Association of CYP2C8, CYP3A4, CYP3A5, and ABCB1 Polymorphisms with the Pharmacokinetics of Paclitaxel

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Abstract

Purpose: To retrospectively evaluate the effects of six known allelic variants in the CYP2C8, CYP3A4, CYP3A5, and ABCB1 genes on the pharmacokinetics of the anticancer agent paclitaxel (Taxol).

Experimental Design: A cohort of 97 Caucasian patients with cancer (median age, 57 years) received paclitaxel as an i.v. infusion (dose range, 80-225 mg/m²). Genomic DNA was analyzed using PCR RFLP or using Pyrosequencing. Pharmacokinetic variables for unbound paclitaxel were estimated using nonlinear mixed effect modeling. The effects of genotypes on typical value of clearance were evaluated with the likelihood ratio test within NONMEM. In addition, relations between genotype and individual pharmacokinetic variable estimates were evaluated with one-way ANOVA.

Results: The allele frequencies for the CYP2C8*2, CYP2C8*3, CYP2C8*4, CYP3A4*3, CYP3A5*3C, and ABCB1 3435C>T variants were 0.7%, 9.2%, 2.1%, 0.5%, 93.2%, and 47.1%, respectively, and all were in Hardy-Weinberg equilibrium. The population typical value of clearance of unbound paclitaxel was 301 L/h (individual clearance range, 83.7-1055 L/h). The CYP2C8 or CYP3A4*5 genotypes were not statistically significantly associated with unbound clearance of paclitaxel. Likewise, no statistically significant association was observed between the ABCB1 3435C>T variant and any of the studied pharmacokinetic variables.

Conclusions: This study indicates that the presently evaluated variant alleles in the CYP2C8, CYP3A4, CYP3A5, and ABCB1 genes do not explain the substantial interindividual variability in paclitaxel pharmacokinetics.

Interindividual variability in drug efficacy and toxicity, resulting in unpredictable patient responses, is commonly observed in all therapeutic areas (1, 2). However, these differences are particularly important in the field of cancer therapy because many anticancer agents have a narrow therapeutic index. It is now well recognized that in addition to environmental and physiologic factors, such interpatient variation is commonly associated with polymorphisms in genes encoding drug-metabolizing enzymes, drug transporters, and/or drug targets. To date, most studies have focused on the analysis of single-phased single nucleotide polymorphisms (SNP) in specific genes. However, there is currently much effort directed towards an understanding of genetic variation within the entire biological and pharmacologic pathways (3).

Among anticancer drugs, paclitaxel is of particular interest because of its broad spectrum of activity against malignant solid tumors, including breast, lung, and ovarian cancer (4). In the conventional thrice-weekly treatment regimen, dose-limiting side effects include hematologic toxicity (mainly neutropenia), whereas peripheral neuropathy becomes dose limiting in the more dose-dense, weekly regimens (5). Although paclitaxel-induced toxicity is dose dependent, the individual susceptibility to side effects varies considerably. As for most other anticancer agents, the administered dose of paclitaxel is normalized by a patient’s body surface area. However, the routine use of body surface area as the only independent variable considered in drug dosing is questionable, and overall, pharmacokinetic/pharmacodynamic variability for paclitaxel remains large (6). Previous studies have revealed relations between paclitaxel pharmacokinetic variables and the likelihood of toxicity and tumor response in non–small cell lung cancer with standard doses of paclitaxel...
Hence, identification of factors that are associated with the clearance of paclitaxel could aid in predicting or adapting appropriate, individualized doses of paclitaxel.

The primary routes of paclitaxel elimination consist of successive hydroxylation reactions mediated by the cytochrome P450 CYP2C8, CYP3A4, and CYP3A5 isozymes (9, 10). Another pathway of elimination is through hepatobiliary and intestinal secretion of the parent drug by the ABCB1 gene product P-glycoprotein (11). It has been suggested that variability in expression and/or function of these proteins accounts for the substantial interindividual differences in drug clearance and thereby contributes to the variability in severity of drug-induced neutropenia as well as efficacy and survival (12). However, nothing is currently known in the Caucasian population about the role of genetic variation in the pharmacokinetics of paclitaxel. In the present study, we retrospectively evaluated whether known variant CYP2C8, CYP3A4, CYP3A5, and ABCB1 alleles are associated with the pharmacokinetic profile of paclitaxel in adult Caucasian cancer patients.

### Materials and Methods

**Patient selection.** Eligibility criteria have been defined by the individual study protocols, as reported previously (6, 7, 13–16). Briefly, eligible patients had at least a pathologically confirmed diagnosis of cancer for which paclitaxel was a therapeutic option. Additional common eligibility criteria included (a) a life expectancy of ≥12 weeks; (b) a WHO performance status of ≤2; (c) no chemotherapy, hormonal therapy, radiotherapy, within 4 weeks before treatment; (d) age above 18 years; (e) adequate bone marrow function (absolute neutrophil count, >1.5 × 10^9/L; platelet count, >75 × 10^9/L), renal function (serum creatinine, ≤1.5 × the upper limit of normal), and hepatic function (serum bilirubin, ≤1.5 × the upper limit of normal; alanine aminotransferase and aspartate aminotransferase, ≤2.5 × the upper limit of normal; and alkaline phosphatase, ≤5 × the upper limit of normal in the presence of only bone metastases and in the absence of any liver disorders). Simultaneous use of any medication, dietary supplements, or other compounds known to inhibit affect the pharmacokinetics of paclitaxel was not allowed. The study protocols were approved by the local ethical review boards, and all patients provided written informed consent before study entry.

**Drug administration.** Paclitaxel (Bristol Myers Squibb, Wallingford, CT) was supplied as a concentrated sterile solution in a mixture of Cremophor EL and ethanol (1:1; v/v) at 6 mg/mL (Taxol). In 82 patients, the drug was administered as a single agent, whereas another 15 patients received paclitaxel immediately followed by a 1-hour infusion of carboplatin. Prior work has shown that carboplatin does not affect the pharmacokinetic profile of unbound paclitaxel (16). Paclitaxel was given i.v. over 1 hour (n = 42), 3 hours (n = 49), or 24 hours (n = 6) at doses of 50 mg/m² (n = 1), 60 mg/m² (n = 2), 70 mg/m² (n = 1), 80 mg/m² (n = 12), 100 mg/m² (n = 42), 130 mg/m² (n = 1), 135 mg/m² (n = 5), 150 mg/m² (n = 3), 175 mg/m² (n = 27), or 225 mg/m² (n = 3). Provided toxic effects were not prohibitive, patients were eligible to continue treatment until there was evidence of progressive disease.

**Pharmacokinetic analysis.** During the first course of treatment, blood samples were collected in glass or polystyrene tubes containing lithium heparin as anticoagulant and immediately centrifuged (at least 2,000 × g at 4°C for 10 minutes) to separate plasma, which was stored at −20°C or below until analysis. These blood samples were obtained at the following time points: immediately before infusion and 0.5, 1, 1.5, 2, 2.5, 3, 5, 7, 10, 13, 15, 25, 33, and 49 hours after the start of paclitaxel infusion (1-hour schedule); 1, 2, 3, 3.08, 3.25, 3.5, 4, 4.5, 5, 7, 9, 15, 21, 27, 35, and 51 hours after infusion (3-hour schedule); or at 1, 22, 23, 23.92, 24.08, 24.15, 25, 26, 27, 30, 36, and 45 hours after infusion (24-hour schedule). Determination of total paclitaxel concentrations in plasma was done by high-performance liquid chromatography with UV detection at 227 nm according to a validated published procedure (17). The lower limit of quantification using 1,000-μL plasma samples was 10 ng/mL, corresponding to 0.0117 μmol/L (accuracy, 99.7%). For interassay precision, quality control samples containing 40, 200, or 400 ng/mL (corresponding to 0.05, 0.23, or 0.47 μmol/L) of paclitaxel were used, resulting in coefficients of variation of 7.3%, 6.3%, and 2.2% and accuracies of 99.1%, 98.5%, and 100.5%, respectively. Determination of the fraction of unbound paclitaxel was done using equilibrium dialysis with a tritiated paclitaxel tracer (Moravek Biochemicals, Brea, CA; ref. 18).

In view of the profound nonlinear disposition of total paclitaxel in humans (19), the pharmacologic consequences of the multiple variant genotypes cannot be predicted based on total plasma levels alone when different dose groups are taken into consideration. Because the area under the plasma concentration-time curve of unbound paclitaxel is a linear function of the dose administered (see below; ref. 14), we focused here on unbound paclitaxel between the genotype groups. Pharmacokinetic variables for unbound paclitaxel were estimated in a nonlinear mixed effects analysis using a linear three-compartment model (14). Empirical Bayesian estimates were obtained and are hereafter referred to as individual estimates. Relations between clearance and the demographic factors described in Table 1, including age, sex, body surface area, liver enzymes, bilirubin, and hematocrit, were also tested for statistical significance within NONMEM. In addition, dose, rate of infusion, and infusion duration were tested for statistical significance. All analyses were done with the first-order conditional estimation method with interaction in the NONMEM.

### Table 1. Baseline patient characteristics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline screening</td>
<td>Total studied 97</td>
</tr>
<tr>
<td>Age (y)</td>
<td>57 (24–81)</td>
</tr>
<tr>
<td>Sex (male/female)</td>
<td>40 (41)/57 (59)</td>
</tr>
<tr>
<td>Body surface area (m²)</td>
<td>1.78 (1.30–2.37)</td>
</tr>
<tr>
<td>Primary tumor site</td>
<td>Bladder 5 (5)</td>
</tr>
<tr>
<td>Breast</td>
<td>39 (40)</td>
</tr>
<tr>
<td>Esophagus</td>
<td>17 (17)</td>
</tr>
<tr>
<td>Lung</td>
<td>10 (10)</td>
</tr>
<tr>
<td>Ovary</td>
<td>18 (18)</td>
</tr>
<tr>
<td>Miscellaneous</td>
<td>8*</td>
</tr>
<tr>
<td>Pretherapy chemistry and hematology</td>
<td>Alkaline aminotransferase (units/L) 20 (2.0–264)</td>
</tr>
<tr>
<td>Aspartate aminotransferase (units/L)</td>
<td>121 (38–1030)</td>
</tr>
<tr>
<td>γ-Glutamyltransferase (units/L)</td>
<td>21 (6.0–187)</td>
</tr>
<tr>
<td>Serum creatinine (μmol/L)</td>
<td>35 (9.0–1567)</td>
</tr>
<tr>
<td>Total bilirubin (μmol/L)</td>
<td>32 (0.3–24)</td>
</tr>
<tr>
<td>Hematocrit (L/L)</td>
<td>0.37 (0.20–0.45)</td>
</tr>
<tr>
<td>WBC (× 10³ per L)</td>
<td>7.2 (2.9–32)</td>
</tr>
<tr>
<td>Absolute neutrophil count (× 10⁹/L)</td>
<td>4.7 (0.90–14)</td>
</tr>
</tbody>
</table>

*Primary sites include adenocarcinoma of unknown primary site (3), head and neck (1), kidney (1), tongue (2), penis (1).
program, version V/VI beta (20), and graphical diagnostics was obtained using the Xpose program (21).

**Pharmacogenetic analysis.** Genomic DNA was extracted from 1 mL of whole blood (n = 5) or plasma (n = 29) using the Gentra PureGene Blood Kit (Gentra, Minneapolis, MN) and the QIaAmp DNA Blood midi kit (Qiagen, Inc., Valencia, CA), respectively, following the manufacturer's instructions, and was reconstituted in a buffer containing 10 mmol/L Tris (pH 7.6) and 1 mmol/L EDTA. SNPs in CYP2C8 were identified from the literature (22, 23). Variations in the genes of interest [CYP2C8*2 (809T>C, 1296F), CYP2C8*3 (416G>A, R139K), CYP2C8*4 (792C>G, 1264M), CYP3A4*3 (1334T>C, M445T), CYP3A5*3C (6986A>G, splice variant), and ABCB1 3435C>T (111451)] were analyzed using Pyrosequencing. Analysis of the CYP3A4, CYP3A5, and ABCB1 genes was done as previously described (24). PCR primers were designed using Primer Express version 1.5 (ABI, Foster City, CA) for CYP2C8*2 (forward, 5'-biontin-CCATGATTGTTAGTG-CAGGCCC-3'; reverse, 5'-CTCTACTCATGATTGTTTAGGCCAGG-3'). CYP2C8*3 (forward, 5'-biontin-ACGGCACTGAGTCACCCACC-3'; reverse, 5'-ATTCTCAGCATTGCTGGCC-3'), and CYP2C8*4 (forward, 5'-TGTCAGGATTACCGGCCGTG-3'; reverse, 5'-biontin-CTCTACTCATGATTGTTTAGGCCC-3'). The Pyrosequencing primers were designed using the Pyrosequencing SNP Primer Design Version 1.01 software (http://www.pyrosequencing.com). CYP2C8 Pyrosequencing primer sequences were as follows: CYP2C8*2 reverse, 5'-TTATC-GATGTTACCGGCCGT-3'; CYP2C8*3 reverse, 5'-TGGAATGGGGGAGA-3'; and CYP2C8*4 forward, 5'-TGTCAGGATTACCGGCAATC-3'. PCR was carried out using AmpliTaq Gold PCR master mix (ABI), 5 pmol of each primer, and 5 to 10 ng of DNA isolated from whole blood or DNA from 1 μL of undiluted plasma. Pyrosequencing was carried out using the Pyrosequencing haplotype and hardwired software (Biotage, Uppsala, Sweden). The genotype was called variant if it differed using the Pyrosequencing hsAPSQ96 instrument and software (Biotage, Foster City, CA) for SNPs of whole blood (n = 5) or plasma (n = 29). Hardy-Weinberg equilibrium was carried out using Clump version 3.0 (http://www.broad.mit.edu/mpg/clump). Genotype-frequency analysis of Hardy-Weinberg equilibrium was carried out using the Xpose program (21).

**Statistical evaluation.** The association of the various genotypes with clearance was evaluated within NONMEM. For individuals with missing genotype information, a mixture model was fit using both genotype and phenotype information. The covariate effect was considered as an effect of presence of functional allele and the association was estimated as clearance = TVCLwt × (1 + Bvar), where TVCLwt is the typical value of clearance in the wild-type group and B is the estimated covariate effect. For CYP3A4*3C, the homozygous variants were most common and was therefore chosen as typical. The covariate effect was considered as an effect of presence of functional allele and the association was estimated as clearance = TVCLvar × (1 + Bvar) and clearance = TVCLwt × (1 + Bvar), respectively. For individuals with missing genotype information, a mixture model for the covariate effects was used. In a mixture model, the likelihood contribution from an individual is the sum of the likelihoods under each model times the probability (size) of the subpopulation. The observed genotype frequencies were used as estimates for the probabilities, and the magnitude of the covariate effects were assumed to be the same as for the subjects where genotype information existed.

The likelihood ratio test was used to evaluate statistical significance of the covariate effects. The objective function value (OFV) obtained in NONMEM is proportional to $-2 \times \log$-likelihood, and the difference in OFV ($\Delta$OFV) between two nested models is approximately $\chi^2$ distributed. Accordingly, a $\Delta$OFV of $\geq 3.84, \geq 6.63,$ and $\geq 10.83,$ between two nested models differing in one variable, corresponds to $P < 0.05,$ $P < 0.01,$ and $P < 0.001,$ respectively. The 95% confidence intervals (95% CI) for the covariate effects were assessed by log-likelihood profiling, which is one alternative method to estimate confidence limits that does not assume symmetry around the estimate, as opposed to calculating confidence limits from the SE obtained in NONMEM (26, 27). In addition, an assessment of the association of the multiple variant genotypes with individual pharmacokinetic variable estimates was done. To relate the pharmacokinetic variable means with the different genotypes, a one-way ANOVA was done using logarithmically transformed individual pharmacokinetic variable estimates. Accordingly, the difference in the mean values between wild type and presence of a variant allele corresponds to the ratio between the groups on the original scale. The 95% CI for the difference was calculated from the SE of the differences (common variance), which represents the 95% CI of the ratio on the original scale. Statistical evaluations of individual variable estimates (individuals with missing genotype values were not included) were done using S-PLUS 6.1 for Windows Professional Edition (Insightful Corp., Seattle, WA).

**Results**

**Patients and treatment.** Complete pharmacokinetic data were available for a total of 97 adult Caucasian patients with cancer (40 males and 57 females) with a median age of 57 years (range, 24-81 years; Table 1). The most frequent primary tumor types were breast cancer (n = 39), ovarian cancer (n = 18), and esophageal cancer (n = 17).

**Paclitaxel pharmacokinetics.** Plasma concentration-time profiles of unbound paclitaxel were adequately described by a linear three-compartment model based on a previously published population pharmacokinetic model (14), as indicated by goodness-of-fit plots (Fig. 1). These plots indicate that there is no bias in the model predictions at any level of the predicted concentration. The left-hand graph further indicates that no multimodality or pronounced skewness in interindividual variability is present.

In this study, we reestimated the population variables and modified the stochastic model. The population variables are presented in Table 2. The typical value of clearance (301 L/h) was consistent with earlier data (14, 28). Paclitaxel disposition was highly variable in the studied cohort, with an estimated coefficient of variation of 44% and individual clearance values ranging from 83.7 to 1,055 L/h. Body surface area and bilirubin were found to be significant covariates for unbound paclitaxel pharmacokinetics ($P < 0.01$), with positive and negative relations to clearance, respectively. However, when infusion duration was included (categorized as short or long infusion duration), only bilirubin was statistically significant. Clearance decreased with increasing bilirubin (2% per mmol/L bilirubin), and typical values ranged from 205 to 348 L/h. The typical value of clearance for the 24-hour infusions was 46.1% lower than for the other schedules. However, inclusion of these covariates did not reduce unexplained interindividual variability in paclitaxel clearance and was therefore not included in the final model. In a separate analysis (data not shown), it was found that these covariate relations did not affect the results or conclusions of the study when included together with the genotypes. The administered dose and rate of infusion were not statistically significant covariates for clearance ($P = 0.77$ and $P = 0.14,$ respectively) when tested within NONMEM.

**Genotyping.** Six SNPs were analyzed in four genes of putative relevance for paclitaxel disposition (Table 3). For two SNPs in the CYP2C8 gene (i.e., CYP2C8*2 and CYP2C8*4), no homozygous variants were observed, as expected based on previously published data obtained from Caucasian individuals (23). In the other main CYP2C8 variant studied, CYP2C8*3 (represented by the R139K polymorphism), the frequency of the rarest allele (q) was 9.2% (Table 3). All genotype frequencies were found to be in Hardy-Weinberg equilibrium. The allele frequencies for CYP3A4*3, CYP3A5*3C, and ABCB1

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3435C>T of 0.5%, 93.2%, and 47.1%, respectively, were very similar to those reported in previous studies involving Caucasians individuals (29–31).

**Genotype-phenotype relations.** Because the mechanistic basis for associations of the studied genetic variants would (primarily) be with clearance, we focused on presenting these results. No statistically significant relations were found in the likelihood ratio test within NONMEM (ΔOFV was between 0.028 and 1.508). The estimated covariate effects with 95% CIs are presented in Table 4. The covariate effects were generally low, and the 95%CI excluded relative differences of a factor two or more for all but two genotypes. The two variants with a possibly larger difference were based on only single subjects. For example, the group heterozygous for CYP2C8*3 had lower typical value of clearance compared with wild type (mean percent difference from wild type, /C0 3.2%; 95% CI, 21.5 to 19.5%), and the homozygous for the variant allele had higher typical value of clearance (mean, 3.19%; 95% CI, 28.6% to 49.9%).

Individual clearance values as a function of the variant genotypes are shown in Fig. 2. Beside the genotypes included in Fig. 2, the single individual heterozygous for CYP3A4*3 had a clearance of 301 L/h compared with a mean value in patients with the wild-type sequence of 333 L/h (n = 93), and the single individual heterozygous for CYP2C8*2 had a clearance of 323 L/h compared with a mean value in patients with the wild-type sequence of 347 L/h (n = 69). All the 95% CIs of the ratio for each genotype included 1, indicating no statistically significant difference between the groups (Fig. 3). In addition, for the genotypes where data from patients with a homozygous variant genotype were available, the three groups were tested using one-way ANOVA, but no significant relations were found (P > 0.69). Differences in other pharmacokinetic variables were also not statistically significantly different between the different genotype groups (data not shown).

**Discussion**

In this study, we tested the hypothesis that the disposition of paclitaxel is dependent on genetic variability in the CYP2C8, CYP3A4, CYP3A5, and ABCB1 genes. The CYP2C subfamily is responsible for the metabolism of ~20% of clinically used drugs, including the 6α-hydroxylation of paclitaxel by the CYP2C8 isoform (10, 32). This subfamily consists of four members, including CYP2C8, CYP2C9, CYP2C18, and CYP2C19, and the corresponding genes are clustered on chromosome 10q24. Whereas polymorphisms in the CYP2C9 and CYP2C19 genes have been shown to result in altered

| Table 2. Population variable estimates for unbound paclitaxel |
|-----------------|---------|--------|
| Variable        | Estimate| RSE (%)|
| CL (L/h)        | 301     | 4.3    |
| V1 (L)          | 225     | 6.0    |
| V2 (L)          | 3450    | 7.8    |
| V3 (L)          | 303     | 6.6    |
| O2 (L/h)        | 132     | 6.6    |
| O3 (L/h)        | 151     | 6.5    |
| Residual error (%) | 21.1 | 4.9    |
| IVCL (CV %)     | 44      | 18*    |
| IVQ1 (CV %)     | 50      | 27*    |
| IVQ2 (CV %)     | 38      | 37*    |
| IVQ3 (CV %)     | 65      | 19*    |
| IVQ4 (CV %)     | 37      | 33*    |
| CorIVV1-CL      | 0.41    | 33*    |
| CorIVV1-CLQ2    | 0.71    | 20*    |
| CorIVV1-CLQ3    | 0.55    | 33*    |
| CorIVV1-CLQ4    | 0.44    | 37*    |
| CorIVVQ2-CLQ3   | 0.38    | 50*    |
| CorIVVQ2-CLQ4   | 0.89    | 22*    |

Abbreviations: RSE, relative standard error (%); CL, clearance; V, volume of distribution; Q, intercompartmental clearance; IV, interindividual variability; CV, coefficient of variation; Corr, correlation between individual estimates.

*RSE is related to the corresponding variance or covariance term.
toxicity of certain anticancer drugs in carriers of a variant allele (33), much less is known about the functional role of variants to the pharmacokinetics of certain anticancer drugs in carriers of a variant allele. The CYP2C8*2 and CYP2C8*4 alleles have been found predominantly in African Americans but not in the Japanese and Caucasians (23), which is consistent with the currently observed frequencies of 0.7% and 2.1% for CYP2C8*2 and CYP2C8*4, respectively. In contrast, the CYP2C8*3 variant (containing 416G>A; R139K) has an allele frequency of up to 14% in Caucasians (34, 35) but is very rare in African Americans and Asians (36). In vitro studies have shown substantially decreased activity of the recombinant CYP2C8.2 and CYP2C8.3 enzymes in the metabolism of paclitaxel (22, 23, 37, 38). Recent clinical investigations also suggest that the CYP2C8*3 variant allele is associated with altered pharmacokinetics of the CYP2C8 substrate drugs repaglinide (39) and ibuprofen (40). In the present analysis, however, CYP2C8*3 was not significantly associated with the pharmacokinetics of paclitaxel. This discrepancy with earlier findings for repaglinide (39) and ibuprofen (40) is possibly related to the fact that, in contrast to paclitaxel, repaglinide is not a substrate for CYP3A4 (39); that ibuprofen is also a substrate for CYP2C9 (40); and that the CYP2C9*2 allele is in linkage disequilibrium with CYP2C8*3 (35). Because the expression and activity of CYP2C8 in the human intestine and liver is relatively low (41), it is possible that individuals carrying the CYP2C8*3 allele still can efficiently eliminate paclitaxel through other compensatory mechanisms, including elimination via CYP3A4 or through hepatobiliary excretion, and that the associations of different genotypes with clearance might not become evident until substrates are coadministered with inhibitors of these pathways. Although direct evidence for this hypothesis is lacking, this possibility is supported by a previous observation that 6-β-hydroxypaclitaxel, formed via CYP2C8, is not the predominant paclitaxel metabolite in all individuals (42). Besides the fact that paclitaxel undergoes several routes of elimination that possibly could compensate for any deficiencies, the reason for not seeing associations of these different genotypes with clearance could also be due to the fact that the frequency of the homozygous variant CYP2C8 genotypes in the currently studied population is low (i.e., <3.26%). As the heterozygous genotypes have one fully functional allele, it is possible that the regulation of that allele is altered to compensate for the deficient allele.

In adults, CYP3A4 and CYP3A5 are the most important among the four CYP3A subfamily members for CYP3A-mediated drug metabolism (i.e., CYP3A4, CYP3A5, CYP3A7, and CYP3A43; ref. 43). Because of the genetic diversity in the genes encoding these proteins (44), it has been proposed that...
genotyping for CYP3A4 and CYP3A5 variants may be useful for prediction of total CYP3A activity. Over 30 SNPs in CYP3A4 have been published; however, most are unlikely to affect CYP3A4 activity in vivo (44–46). Due to the very low allele frequency of the CYP3A4*3 variant evaluated in the present study (0.5%), this polymorphism most likely has no relevance to CYP3A4 activity and function in the Caucasian population.

In contrast to CYP3A4, the CYP3A5 protein isoform is known to be expressed in only a small percentage of Caucasian individuals, and this has been linked to a common transition in intron 3 of the CYP3A5 gene (CYP3A5*3C), which introduces a frameshift during translation and results in a truncated, nonfunctional protein (47, 48). Approximately 85% to 95% of Caucasian subjects are homozygous variant for CYP3A5*3C and thus are deficient in functionally active CYP3A5 (49), which is consistent with the currently observed genotype frequency of 87.4%. In the present study, no association was noted between the CYP3A5*3C variant and paclitaxel pharmacokinetics. This is similar to findings obtained in healthy subjects and cancer patients using the CYP3A phenotyping probes midazolam (50–53), erythromycin (51, 54), and nifedipine (55), although one recent study involving a predominantly Caucasian population of cancer patients observed a 1.4-fold higher midazolam clearance in four patients with the CYP3A5*1/*3C genotype compared with 39 patients with the CYP3A5*3C/*3C genotype (56).

The extent to which the CYP2C8 and CYP3A isoforms metabolize paclitaxel is likely to be determined, at least in part, by intracellular drug concentrations in the liver and, to a lesser extent, the intestine. This process, in turn, is partially dependent on the efflux transporter P-glycoprotein, which is localized in the apical membrane of hepatocytes and enterocytes. It has been suggested that drug accumulation in these cells inversely reflects the activity of P-glycoprotein (57). In recent years, various genetic variants in the gene encoding P-glycoprotein (i.e., ABCB1) have been described that may affect transporter expression or function (58). The most extensively studied ABCB1 variant to date is a common synonymous mutation at the transition C to T at nucleotide position 3435 at a wobble position in exon 26 (59). Although this transition does not change its encoded amino acid, recent findings suggest that this variant is associated with altered protein expression in different human tissues (60), and this may result in decreased hepatobiliary and/or intestinal secretion of substrate drugs like paclitaxel.
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The lack of statistically significant relations in this study does not necessarily mean that there are none, especially in light of the few individuals studied with a homozygous variant genotype. However, the 95% CIs of the genotype effects are sufficiently narrow and/or genotype heterogeneity sufficiently small to conclude that the studied variants in the CYP2C8, CYP3A4, CYP3A5, and ABCB1 genes do not cause a substantial interindividual difference in paclitaxel clearance. Moreover, additional genetic variants or haplotypes of importance to paclitaxel pharmacokinetics may yet be discovered. Further investigation is needed to determine the relative role of genetic variation and environmental variables (e.g., concommitant drugs or herbs) on the pharmacokinetics of paclitaxel.

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