Utilization of Human Liver Microsomes to Explain Individual Differences in Paclitaxel Metabolism by CYP2C8 and CYP3A4

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Abstract. Paclitaxel is widely used for treatment of malignant tumors. Paclitaxel is metabolized by CYP2C8 and CYP3A4, and these enzymes are known to differ between individuals, although the details have not been clarified. Recent progress in pharmacogenetics has shown that genetic polymorphisms of metabolic enzymes are related to these individual differences. We investigated the effect of the polymorphisms on paclitaxel metabolism by analyzing metabolic activities of CYP2C8 and CYP3A4 and expressions of mRNA and protein. Production of 6α-hydroxypaclitaxel, a metabolite of CYP2C8, was 2.3-fold larger than 3'-p-hydroxypaclitaxel, a metabolite of CYP3A4. Significant inter-individual differences between these two enzyme activities were shown. The expressions of mRNA and protein levels correlated well with the enzyme activities, especially with CYP3A4. Although it was previously reported that CYP2C8*3 showed lower activity than the wild type, two subjects that had the CYP2C8*3 allele did not show lower activities in our study. Inter-individual differences in paclitaxel metabolism may be related to CYP2C8 and CYP3A4 mRNA expression. CYP2C8 is the primary metabolic pathway of paclitaxel, but there is a “shifting phenomenon” in the metabolic pathway of paclitaxel in the liver of some human subjects.

Keywords: liver, paclitaxel, CYP, polymorphism, individual difference

Introduction

Paclitaxel, an extract from the bark of the Pacific yew, Taxus brevifolia, was discovered to have an anti-cancer effect and is now frequently used for treatment of malignant tumors such as breast cancer, lung cancer, ovarian cancer, and gastric cancer. Like many drugs, paclitaxel is metabolized mainly in the liver by cytochrome P450 enzymes. Paclitaxel is known to be metabolized mainly by two subtypes of P450, CYP2C8 and CYP3A4, but the details are still unclear. According to recent research in pharmacogenetics, genetic polymorphisms of several metabolic enzymes such as CYP enzyme subtypes can explain inter-individual differences. Details of the relationship between paclitaxel metabolism and genetic polymorphisms of cytochrome P450 were previously reported by Dai et al. (1). They reported that the metabolic activities of CYP2C8*2 and CYP2C8*3 were lower than those of CYP2C8*1 (wild type). In the human liver, CYP3A enzymes are predominantly expressed, and the expression of CYP2C8 is smaller than that of CYP3A. However, there is no report that elucidates the relationships among these CYP subtypes and their polymorphisms, CYP2C8 and CYP3A4 mRNA expression, protein expression, and the activities of these enzymes in metabolizing paclitaxel. To evaluate these relationships, we investigated the metabolic activities of CYP2C8 and CYP3A4, the effect of the polymorphisms, and the expressions of mRNA and protein of these enzymes on paclitaxel metabolism.

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Materials and Methods

Livers and microsomes
Liver tissues samples and their microsomes were obtained from 20 unmatched organs of transplantation donors of Caucasian and Hispanic subjects and utilized in our study. Those were supplied from The National Disease Research Interchange (Philadelphia, PA, USA) through The Biochemical Research Institute, HAB Research Organization (Chiba). This study was approved by the ethics committee of St. Marianna University School of Medicine (Kanagawa).

Paclitaxel-6α-dehydrogenase and paclitaxel-3′-p-dehydrogenase activities
Paclitaxel-6α-dehydrogenase (as CYP2C8) and paclitaxel-3′-p-dehydrogenase (as CYP3A4) activities in human liver microsomes were determined by high performance liquid chromatography (HPLC). The standard incubation mixture (1 ml total volume) contained paclitaxel (Sigma Chemical Co., St. Louis, MO, USA) (8 μM as a substrate, and 2, 4, 6, 8, 10, 12, 16, and 32 μM for evaluation of kinetic parameters), the microsomal protein fraction of human livers (1 mg protein/ml), an NADPH-generating system, which contained 1 mM NADP+ (Oriental Yeast Co., Tokyo), 10 mM glucose 6-phosphate (Oriental Yeast Co.), 10 mM MgCl2, and 2 U/ml glucose-6-phosphate dehydrogenase (Oriental Yeast Co.). The reaction was initiated by adding of the NADPH-generating system and was incubated for 120 min. The reaction was terminated by adding 5 ml ethyl acetate (Wako Pure Chemical Industries, Osaka), and then 4-pregnen-20α-ol-3-one (75 ng) was added as an internal standard.

HPLC analysis was performed using a PU-980 Intelligent HPLC pump (JASCO, Tokyo), AS-950 Intelligent Sampler (JASCO), LG-980-02 Ternary Gradient Unit (JASCO), HV-992-01 Column Selection Unit (JASCO), and COSMOCIL 5C18-AR-2 column (4.6 × 150 mm; Nacalai Tesque, Kyoto). The extraction product was eluted isocratically with 20 mM ammonium acetate (pH 3.7)-acetonitrile-methanol (Sigma Aldrich Japan, Tokyo) (5:4:1, v/v/v) at a flow rate of 1 ml/min. The eluent was monitored by a UV-975 Intelligent UV/VIS Detector (JASCO). Under these conditions, the retention times of paclitaxel, 3′-p-hydroxypaclitaxel, 6α-hydroxypaclitaxel, and 4-pregnen-20α-ol-3-one were 6.4, 8.6, 13.0, and 14.8 min, respectively (Fig. 1). These conditions were determined by referring to previous reports (2 – 6) and used with slight modification.

Extraction and amplification of genomic DNA
Genomic DNA was isolated from the human liver tissues using the GenomicPrep™ Cells and Tissue DNA Isolation Kit (Amersham Biosciences Corp., Piscataway, NJ, USA). In brief, after the liver tissue was lysed with the cell lysis solution, the tissue lysate was added to RNase A solution to isolate RNA, and proteins were removed with the protein precipitation solution. DNA hydration solution was added to these purified samples.

This DNA was used to determine the allele frequencies of the single nucleotide polymorphisms (SNPs) using PCR-restriction fragment length polymorphism (RFLP) genotyping. PCR primers were designed as described below and purchased from Nissinbo Industries, Inc. (Tokyo). All PCR reactions involved amplification using 500 ng genomic DNA and TaKaRa Taq™ (Takara Shuzo Co., Ltd., Shiga) with a PTC-2000 Peltier Thermal Cycler (MJ Research, Waltham, MA, USA). Forty cycles of amplification were performed with 1-min denaturation at 94°C, followed by annealing for 2 min at 55°C and synthesis for 3 min at 72°C.
**RFLP analysis**

A PCR-based RFLP genotyping test for the CYP2C8 Ile269Phe polymorphism named CYP2C8*2 was developed using CYP2C8 specific primers. The resulting 312-bp products were digested overnight with BclI and resolved on 4% agarose gels by the method of Dai et al. (1). Although BclI cut the PCR products from the wild-type CYP2C8*1 allele into 214-bp and 98-bp fragments, PCR products from the homozygous CYP2C8*2 allele remained uncut. For the Arg139Lys mutation, two exon specific primers flanking the exon 3 mutations were used (1). The 347-bp PCR products of CYP2C8*1 were digested by BseRI into fragments of 310-bp and 37-bp, while the PCR products of the homozygous Arg139Lys allele remained uncut.

**Sequencing analysis**

The genomic DNA were amplified using specific primers for CYP2C8*3, CYP3A4*3, CYP3A4*4, CYP3A4*5, CYP3A4*8, CYP3A4*11, CYP3A4*12, CYP3A4*13, CYP3A4*16, CYP3A4*17, CYP3A4*18, and CYP3A4*19. Sequences of the primers are shown in Table 1.

Amplified genomic DNA was purified, removing the primers using MicroSpin S-400 HR Columns (Amersham Biosciences). PCR for sequencing analysis was performed with this purified DNA, and the PCR product was extracted by the ethanol precipitation method. The product was dissolved in Template Suppression Reagent (TSR), and the solution was sequenced using an ABI Prism 3100-Avant sequencing analyzer (Applied Biosystems Japan Ltd., Tokyo).

**RNA extraction and reverse-transcriptase (RT) reaction**

Total RNA was extracted from liver tissues with the RNAagent Total RNA Isolation System (Promega, Madison, WI, USA). Total RNA (2 μg) was reverse-transcribed with a RETROscript™ kit (Ambion Inc., Austin, TX, USA) in a final volume of 20 μl at 42°C for 1 h.

**Real-time PCR**

eDNA was synthesized by the RT reaction as described above, and quantitative analysis was performed with an 3502S Light Cycler (Roche Diagnostics, Basel, Switzerland) as described previously with slight modification (7). Briefly, RNA was purified from liver tissues and RT was carried out as described above. PCR was performed in a 20 μl total reaction volume containing 2 μl eDNA, primer-specific CYP2C8 or GAPDH, and SYBR Green PCR Master Mix, according to the manufacturer’s protocol using SYBR Green Kits (Applied Biosystems, Japan). PCR was performed in 20 μl of total reaction volume containing 2 μl of cDNA, specific primers for CYP2C8 or GAPDH, 4 mM MgCl2, and SYBR Green (Roche Diagnostics). The cycling protocol for CYP2C8 consisted of one cycle of 10 min at 95°C, followed by 40 cycles of denaturation for 15 s at 95°C, annealing for 10 s at 55°C, and extension for 10 s at 72°C. The primers for CYP2C8 were 5'-ACGTGATGTCCACTAC-3' (sense) and 5'-CTGCTGAGAAAGGCATGAAG-3' (antisense). The cycling protocol for GAPDH consisted of one cycle of 10 min at 95°C, followed by 40 cycles of denaturation for 15 s at 95°C, annealing for 10 s at 55°C, and extension for 10 s at 72°C. The primers for GAPDH were 5'-ACGTGATGTCCACTAC-3' (sense) and 5'-CTGCTGAGAAAGGCATGAAG-3' (antisense). The cycling protocol for GAPDH consisted of one cycle of 10 min at 95°C, followed by 40 cycles of denaturation for 15 s at 95°C, annealing for 10 s at 60°C (and 87°C for 1 s) and extension for 10 s at 65°C. The primers for GAPDH

<table>
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<th>Table 1. Specific primers for genotyping of CYP3A4 polymorphisms</th>
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were 5'-GACAACTTTGGTATCCGTGGA-3' (sense) and 5'-TACCAGGAATGAGCTTGAC-3' (antisense).

**Western blot analysis of CYP2C8 protein**

Western blot analysis was performed as previously reported (8) with slight modification. Hepatic microsomal protein concentrations were determined by the method of Lowry et al. (9). After boiling at 100°C for 2 min, samples containing 2 mg of protein were subjected to electrophoresis on 10% sodium dodecyl sulfate-polyacrylamide gel (SDS-PAGE) and then transferred to Hybond-ECL membranes (Amersham Life Sciences, Inc., Arlington Heights, VA, USA) for 50 min. The membranes were blocked with Tris-buffered saline containing 0.05% Tween 20 (TTBS) with 5% nonfat powdered milk overnight at 4°C. After washing three times for 10 min with TTBS, membranes were incubated for 90 min with primary antibodies for CYP2C8 in TTBS containing 5% nonfat powdered milk diluted 1:2500 at room temperature. Antibodies for CYP2C8 were purchased from Nosan Corporation (Kanagawa). Membranes were then incubated with secondary antibody against rabbit immunoglobulin G (IgG) at a 1:200 dilution for 1 h at room temperature after being washed as described above. The Western blot was developed with an ECL plus Western Blotting Detection System (Amersham Biosciences, Buckinghamshire, UK) using LAS-3000 (Fuji Photo Film, Tokyo). Autoradiograms were quantitated by a scanning method using computer densitometry software Science Lab 2001 (Fuji Photo Film).

**Statistics**

Data are shown with the mean ± S.E.M. Differences between the groups were analyzed by ANOVA, followed by Scheffe’s method. The correlation between CYP2C8 and CYP3A4 activities, protein, and mRNA were evaluated by regression analysis. A probability value of less than 0.05 was considered statistically significant.

**Results**

**Amounts of paclitaxel metabolites**

Paclitaxel was metabolized to 6α-hydroxypaclitaxel by CYP2C8 and to 3'-p-hydroxypaclitaxel by CYP3A4. We estimated the amounts of these metabolites and the unaltered substance, paclitaxel. The average amounts of 6α-hydroxypaclitaxel and 3'-p-hydroxypaclitaxel were 40.1 ± 10.0 ng·min⁻¹·mg protein⁻¹ and 16.7 ± 4.1 ng·min⁻¹·mg protein⁻¹, respectively (Fig. 2). Following incubation, the unchanged substrate concentration was 4.7 ± 0.3 μg/ml. The formation of 6α-hydroxypaclitaxel exhibited monophasic Michaelis-Menten kinetics. The V_max value was 32.0 μM and the K_m value was 12.1 μM. The formation of 3'-p-hydroxypaclitaxel also exhibited monophasic Michaelis-Menten kinetics. The V_max value was 16.0 μM and the K_m value was 3.3 μM.

**CYP2C8 mRNA expression and protein level**

We regarded the amounts of CYP2C8 metabolites reported above as evidence of enzyme activities. The CYP2C8 mRNA expression level estimated by RT-PCR and adjusted to GAPDH was 0.324 ± 0.088 and showed large differences among the samples. The Western blotting results of 47.03 ± 6.74 fmol/mg protein for the CYP2C8 protein level reflected these individual differences.

**CYP3A4 mRNA expression and protein level**

We also regarded the amounts of CYP3A4 metabolites as enzyme activities. We previously reported the CYP3A4 mRNA expression level adjusted to GAPDH and the CYP3A4 protein level (10). In this study, we confirmed that they were 0.324 ± 0.088 and 19.2 ± 5.4 pmol/mg protein, respectively.

**Three-way correlation between CYP2C8 activity, mRNA, and protein**

The three-way correlation between CYP2C8 activity and protein, CYP2C8 activity, and mRNA and CYP2C8 protein and mRNA is shown in Fig. 3. CYP2C8 activity was well correlated with the CYP2C8 protein level.
CYP and Paclitaxel  

CYP2C8 activity also tended to be related to CYP2C8 mRNA expression, but the correlation did not reach significance. The protein expression of the two samples was too high.

Three-way correlation between CYP3A4 activity, mRNA, and protein

Previously, we reported that CYP3A4 mRNA, the protein level, and testosterone 6β-hydroxylase activity, as a marker of CYP3A activity, were strongly correlated (10). We determined formation of the product 3′-p-hydroxypaclitaxel as the result of CYP3A4 activity in this study and examined the relationship between the product, protein, and mRNA. The three-way correlation between CYP3A4 activity, mRNA, and protein was shown to be strong (Fig. 3).

Ratio between 6α-hydroxypaclitaxel and 3′-p-hydroxypaclitaxel

The mean ratio of 6α-hydroxypaclitaxel to 3′-p-hydroxypaclitaxel in the 20 human livers was 72.7 to 27.3 (Fig. 4). Two subjects (#13 and #19 in Fig. 5) showed an amount of 3′-p-hydroxypaclitaxel that was larger than that of 6α-hydroxypaclitaxel. The ratio in these two subjects was 26.7 to 73.3, respectively.

In these two subjects, the concentrations of 6α-
hydroxypaclitaxel were 11.05 and 10.28 ng·min⁻¹·mg protein⁻¹, and the concentrations of 3'-p-hydroxy- paclitaxel were 42.89 and 21.06 ng·min⁻¹·mg protein⁻¹, respectively. When these two subjects were excluded, the ratio of 6α-hydroxy-paclitaxel to 3'-p-hydroxy-paclitaxel was 77.8 to 22.2.

**Genotyping**

The genotypes of CYP2C8 and CYP3A4 of the 20 liver samples were determined. Although there was no mutation in CYP3A4, CYP2C8 had several mutations in these subjects. The CYP2C8*2 allele was not found in this study, but the CYP2C8*3 allele, which requires two SNPs in a subject, was observed. Two subjects were heterozygous for G416A and A1196G SNPs. Additionally, two other subjects had only one SNP component of CYP2C8*3 (Table 2). The mean product of 6α-hydroxy-paclitaxel in 16 subjects, excluding the four heterozygous subjects, was 40.0 nmol·min⁻¹·mg protein⁻¹. The mean product of 6α-hydroxy-paclitaxel in the four heterozygous subjects was 40.6 nmol·min⁻¹·mg protein⁻¹. These data shows that these four mutations of CYP2C8 were not related to the 6α-hydroxy-paclitaxel production in this study.

**Discussion**

Paclitaxel is now widely used for cancer chemotherapy. In general, the dosage is determined by the patient’s body surface area, rather than by his or her metabolic activities. In this study, we observed significant individual differences in paclitaxel metabolism in human liver microsomes. If this result is applicable in vivo, large differences in blood concentrations of paclitaxel among patients will occur, depending on individual enzyme activities. When the plasma concentration of paclitaxel is high, its toxicity can be severe. On the other hand, the efficacy of paclitaxel will be insufficient when the concentration is low. On such occasions, it is likely that clinicians will abandon the administration of paclitaxel due to its ineffectiveness.

The total P450 concentrations of the microsomes used were within 0.10 to 0.77 nmol/mg protein (data derived from the HAB Research Organization home page: http://www.hab.or.jp). Therefore, the results of microsomes used here may be appropriate for in vitro experiments.

It was reported that paclitaxel is metabolized by CYP2C8 and CYP3A4 (11). CYP3A4 expression is more dominant than CYP2C8 expression in the human liver. Drug metabolism usually involves the affinity and the amount of the enzyme. In cases in which two enzymes are involved in the metabolism of a drug, the rate of metabolism of a drug depends on the relationship between the amount of each enzyme and its affinity for the drug. Whether CYP2C8 or CYP3A4 is the predominant enzymes in the metabolism of paclitaxel in human liver is unclear. In the present study, we demonstrated that, except for two cases, the primary enzyme involved in paclitaxel metabolism in human liver microsomes was CYP2C8. Although CYP3A4 is expressed dominantly in the human liver (30.2%) and CYP2C8 is expressed less frequently (5.2%), CYP2C8 was the primary metabolizer of paclitaxel in the human liver because the product of CYP2C8 enzyme was two times that of CYP3A4.

We estimated the kinetic parameters of the microsomes for the 6α-hydroxylation and 3'-p-hydroxylation of paclitaxel. In the present data, the V_max values and K_m values for paclitaxel 6α-hydroxylation and 3'-p-hydroxylation were different. Similar to our results, Cresteil et al. (11) also reported that the V_max values of synthesis of the two metabolites were quite different. The mean ratio of 6α-hydroxy-paclitaxel to 3'-p-hydroxy-paclitaxel in the liver was 72.3 to 27.3. These data suggest that enzymatic dominance of paclitaxel metabolism may relate to velocities of the synthesis of the 6α-hydroxy-paclitaxel and 3'-p-hydroxy-paclitaxel.

Ordinarily, there are several cases with no correlation among enzyme activity, protein expression, and mRNA level. On the other hand, we previously reported that there was a positive three-way correlation between

![Figure 5](http://example.com/figure5.png)

**Figure 5.** Ratio between 6α-hydroxy-paclitaxel and 3'-p-hydroxy-paclitaxel. Black column: 6α-hydroxy-paclitaxel; white column: 3'-p-hydroxy-paclitaxel. The horizontal line indicates the over-all mean ratio. The numbers showed subjects’ identification number. Detailed methods are presented in Materials and Methods.

**Table 2.** The number of CYP2C8*3 polymorphism

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<tr>
<th>Genotype</th>
<th>wt/wt</th>
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<th>*3/*3</th>
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<tr>
<td>Number of subjects</td>
<td>16</td>
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#, the number of subjects including *3 positive.
CYP3A4 mRNA, protein and enzyme activity in human liver (10). We observed a significant positive correlation between CYP2C8 protein and enzyme activity. Because only two samples had extremely high protein expressions compared to other samples, a significant correlation between CYP2C8 mRNA and protein was not observed, whereas there seemed to be weak relationship between the two. These results suggest the possibility that the activity of CYP2C8 and CYP3A4 might be related to the transcriptional mechanism of each. The transcriptional factors are related to the transcriptional mechanisms of genes. It was reported that the pregnane X receptor (PXR) and the constitutive androstane receptor (CAR) play important positive roles in the transcription of CYP2C8 and CYP3A4 (12). As reported above, we found the CYP2C8 and CYP3A4 enzyme activities correlated with protein expression and mRNA levels, respectively. Furthermore, the transcriptional mechanism may relate to individual differences in the metabolism of paclitaxel. At least, some transcriptional factors may relate to individual differences in paclitaxel metabolism. It is possible that transcriptional factors including PXR, CAR, and others may relate to individual differences in paclitaxel metabolism.

We found polymorphic subjects heterozygous for CYP2C8*3. However, no subjects with CYP3A4*3, CYP3A4*4, CYP3A4*5, CYP3A4*8, CYP3A4*11, CYP3A4*12, CYP3A4*13, CYP3A4*16, CYP3A4*17, CYP3A4*18, or CYP3A4*19 were found in the present study. A previous study of polymorphisms of CYP2C8 reported that the subjects with CYP2C8*2 and CYP2C8*3 were defective in metabolism of paclitaxel (1). In our study, gene polymorphisms of CYP3A4 were not observed, but those of CYP2C8*3 were found. We also found that there were individual differences in paclitaxel metabolism in human liver, and these were observed within the groups of CYP2C8*1 and CYP2C8*3. Furthermore, we did not confirm that 6α-hydroxy-paclitaxel, a CYP2C8 metabolite of paclitaxel, was significantly different in CYP2C8*1 and CYP2C8*3 subjects. Dai et al. (1) suggested the paclitaxel 6α-hydroxylation of CYP2C8*3 was decreased 10% compared with activity in the wild type. On the other hand, Soyama et al. (13) suggested that paclitaxel metabolism in subjects homozygous for CYP2C8*3 was decreased to 75% of the wild type. Consistent with the results of Soyama et al. (13), Bahadur et al. (14) also reported that paclitaxel 6α-hydroxylation by CYP2C8*3-positive livers significantly decreased, but the extent was small. In our study using a small number of liver microsomes heterozygous for CYP2C8*3, a difference in the activity of 6α-hydroxylase depending on CYP2C8*3 polymorphism was not observed. These data suggested that the polymorphisms of CYP2C8*2, CYP2C8*3, CYP3A4*3, CYP3A4*4, CYP3A4*5, CYP3A4*8, CYP3A4*11, CYP3A4*12, CYP3A4*13, CYP3A4*16, CYP3A4*17, CYP3A4*18, and CYP3A4*19 did not translate to individual differences in the paclitaxel metabolic pattern in the present study.

As shown in the present data, the primary metabolic pathway of paclitaxel in the majority of subjects was through CYP2C8, but two subjects showed a dominant pathway through CYP3A4. Sonnichsen et al. (15) reported that paclitaxel was dominantly metabolized by increased CYP3A4 that was induced by other drugs (such as barbiturates) and that it was higher compared to CYP2C8 activity in hepatocytes. In the present data for two subjects, the 6α-hydroxy-paclitaxel activity (as CYP2C8) was low (11.05 and 10.28 ng·min⁻¹·mg protein⁻¹; the mean value was 40.06 ng·min⁻¹·mg protein⁻¹), and that of 3’α-hydroxy-paclitaxel (as CYP3A4 activity) was higher (42.89 and 21.06 ng·mg protein⁻¹·min⁻¹; the mean value was 166.55 ng·mg protein⁻¹·min⁻¹) compared to the mean value. Therefore, the ratio of 3’α-hydroxy-paclitaxel to 6α-hydroxy-paclitaxel metabolites was 0.34, except for two subjects whose metabolic pathway of paclitaxel showed a reversed ratio of 3’α-hydroxy-paclitaxel to 6α-hydroxy-paclitaxel. In the case of drug metabolism via multiple pathways, when the primary pathway of enzyme activity is sufficiently decreased, the other pathway becomes dominant (15). At least, our data suggest a shift from primary metabolic pathway to another metabolic pathway in some subjects in which the primary pathway is decreased.

In conclusion, there are individual differences in the CYP2C8- and CYP3A4-mediated metabolism of paclitaxel. These individual differences in paclitaxel metabolism may be related to CYP2C8 protein expression and CYP3A4 mRNA expression and protein expression in the liver. CYP2C8 is the primary metabolic pathway of paclitaxel; however, there was a “shifting phenomenon” in the pathway of paclitaxel metabolism in two of our subjects.

References


