreased enzymatic activity was found in a Japanese patient who showed a higher than normal value for the area under the plasma concentration-time curve (AUC) for tegafur.[15] It should be remembered that the catalytic activity for converting tegafur to 5-FU is not specific for CYP2A6, because this activity is also possessed by CYP1A2 and CYP2C8.[7] In addition, cytosolic thymidine phosphorylase is also involved in the conversion of tegafur to 5-FU.[24,25] Therefore, the impact of genetic polymorphisms of *CYP2A6* on in vivo tegafur pharmacokinetics remains to be clarified.

CYP2B6 and cyclophosphamide

CYP2B6 is involved in the metabolic activation of cyclophosphamide and ifosfamide.[26] Although the contribution of CYP2B6 to the activation of ifosfamide is relatively low (20% of the total activity, whereas CYP3A4 contributes 40% of the total activity), its contribution to cyclophosphamide activation is extremely high (80% of the total activity, whereas CYP3A4 contributes only 4% of the total activity).[27,28] 4-Hydroxycyclophosphamide, the main metabolite formed by CYP2B6, equilibrates with aldophosphamide, and can then undergo chemical decomposition into phosphoramide mustard and acrolein.[29] Phosphoramide mustard is an active DNA alkylating metabolite and acrolein is a toxic byproduct, which causes hemorrhagic cystitis.

Several variant alleles for the *CYP2B6* gene have been reported. Lang et al.[30] have reported that the C1459T (Arg487Cys) polymorphism in the *CYP2B6*5* and *CYP2B6*7* alleles shows decreased protein levels compared with the wild type. Ariyoshi et al.[31] have reported that the G516T (Gln172His) polymorphism found in the *CYP2B6*6, CYP2B6*7, CYP2B6*9*, and *CYP2B6*13* alleles shows increased enzymatic activity compared with the wild type. Jinno et al.[32] expressed *CYP2B6*2* (Arg22Cys), *CYP2B6*3* (Ser259Arg), *CYP2B6*4* (Lys262Arg), *CYP2B6*5* (Arg487Cys), *CYP2B6*6* (Gln172His and Lys262Arg), and *CYP2B6*7* (Gln172His, Lys262Arg, and Arg487Cys) in COS-1 cells. They reported that CYP2B6.4, CYP2B6.6, and CYP2B6.7, sharing a common mutation (Lys262Arg), exhibited higher Vmax and Vmax/Km values than the wild type for 7-ethoxy-4-trifluoromethylcoumarin *O*-deethylation.[32] Recently, novel alleles possessing SNPs in the coding region (*CYP2B6*8 – CYP2B6*15*) and in the 5′-flanking region (*CYP2B6*1B – CYP2B6*1N*) have also been reported.[33–35] Among them, several alleles exhibited decreased or undetectable enzymatic activity.

Xie et al.[36] reported that *CYP2B6*6* carriers have a significantly higher catalytic ability for cyclophosphamide 4-hydroxylation in vitro compared with *CYP2B6*1* carriers. In Japanese, *CYP2B6*2*, *CYP2B6*4*, *CYP2B6*5*, and *CYP2B6*6* have been found with low allele frequencies.[37] In our preliminary study with Japanese patients, we found that the AUC values of cyclophosphamide tended to be lower in subjects possessing the *CYP2B6*6* allele than in subjects with the wild type (unpublished data). Further in vivo studies are required to determine the clinical impact of *CYP2B6* polymorphisms on the outcome of treatment with cyclophosphamide.

CYP2C8 and paclitaxel

Paclitaxel, derived from the needles and bark of the Western yew, *Taxus brevifolia*, exerts its cytotoxic action through the promotion of microtubule assembly and stabilization by preventing depolymerization.[38] CYP2C8 is a key enzyme for the detoxification of paclitaxel to form 6α-hydroxypaclitaxel, which is approximately 30 times less toxic than paclitaxel.[39,40]

Several polymorphisms have been described for the *CYP2C8* gene. Dai et al.[41] reported that *CYP2C8*2* (Ile269Phe) and *CYP2C8*3* (Arg139Lys, Lys399Arg) showed decreased paclitaxel 6α-hydroxylase activity in vitro. It has been reported that the median paclitaxel 6α-hydroxylase activity in liver microsomes from heterozygotes of *CYP2C8*4* (Ile264Met) was lower than that in the wild type, although the difference was not significant.[42] The *CYP2C8*5* allele has a deletion of adenine 475, which is expected to cause amino-acid alterations from codon 159, and an early stop codon at residue 177.[43] Soyama et al.[44] found an SNP causing an amino-acid change of Pro404Ala in a Japanese subject and reported that the in vitro clearance of paclitaxel 6α-hydroxylation of the variant was reduced in comparison with that of the wild type, because of the labile protein.

Recently, we investigated the interindividual variability of the pharmacokinetics of paclitaxel and its metabolites in Japanese patients with ovarian cancer in relation to genetic polymorphisms of the *CYP2C8* gene (unpublished data). However, we could not find a relation between the *CYP2C8* genotype and the pharmacokinetics/pharmacodynamics of paclitaxel, owing to the very rare allele frequency (only the *CYP2C8*5* allele in 0.25% of Japanese).[45] Therefore, genotyping of the *CYP2C8* gene might have limited utility in predicting adverse effects from paclitaxel in Japanese

cancer patients. In contrast, these variant alleles are more frequent in Caucasians and African-Americans (2%–15%).[41,42] Studies in these populations will provide more critical information on the effects of *CYP2C8* SNPs on the pharmacokinetics of paclitaxel.

CYP2D6 and tamoxifen

The *CYP2D6* gene is one of the best-studied human CYPs. The molecular basis of the variations in CYP2D6 activity is well understood. Correlations between the phenotype and genotype have been extensively studied for various drugs.[46,47] Currently, at least 88 different allelic variants of *CYP2D6* have been identified. CYP2D6 activity is absent in 5%–10% of European and North American Caucasian populations.[48,49] More than 95% of Caucasian poor metabolizers can be identified by screening for the *CYP2D6*3* (frameshift), *CYP2D6*4* (splicing defect), *CYP2D6*5* (whole deletion), and *CYP2D6*6* (frameshift) alleles.[50] The remaining poor metabolizers are likely to be homozygous or heterozygous for a range of different inactive alleles. In addition, gene duplication is responsible for ultrarapid metabolism in 1%–3% of the European population, 8% of southern European populations, and up to 20% of some Arabian and North African populations.[51] Some individuals in this category have 13 copies of *CYP2D6* arranged as tandem repeats, but a single gene duplication event more commonly occurs. In Japanese, the frequency of poor metabolizers is relatively low (around 0.5%).[52] Furthermore, many individuals who are classified as intermediate metabolizers may be either heterozygous for one or the inactive alleles or homozygous for alleles associated with impaired metabolism. The *CYP2D6*10* allele (Pro34Ser) is particularly common in Japanese (allele frequency is approximately 40%) and is associated with decreased enzymatic activity.[53]

Concerning anticancer drugs, CYP2D6 plays a role in the conversion of tamoxifen, which is a selective estrogen receptor modulator.[54] Tamoxifen is widely used for all stages of estrogen receptor-positive breast cancer. There is wide interindividual variability in the clinical efficacy and side effects of tamoxifen.[55,56] The mechanisms underlying the variable response to tamoxifen have been the subjects of intense study, but remain obscure. Tamoxifen is converted to the more potent antiestrogen 4-hydroxytamoxifen by CYP2D6.[54] The formation of 4-hydroxy-*N*-desmethyl tamoxifen from *N*-desmethyl tamoxifen is also catalyzed by CYP2D6.[57,58] One hypothesis is that altered patterns of metabolism of tamoxifen might contribute to the interindividual variability. Stearns et al.[57] reported that subjects who carried a variant allele for *CYP2D6* had significantly lower plasma concentrations of the antiestrogenic metabolite 4-hydroxy-*N*-demethyl tamoxifen than subjects who carried wild-type alleles. However, it is not clear whether patients with low CYP2D6 activity and a low 4-hydroxy-*N*-demethyl tamoxifen concentration will experience less clinical benefit from tamoxifen. Recently, Desta et al.[58] have comprehensively characterized tamoxifen biotransformation and reported that CYP3A4 is also a major enzyme involved in the principal tamoxifen sequential metabolic routes. Thus, further in vivo studies should be performed to determine the impact of genetic polymorphisms of *CYP2D6* on tamoxifen pharmacokinetics/pharmacodynamics.

CYP3A and docetaxel and etoposide

The CYP3A subfamily is the predominant isoform in human liver (30%–50% of total CYP content)[59] and contains four members, CYP3A4, CYP3A5, CYP3A7, and CYP3A43.[60–62] CYP3A4 is abundantly present in human liver and intestine.[59] CYP3A5 shows polymorphism in its expression, with universal expression in intestinal and fetal liver, but detectable expression in only 30% of adult livers.[63] CYP3A7 is universally expressed in fetal liver, but is also expressed in some adult livers. Compared to other CYP3A isoforms, CYP3A43 mRNA is expressed at lower levels in the liver (0.1%–0.2% or CYP3A4 transcript).[64,65] To date, information concerning the function of CYP3A43 is limited.

CYP3A is the most important isoform that catalyzes more than 50% of all drugs.[66] Because CYP3A4 and CYP3A5 have overlapping substrate specificity, it is difficult to estimate the contribution of each member to the total metabolism. A wide interindividual variation in the catalytic activity of CYP3A has been reported in the general population.[67,68] The variable expression of CYP3A5 and CYP3A7 may account in part for the degree of variation seen in the metabolism of CYP3A4 substrates.

A number of recent studies have improved our understanding of the molecular basis of interindividual variations in the levels of CYP3A4 and in the expression of CYP3A5. In the case of *CYP3A4*, several variant alleles that affected the coding region, *CYP3A4*2* to *CYP3A4*19*, have been identified. The *CYP3A4*2* (Ser222Pro), *CYP3A4*4* (Ile118Val), and *CYP3A4*5* (Pro218Arg) alleles were shown to encode a protein with decreased activity.[69,70] *CYP3A4*6* causes a frameshift and it is related to impaired metabolism.[70–72] The *CYP3A4*17* (Phe189Ser) and *CYP3A4*18* (Leu293Pro) alleles result in decreased and increased activity compared with the wild type, respectively.[73] In Japanese, *CYP3A4*6*, *CYP3A4*11* (Thr363Met), *CYP3A4*16* (Thr185Ser), and *CYP3A4*18* alleles have been detected.[74] All the nonsynonymous mutations are seen at low frequencies and seem unlikely to be able to fully explain the interindividual variations in CYP3A4 activity. Although a number of SNPs in the 5′-flanking region have also been detected, they do not appear to be associated with altered transcriptional activity.[74–77]

Polymorphisms of *CYP3A5*, which can account for the variation in the expression of this gene, have been found. In particular, the *CYP3A5*3* allele, which has an SNP in intron 3 (A6986G), leads to alternative splicing and protein truncation.[63] This allele is the most common in all ethnic groups,

and the allele frequency in Japanese is 75%.[78] Rare alleles, *CYP3A5*4–CYP3A5*10*, causing an amino-acid change, splicing defect, or frameshift, have also been identified.[79–81] The polymorphisms in *CYP3A5* may result in the altered hepatic clearance of several drugs.

With regard to anticancer drugs, CYP3A4 is involved in the metabolism of etoposide and teniposide,[82] vinblastine,[83,84] vincristine,[83] vindesine,[85] doxorubicin,[86] ifosfamide,[26,87] and docetaxel.[88] The reduced docetaxel clearance was correlated with low CYP3A4 activity, measured by erythromycin breath test.[89] Patients with the worst toxicities were the patients with the lowest erythromycin breast test results and docetaxel clearance.[89] The significance of the *CYP3A5* polymorphism in docetaxel clearance has not been defined.[90] Concerning the disposition of etoposide, Kishi et al.[91] have reported that the *CYP3A5*3* polymorphism is associated with lower etoposide clearance than the wild type in African-Americans. However, the impact of *CYP3A* polymorphisms on the pharmacokinetics of anticancer drugs has not been fully evaluated. Because the effects of genetic polymorphisms of *CYP3A* on the pharmacokinetics of drugs are complex, further studies are needed to characterize them clinically.

Conclusion

A major problem in cancer chemotherapy is the prediction of tumor responses and toxicity.[92] The unpredictable disposition of drugs may result in undertreatment, leading to insufficient therapeutic effects, or overtreatment, leading to toxicity. Genetic variability in drug-metabolizing enzymes may be a determinant of the variations in these outcomes. Many of the polymorphisms have been demonstrated to show functional significance, but, in some cases, the significance is still not completely clear. Concerning drug-metabolizing enzymes other than CYP, such as thiopurine methyltransferase (TPMT), dihydropyrimidine dehydrogenase (DPYD), thymidylate synthase (TYMS), and UDP-glucuronosyltransferase (UGT), there are emerging data showing associations between polymorphisms and the pharmacokinetics/pharmacodynamics of anticancer drugs.[93,94] In contrast, pharmacogenetic studies of CYP enzymes for anticancer drugs, especially in vivo studies, have been limited. Pharmacogenetic screening prior to cancer therapy will contribute to the precise prescription of treatment. To utilize genetic information for the individualization of treatment for cancer, more retrospective in vivo studies need to be performed.

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