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ORIGINAL ARTICLE

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Induction of cytochrome P450 3A4 by docetaxel in peripheral mononuclear cells and its expression in lung cancer

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Abstract Several recent studies have demonstrated that the cytochrome p450 (CYP) family plays an important role in the metabolism of taxanes. However, the role of CYP gene expression in tumors and peripheral mononuclear cells (PMN) is unknown. We therefore investigated the levels of CYP3A4 and CYP2C gene expression using reverse transcription polymerase chain reaction (RT-PCR) in PMN from 16 previously untreated lung cancer patients to determine whether the expression of the two genes is induced by docetaxel (TXT). Neither the CYP3A4 nor the CYP2C gene was induced after administration of carboplatin (CBDCA) alone. Expression of the CYP3A4 gene was induced by the administration of TXT alone or TXT and CBDCA, but expression of the CYP2C gene was unaffected. We also measured the expression of both genes using RT-PCR in 20 autopsy samples (ten non-small-cell lung cancers and their corresponding normal lung tissues) obtained from patients who had not received any chemotherapy during life. The level of CYP2C gene expression in samples of lung cancer was significantly higher than in normal lung tissue, but the level of CYP3A4 gene expression was not. These results suggest that the CYP3A4 gene is induced by TXT, and that it plays an important role in intracellular TXT metabolism.

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Introduction

The taxanes docetaxel (TXT) and paclitaxel (TXL) are one of the most promising types of drug for cancer chemotherapy because of their unique mechanism of action and excellent antitumor activity [11]. Several mechanisms of resistance to taxanes have been demonstrated: (1) decreased drug accumulation via the drug efflux pump [7, 9, 10, 23], (2) increased metabolism [19, 24, 33, 34], (3) altered tubulin expression [12, 18, 28, 31], and (4) altered microtubule-associated protein expression [25].

The oxidative metabolism of drugs varies markedly between individuals mostly because of variability in the expression of different cytochrome p450 (CYP) enzymes in the liver and extrahepatic tissues. Specific CYP enzymes involved in the metabolism of anticancer drugs have recently been identified [19]. Since the taxanes are also metabolized and inactivated by CYP enzymes (CYP3A4 for TXT, and CYP2C8 and CYP3A4 for TXL), the metabolism of taxanes is likely to contribute to the sensitivity of a patient to these drugs [13, 30, 33]. However, the role of specific CYPs in the metabolism of taxanes in vivo remains uncertain. Thus, understanding the role of the specific CYP that is involved in the drug metabolism should be useful in determining the effect of taxanes and for avoiding drug interactions.

In this study, therefore, the in vivo role of CYP isoforms in relation to TXT was investigated by examining the levels of CYP3A4 and CYP2C gene expression in peripheral mononuclear cells (PMN) before and after TXT administration. Furthermore, in order to examine the baseline expression of CYP isoforms in lung cancer tissue compared to that in normal lung tissue, we examined the level of CYP3A4 and CYP2C gene expression in human non-small-cell lung cancer tissue compared to that in corresponding samples of normal lung tissue.

Materials and methods

Patients and isolation of PMN

We obtained PMN from 16 patients with advanced lung cancer who were admitted to Hiroshima University Hospital between March 1997 and August 1998, after written informed consent had been obtained. None of the patients had previously received chemotherapy. Patients were not premedicated with dexamethasone or any other corticosteroid. Heparinized blood samples (5 ml) were taken just before treatment (0 h), and 6 and 24 h after the last administration of carboplatin (CBDCA) or TXT. The PMN were separated immediately using a lymphocyte preparation medium (Lymphoprep; NYCOMED PHARMA, Oslo, Norway) as described previously [27]. The resulting pellets were used for RNA extraction or stored at –80°C until analysis.

Autopsy samples

Twenty autopsy samples from each of ten patients with non-small cell lung cancer who had been admitted to Hiroshima University Hospital between January 1994 and September 1997 were studied. None of the patients had received chemotherapy. Fresh specimens of primary lung tumors and normal lung tissues were taken after informed consent had been obtained. The tumor specimens were not contaminated by either necrotic parts or normal lung tissue. The tissues were frozen in liquid nitrogen and stored at –80°C until analysis.

RNA extraction

Total cellular RNA was extracted using the guanidinium isothiocyanate-phenol method as described previously [26].

Reverse transcription-polymerase chain reaction (RT-PCR)

cDNA was synthesized using random hexamer primers (Amersham, Little Chalfont, UK) with Superscript RNase H reverse transcriptase (GIBCO-BRL, Bethesda, Md.) as described previously [26]. The reverse-transcribed cDNA from each sample was amplified by PCR using primers based on CYP3A4 and CYP2C, as described previously [3, 15]. The primer set of CYP2C included all known CYP2C forms (CYP2C8, CYP2C9, CYP2C10, CYP2C17, CYP2C18, and CYP2C19) and did not differentiate between them. The sequences of the CYP3A4 and CYP2C primers used were: CYP3A4 forward 5′-CCAAGCTATGCTCTTCACCG-3′ and reverse 5′-TCAGGCTC-CACTTACGGTGC-3′; and CYP2C forward 5′-GCTAAAGTCCAGGAAGAGATTG-3′ and reverse 5′-GCTGAGAAAGGCATGAAGTA-3′. After predenaturation at 94°C for 5 min, the cDNA was added to 5 µl of the PCR mixture which comprised 1 µl 10×PCR buffer (100 m*M* Tris-HCl, pH 9.0, 500 m*M* KCl), 1 µl 15 m*M* $MgCl_2$, 2 µl distilled water, 0.2 µl 20 m*M* dNTPs (Takara, Tokyo, Japan), 0.2 µl 50 µ*M* forward primer, 0.2 µl 50 µ*M* reverse primer, and 0.4 µl (0.2 U) Taq polymerase (Promega, Madison, Wis.).

Amplification was carried out using a thermal cycler (Geneamp PCR System 2400; Perkin Elmer Applied Biosystems Division, Norwalk, Colo.). Each amplification cycle for the reactions using the CYP3A4 primers comprised denaturation at 94°C for 30 s, annealing at 58°C for 30 s, and extension at 72°C for 1 min, followed by a final incubation at 72°C for 7 min. Each cycle for amplification with the CYP2C primer comprised denaturation at 94°C for 30 s, annealing at 65°C for 30 s and extension at 72°C for 1 min, followed by a final incubation at 72°C for 7 min. In order to determine the optimal number of cycles, the accuracy of the quantitative PCR procedure was tested in titration experiments, as described previously [26]. The optimal number of cycles was 25 for CYP3A4, and 27 for CYP2C. The PCR products of CYP3A4 and CYP2C cDNA were 323 and 329 bp long, respectively. We used the β-actin gene as the internal control, and the PCR conditions and the sequences of β-actin primers were as described previously [26].

Quantitation of the PCR products and analysis of mRNA expression

The PCR products were electrophoresed on 2% (w/v) agarose gels, transferred to nylon membranes (Hybond N+; Amersham) and detected by hybridization with ^{32}P-labeled cDNA probes. After washing each filter the radioactivity level was measured with the aid of a laser imaging analyzer (BAS-2000; Fuji Photo Film, Tokyo, Japan). The PCR products of CYP3A4 and CYP2C described above were used as the cDNA probes, and the cDNA probe for β-actin has been as described previously [26]. The radioactivity associated with the level of gene expression in each sample is expressed relative to that from the β-actin expression level in that sample.

Statistical analysis

Contingency table analyses based on χ^2 statistics were used to determine the significance of associations between categorical variables. Differences in levels of expression between two groups were analyzed using the Mann-Whitney *U*-test. All of the gene expression levels were skewed toward higher expression levels, and were subjected to logarithmic transformation before being subjected to a parametric test (analysis of variance). In this way they more closely approximated a normal distribution. The statistical calculations and tests were performed using Stat View J4.11 Software (ABACUS Company, Calif.) and a Macintosh computer. All of the statistical tests were two-sided. The data are expressed as medians and ranges, and differences with *P*-values of less than 0.05 were considered to be statistically significant.

Results

Induction of CYP3A4 in PMN by TXT

We monitored the level of CYP3A4 and CYP2C gene expression in PMN from 16 patients with advanced previously untreated lung cancer who had been treated with either CBDCA alone (calculated using Calvert's formula: target area under the concentration curve (AUC); 7 mg/ml per min), TXT alone (60 mg/m^2), or TXT (50 mg/m^2) followed by CBDCA (calculated using Calvert's formula: target AUC; 5 mg/ml per min). The characteristics of the patients are presented in Table 1.

Table 1 Characteristics of patients who provided PMN

All patients	16
Age (years)	
Median	65
Range	51–79
Sex (male/female)	11/5
Smoker (yes/no)	13/3
Histology	
Adenocarcinoma	10
Squamous cell carcinoma	6
Stage (IIIB/IV)	2/14
Chemotherapy	
CBDCA	10
CBDCA + TXT	3
TXT	3

Table 2 Gene expression levels in PMN. The values are median (range)

	Gene expression levels		
	0 h	6 h	24 h
CBDCA alone			
3A4	0.032 (0.019–0.203)	0.032 (0.009–0.076)	0.039 (0.013–0.093)
2C	0.231 (0.074–0.946)	0.248 (0.090–0.527)	0.193 (0.051–0.459)
TXT alone or TXT plus CBDCA			
3A4	0.285 (0.125–0.548)	0.486 (0.366–0.742)	0.488 (0.315–0.549)*
2C	0.302 (0.026–0.472)	0.234 (0.116–0.555)	0.251 (0.183–0.609)

*$P < 0.05$

Table 3 Characteristics of patients sampled at autopsy

All patients	10
Age (years)	
Median	69
Range	51–86
Sex (male/female)	8/2
Smoker (yes/no)	9/1
Histology	
Adenocarcinoma	6
Squamous cell carcinoma	3
Large-cell carcinoma	1
Interval between death and autopsy (h)	
Median	3
Range	1–16

There were 11 males and 5 females ranging in age from 51 to 79 years (median 65 years). Most of the patients (13/16) were smokers. First we examined the expression level of both genes in the PMN from patients who were treated with CBDCA alone. However, neither gene was induced after this treatment (Table 2). Next, we examined the expression levels of both genes in PMN from patients who were treated with TXT alone or TXT followed by CBDCA. The CYP3A4 gene was induced by administration of TXT alone or TXT plus CBDCA. The CYP2C gene was not induced by these treatments (Table 2).

Expression levels in lung cancer specimens

We analyzed the levels of CYP3A4 and CYP2C gene expression in 20 autopsy samples (10 non-small-cell lung cancers, 10 corresponding normal lung tissues) obtained from ten patients, whose characteristics are presented in Table 3. There were eight males and two females ranging in age from 51 to 86 years (median 69 years). All these patients had non-small-cell carcinoma, and almost all of them (9 of 10) had been smokers. The intervals between death and autopsy ranged from 1 to 16 h (median 3 h).

There was considerable variability in the level of expression of both the CYP3A4 and CYP2C gene among lung tumor tissue and normal lung tissue. The median level of CYP3A4 gene expression was 0.016 (range 0.010–0.040) in normal lung tissue and 0.023 (range 0.005–0.104) in lung tumor tissue. There were no significant differences between normal lung tissue and tumor tissue (Fig. 1). On the other hand, the median level of CYP2C gene expression were 0.009 (range 0.001–0.052) in normal lung tissue and 0.046 (range 0.009–0.129) in lung tumor tissue. The level of CYP2C gene expression in the tumor was significantly higher than in normal lung tissue ($P < 0.05$, Fig. 1).

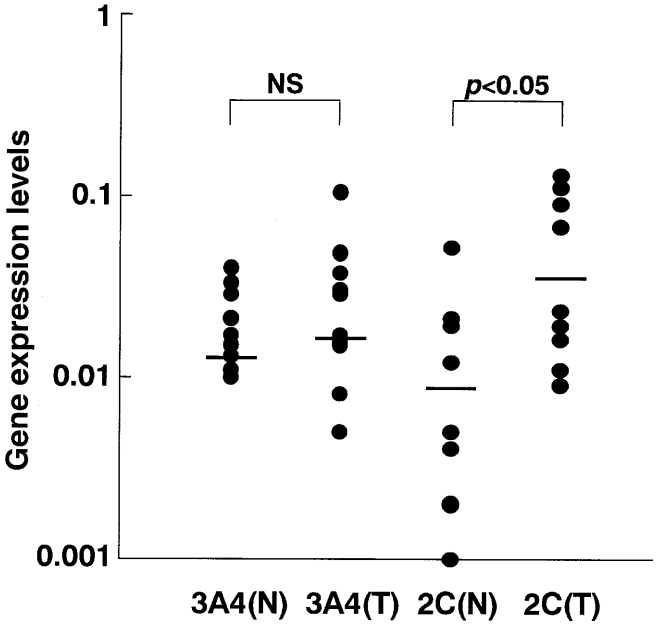

Fig. 1 Expression of the CYP 3A4 and CYP2C genes in lung tumor tissue in comparison with normal lung tissue (*bars* median gene expression levels; *N* normal lung tissue, *T* lung tumor tissue, *NS* not significant)

Discussion

In the study presented here, we demonstrated that the level of CYP3A4 gene expression in PMN increased after TXT exposure, whereas that of the CYP2C did not. One of the interesting aspects of CYP is that some of the genes, including CYP1A1, CYP2C9, CYP2E1, and CYP3A4, are inducible [21]. Recently, Kostrubsky et al. [20] have shown that CYP3A4 mRNA is increased by TXL in human hepatocytes. We found increases in CYP3A4 mRNA for PMN after TXT administration, and these results indicate that both these taxanes are inducers of CYP3A4.

From a biological viewpoint, induction is an adaptive response that protects cells from xenobiotics, resulting in a reduction in the pharmacologic effect because of increased drug metabolism and detoxification activity. Indeed, pretreatment with corticosteroids, which are potent inducers of CYP3A4, has been shown to increase CYP3A4 activity and enhance the metabolism of TXL [1, 24]. Furthermore, high levels of formation of *p*-hydroxy-phenyl-C3′-paclitaxel, which is a minor metabolite catalyzed by CYP3A4, have been observed in a patient who had been treated with inducers of CYP3A4 [8]. Since TXT is metabolized by CYP3A4, treatment with TXT may result in the autoinduction of metabolism itself.

Enhanced intracellular metabolic activity usually limits the effectiveness of anticancer drugs, but interindividual variability does exist. One reason for this is alteration in drug metabolism enzymes. Mutations in the gene for a drug-metabolizing enzyme could result in enzyme variants with higher, lower or no activity, or may even result in the absence of the enzyme. Polymorphism of CYP enzymes, such as the CYP2C or CYP2D subfamily, has been described [17]. Although, genetic polymorphism of CYP3A4 has been recently reported, no apparent relationships between the genotypes and the activity or amount of CYP3A4 were found [2]. On the other hand, Marre et al. [22] have shown that the interindividual variability in TXT biotransformation is related to variability in the expression of the CYP3A subfamily. Kostrubsky et al. [20] have shown that increases in CYP3A4 mRNA correlate with increases in the levels of immunoreactive CYP3A4 in human hepatocytes. It seems likely, therefore, that the level of CYP3A4 gene expression may be important for TXT metabolism activity.

The interaction of TXT with coadministered drugs that are metabolized by CYP3A4 is a clinical problem. In fact, it has been suggested that pharmacokinetic interactions occur when TXT is combined with either doxorubicin or etoposide [6]. Furthermore, it has been shown that TXT metabolism is inducible by CYP3A4 inducers, including dexamethasone, which have been used as a pretreatment for decreased hypersensitivity reactions with TXT [22]. However, there were no changes in AUC of TXT between patients who were receiving dexamethasone and those who were not [4]. Further studies are required to elucidate drug interactions with TXT and this information would be of great use in designing optimal treatment protocols for TXT combined chemotherapy.

Since TXT is often used with platinum drugs, and we obtained lung tissue samples from patients who were given TXT with CBDCA, the drug-drug interaction of TXT with the platinum drug should be also examined. In a recent in vitro study it was demonstrated that cisplatin (CDDP) does not affect the metabolism of taxanes [22, 34]. However, previous clinical phase I trials have demonstrated that the sequence of administration of CDDP before taxanes induces more profound myelosuppression than the alternate sequence [29, 32]. Moreover, a higher AUC of 6α-hydroxypaclitaxel, the major TXL metabolite produced by CYP2C8, was observed when CBDCA was administered before TXL, although no sequence-dependent pharmacokinetic interactions for the AUC of TXL or maximal plasma concentration were found [16]. Therefore, we investigated changes in the level of CYP3A4 and CYP2C expression in PMN before and after the administration of CBDCA alone. We observed no induction of either of the genes under these conditions. Our findings indicate that CBDCA does not affect either CYP3A4 or CYP2C gene expression.

We observed an increase in the expression of the CYP2C gene in non-small-cell lung cancer compared with that in normal lung tissue, suggesting that the metabolic activity of drugs catalyzed by CYP2C is increased in lung cancer. Since the major metabolite of TXL results from the action of CYP2C8 [30], the metabolism of TXL may be increased in non-small-cell lung cancer compared to normal lung tissue. Previously, Huang et al. [15] have shown that the expression of both the CYP3A4 and CYP2C genes in breast cancer is not different from that in normal breast tissue. These results indicate that the expression of CYP isoforms is different among cancer types.

Finally, recent reports have shown that the prediction of the metabolic activity of CYP3A4 is useful for TXT combined chemotherapy. Hirth et al. [14] have shown that the erythromycin breath test, an indicator of CYP3A4 function, could be used as a predictor of toxicity in patients after treatment with TXT. Yamamoto et al. [35] have shown that by measuring 24-h urinary 6β-hydroxycortisol levels (the metabolite of cortisol catalyzed by CYP3A4) after administering exogenous cortisol, it is possible to evaluate the interpatient variability of CYP3A4 activity. Furthermore, Bruno et al. [5] have suggested that the first cycle AUC of TXT is a significant predictor of time to progression in non-small-cell lung cancer. We plan to examine whether the level of CYP3A4 gene expression in PMN can be used as a predictor of toxicity after treatment with TXT and/or TXT pharmacokinetics.

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