A Prospective Pharmacokinetic Study of Docetaxel in Breast Cancer Patients in Relation to CYP3A4 Activity

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Abstract

Purpose: To study the correlation between pharmacokinetics & pharmacodynamic of docetaxel and CYP3A4 activity in Egyptian cancer patients.

Patients and methods: Fourteen Egyptian female Patients with metastatic breast cancer, World Health Organization (WHO) performance status 0 to 2, had received prior chemotherapy regimen, were treated with single-agent docetaxel (100 mg/m²), given every 21 days. Hydrocortisone 300 mg IV was administered 2 days before docetaxel treatment and Cytochrome 3A4 activity was determined by measuring the level of urinary metabolites of 6β-hydroxy cortisol (6β-OH) and cortisol (FC). For the pharmacokinetic study, Blood samples were taken before and after IV infusion for 1 hr of 100 mg/m² docetaxel. The level of the drug was determined using HPLC and the correlation between pharmacokinetics and CYP3A4 activity were determined.

Results: After cortisol administration, the total amount of 24-hour urinary 6β-OH and FC were 19.97 ± 10.43 and 16.84 ± 10.36 mg/24 h (mean ± SD) respectively. On the other hand, the 6β-OH/FC ratio after cortisol administration was 1.86 ± 1.93. The pharmacokinetic parameters of docetaxel were clearance 19.9 ± 4.5 L/hr, the volume of distribution 65.6 ± 28.6 L (mean ± SD) and AUC 7.2 µg/ml·hr (range 5-8.8 µg/ml·hr) ± SD. A significant correlation was found between 6β-OH/FC ratio and neutropenia (p=0.04) in addition correlation between 6β-OH and Cmax (p=0.04).

Conclusion: The interpatient variability of CYP3A4 activity in each patient could be predicted by measuring the total amount of 24 hour urinary 63-OHF after cortisol administration. Individualized dosing to optimize drug exposure for each patient could be performed based on this method. A farther study of fixed versus individualized dosing of docetaxel is needed to determine whether individualized chemotheraphy with the application of this method can reduce PK and toxicity variability.

Keywords: Docetaxel pharmacokinetic; CYP3A4 activity; Neutropenia; Response

Introduction

Docetaxel (DCX) is a taxoid derivative that displays antitumoral activity against many solid tumors, including prostate, lung, ovarian and breast cancers [1] and promising activity against metastatic breast cancer [2]. Individuals display significant differences in terms of efficacy and adverse effects after exposure to docetaxel. The drug is not effective for all breast cancers patients; an identical dosage of a drug can result in widely different concentrations of the therapeutically active compound or metabolites [3]. Therefore, it is very important to develop a diagnostic method for the prediction of the response to docetaxel in order to avoid over or under treatment. Currently, it is impossible to identify, before the initiation of therapy, the patients for whom docetaxel will be used.

The presence of genetic variability in both content and catalytic activity of enzymes involved in drug metabolism could lead to clinically important variations in efficacy and adverse effects of some drugs. The cytochrome P450 is a family of heme-containing enzymes responsible for the metabolism of many drugs including taxane [4]. Docetaxel is metabolized by CYP3A4 in the liver into four major metabolites with minimal or no antitumor activity so that metabolism of docetaxel depends on the enzyme activity of CYP3A4 in the liver of individual patients. The CYP3A4 enzyme displays large interpatient differences in both content and catalytic activity in humans. These differences exist even in the absence of medications known to induce or inhibit the enzyme and are thus likely to reflect genetic variability [4,5].

We hypothesized that the interpatient variability of docetaxel pharmacokinetics and pharmacodynamic is due differences in CYP3A4 activity. Exogenous cortisol was used as a probe to measure CYP3A4 activity through determination of its urinary 6β-hydroxy metabolite (6β-OHC) and free cortisol (FC) metabolites [6].

Material and Methods

Drugs

The docetaxel (Taxotere® Sanofi-Aventis, Paris, France) vial was obtained as concentrated sterile solution that contained 20 or 80 mg of the drug in 0.5 ml polysorbate 80. Hydrocortisone (Solu-cortif, EIPICO, Cairo, Egypt) was available as a vial containing 100 mg lyophilized powder. Both drugs were from the drug store of the National Cancer Institute (NCI) Hospital.

Chemical and reagents

For HPLC, an authentic sample of docetaxel was supplied by National Organization for Drug Control and Research (NODCAR,

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and plasma samples were stored at -20 °C until assayed. Two days after the cortisol administration, a dose of 100 mg/m2 of docetaxel was diluted in 5-ml aliquot was stored at -20 °C until assayed. Two days after the administration, a dose of 100 mg/m2 of docetaxel was diluted in 1-ml of patient plasma sample, 100 µl of ammonium acetate buffer (pH 5) and 7 ml of diethyl ether were added in a glass tube. Tubes were mixed by vibration for 3 min and then centrifuged at 3500 g for 5 min. The organic layer was quickly dried under nitrogen at ambient temperature. The residue was next reconstituted with 1 ml of the mobile phase. Separation was performed using a Gemini Nux (150×4.6 mm, 5 µm particle size). The mobile phase consisted of methanol: water (45:50:5, v/v). Chromatographic separation was monitored at 227 nm.

Determination of blood α-1-acid glycoprotein

Alpha acid glycoprotein was determined in plasma of the patients before the treatment using human α-1-Acid Glycoprotein, ELISA Kit (AssayMax, ASSAYPRO, Canada) following authors’ instructions [10].

Statistical analysis

Numerical data were expressed as the mean and standard deviation (SD), median and range as appropriate. Qualitative data were expressed as frequency and percentage. The bi-exponential equation was used to calculate the AUC and PK parameters of docetaxel. Spearman’s rho method was used to determine the correlation between different parameters. Fisher’s exact test used to determine the difference in response between the subgroups. A two-sided p-value of ≤0.05 was considered significant. All statistical analysis was performed using Graph Pad Prism 5.

Results

Patient characteristics

The baseline pretreatment characteristics of all the studied patients are listed in the Table 1. The majority of patients (92%) had a performance state: 0-2 (according to WHO classification), neutrophil count ≥1.0×10^9/l, platelet count ≥100×10^9/l, serum creatinine level ≤1.5 mg/dl, serum total bilirubin level ≤1.5 mg/dl, and serum transaminases ≤150U/L were treated with docetaxel 100 mg/m every 21 days. The Exclusion criteria included the following: Pregnancy or lactation, concomitant radiotherapy or chemotherapy, and a known history of severe concomitant diseases or with elevated serum bilirubin hypersensitivity to polysorbate 80.

Pre-treatment, and follow-up evaluation

All the patients were subjected to the following, Full history taking, full clinical examination and laboratory investigations including: complete blood picture, serum creatinine and liver function tests (serum bilirubin level, serum alkaline phosphatases, serum transaminases and serum albumin), radiological investigations including chest CT, abdominal ultrasound, and bone scan according to patient’s symptoms. Clinical and the radiological response were assessed every 2 cycles.

Drug administration and Sample collection

At the first day, a dose of 300 mg hydrocortisone in 100 ml of 0.9% saline was administered (at 9-12 am) intravenously for 30 min. The urine was collected for 24 hours and total volume was recorded. Then a 5-ml aliquot was stored at -20 °C until assayed. Two days after the cortisone administration, a dose of 100 mg/m2 of docetaxel was diluted in 250 ml of 5% glucose and administered for 1-hour IV infusion. Blood samples for pharmacokinetic (PK) studies were obtained from all patients in the first cycle of therapy. The blood samples were collected before infusion, 30 min after the beginning of infusion, at the end of infusion, 15, 30 and 60 minutes, and 3, 5, and 24 hours after the end of infusion. Whole blood samples were collected into heparinized tubes and plasma samples were stored at -20 °C until assayed.

Methods

Estimation of CYP3A4 activity by urinary metabolite of exogenous cortisol

We chose hydrocortisone as an exogenous cortisol for the measurement of endogenous urinary 6β-OH/FC. It is simple and completely noninvasive and could have a practical advantage over the other methods [7]. Urine was centrifuged at 3200g for 5 min and extracted adopting liquid-liquid extraction method [8] with an ethyl acetate/isopropanol mixture (85/15: v/v). The organic layer was washed with a basic solution of 1 N sodium hydroxide, separated and then evaporated at 56°C under a stream of nitrogen. The residue was then dissolved in 1 ml of mobile phase. Separation was performed using an ultracarb ODS, C18 column (20 µm particle, 250×4.6 mm) and HPLC system Gilson, a solvent delivery pump (Gilson 321) equipped with UV detector (Gilson visible-155) and coupled with 243 autosampler and chromatographic maxima 830 data integration package were used. The mobile phase consisted of methanol: water (57.5:42.5, v/v) was pumped at flow rate of 1 ml/min and the chromatographic separation was monitored at 242 nm.

Docetaxel pharmacokinetics

1-ml of patient plasma sample, 100 µl of ammonium acetate buffer (pH 5) and 7 ml of diethyl ether were added in a glass tube. Tubes were mixed by vibration for 3 min and then centrifuged at 3500g at 4°C for 5 min. The organic layer was quickly dried under nitrogen at ambient temperature. The residue was next reconstituted with 1 ml of the mobile phase. Separation was performed using a Gemini Nux (150×4.6 mm, 5 µm particle size). The mobile phase pumped at a flow rate of 1.8 ml/min consisted of acetonitrile, 35 mM ammonium acetate buffer (pH 5), tetrahydrofuran (45:50:5, v/v). Chromatographic separation was monitored at 227 nm.

alpha and beta half-lives were 8.8 minutes and 4.5 hours. The docetaxel (0.1-10.7), respectively (Table 4).

cortisol to the total dose taken 300 mg were 6.9% (0.2-12.8) and 6.3% (0.6-8.1). The median percent of metabolite and unchanged form of (Figure 1). The 6β-OHF/FC ratio after cortisol administration was 1.2 were 20.7(0.8-38.4) mg/24 h and 19.1 (0.5-32.2) mg/24 h, respectively

Toxicity The median level (range) of 24 hour urinary 6β-OHF and FC were 23.0 (9.0-55.0) 10-50


creatinine (mg/dl) 0.7 ± 0.2 0.7 (0.4-1.5) 0.5-1.2


total protein (g/dl) 7.5 ± 0.5 7.5 (6.9-8.7) 6.8-8.8


Activity of CYP 3A4

The median level (range) of 24 hour urinary 6β-OHF and FC were 20.7(0.8-38.4) mg/24 h and 19.1 (0.5-32.2) mg/24 h, respectively (Figure 1). The 6β-OHF/FC ratio after cortisol administration was 1.2 (0.6-8.1). The median percent of metabolite and unchanged form of cortisol to the total dose taken 300 mg were 6.9% (0.2-12.8) and 6.3% (0.1-10.7), respectively (Table 4).

Pharmacokinetic parameters are listed in the Table 5. The mean alpha and beta half-lives were 8.8 minutes and 4.5 hours. The docetaxel clearance was 19.9 ± 4.5 L/hr, and AUC (Mean=7.2 µg/ml.hr, SE=0.313, 7.9 ± AUC ≥ 6.5). The volume of distribution was 65.6 ± 28.6 L.

Pharmacodynamic effects

Assessment of toxicity was done after the first cycle of the treatment while the response was evaluated every 2 cycles. Table 6 shows the change in hematological values during the three weeks after the first cycle of treatment. WBC count and neutrophile % declined through the first week after docetaxel infusion then begin to recover during the second week of treatment in most of the patients and finally return to normal values during the third week of treatment. There are no marked changes in other values.

Neutropenia grade 3-4 was the predominant toxicity (71%) related to docetaxel treatment. Only one patient had febrile neutropenia. The percentage decrease in ANC was 48.6% (Table 7). Non-hematologic toxicities, such as gastrointestinal (mucositis, diarrhea, nausea, vomiting), arthralgia, fatigue and hepatic toxicities (hyperbilirubinemia, aminotransferase elevations), were mild in most of the patients. Four patients (28.5%) achieved a partial response and one patient achieved a complete remission.

There was a positive correlation between increased activity of CYT3A4 (6β-OHF/FC ratio) and percentage of decrease in absolute neutrophil count (ANC) (Spearman correlation, r=0.56, p=0.04). (Figure 2). Also, positive correlation between the total amount of 6β-OHF and Cmax achieved with docetaxel (Spearman correlation, r=0.54, p=0.04) (Figure 3). Even after cortisol administration, no correlation was detected between docetaxel CL and 6β-OHF/FC

![Figure 1: Interpatient variability in urinary metabolite 6β-hydroxycortisol (mg/day) in fourteen breast cancer patients. All patients received 300 mg hydrocortisone as IV infusion for 30 minutes.](image1)

![Figure 2: Correlation between 6β-hydroxycortisol/cortisol ratio and percentage decrease in absolute neutrophil count (Spearman correlation, r=0.56, p=0.04).](image2)
Table 4: The mean and range of 24 hr urinary metabolite levels of 6β-OHF, FC and 6β-OH/FC ratio after 300 mg cortisol administration.

<table>
<thead>
<tr>
<th>Pharmacokinetic parameters</th>
<th>Mean ± SD</th>
<th>Median (Range)</th>
</tr>
</thead>
<tbody>
<tr>
<td>AUC µg/ml/hr</td>
<td>7.2 ± 1.1</td>
<td>7.3 (5.8-8.8)</td>
</tr>
<tr>
<td>C max µg/ml</td>
<td>2.4 ± 0.6</td>
<td>2.6 (1.1-3.4)</td>
</tr>
<tr>
<td>Clearance L/hr</td>
<td>19.9 ± 4.5</td>
<td>20.3 (14.1-29.0)</td>
</tr>
<tr>
<td>Clearance L/hr/(mg/2)</td>
<td>13.7 ± 3.1</td>
<td>13.6 (8.7-20.0)</td>
</tr>
<tr>
<td>Tα minute</td>
<td>8.8 ± 1.0</td>
<td>9.5 (7.9-11.0)</td>
</tr>
<tr>
<td>Tββ hours</td>
<td>4.5 ± 1.3</td>
<td>5.0 (3.1-7.5)</td>
</tr>
<tr>
<td>Vd L</td>
<td>65.6 ± 28.6</td>
<td>58.1 (37.3-126.4)</td>
</tr>
</tbody>
</table>

Table 5: Pharmacokinetic parameters of 100 mg/m² of docetaxel for 1 hr infusion in Egyptian breast cancer patients.

<table>
<thead>
<tr>
<th>Hematological changes</th>
<th>Mean ± SD</th>
<th>Median (Range)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neutrophil %</td>
<td>76.3 ± 10.5</td>
<td>79.2 (57-105)</td>
</tr>
<tr>
<td>WBC (×10³/µl)</td>
<td>6.9 ± 2.65</td>
<td>5.5 (3.0-8.1)</td>
</tr>
<tr>
<td>ANC (µl¹/µl)</td>
<td>526.4 ± 8.5</td>
<td>278.3 (5.5-519.9)</td>
</tr>
<tr>
<td>HGB (g/dl)</td>
<td>12.1 ± 1.5</td>
<td>11.2 (1.1-13.6)</td>
</tr>
<tr>
<td>RBC (×10³/µl)</td>
<td>4.0 ± 0.67</td>
<td>4.2 (0.7-7.5)</td>
</tr>
<tr>
<td>PLT (×10³/µl)</td>
<td>318.0 ± 142.0</td>
<td>289.0 (112.0-920.0)</td>
</tr>
<tr>
<td>ALT (IU/L)</td>
<td>20.6 ± 8.61</td>
<td>21.9 (7.9-21.2)</td>
</tr>
<tr>
<td>AST (IU/L)</td>
<td>22.93 ± 7.82</td>
<td>24.3 (7.5-23.4)</td>
</tr>
</tbody>
</table>

The percent decrease in ANC=74 ± 9% (Mean ± SD); *After treatment ALT: Alanine aminotransferase; ANC: Absolute neutrophil count; AST: Aspartate aminotransferase; HGB: Hemoglobin; PLT: Platelet; RBC: Red blood cell count; SD: Standard deviation; WBC: White blood cell count.

Table 6: Hematological changes during the three weeks after the first cycle of 100 mg/m² docetaxel treatment.

(= 0.0119) and no correlation with the total amount of 24-hour urinary 6β-OHF after cortisol administration (T6β-OHF) (r=0.0659).

Then the patients were stratified into two subgroups according to

6β-OH/FC ratio we find that:

<table>
<thead>
<tr>
<th>Group</th>
<th>6β-OH/FC ratio ≥1</th>
<th>6β-OH/FC ratio &lt;1</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>19.2 ± 10.4</td>
<td>7.1</td>
</tr>
<tr>
<td>2</td>
<td>16.0 ± 10.3</td>
<td>14.2</td>
</tr>
<tr>
<td>3</td>
<td>1.8 ± 1.9</td>
<td>1.2</td>
</tr>
<tr>
<td>4</td>
<td>6.8 ± 3.4</td>
<td>6.9</td>
</tr>
<tr>
<td>5</td>
<td>5.6 ± 3.4</td>
<td>6.3</td>
</tr>
</tbody>
</table>

Discussion

Docetaxel is primarily metabolized by CYP3A4, in particular by isofom CYP3A4, its metabolites are substantially less active than the parent drug and are considered as a major route of inactivation. All the patients involved in this study have normal hepatic function, none of them had received known potent inhibitors or inducers of CYP3A4 with the exception of dexamethasone which is used as premedication, and thus, it appears that the variation may reflect genetic differences in the metabolism of docetaxel. Although, other factors as genetic polymorphism, epigenetic influences or non-genetic related to host factors may be implemented in this variation [5]. In this study, the Egyptian breast cancer patients showed a decrease in docetaxel clearance compared to European [12] and Japanese patients [13]. The mean clearance of docetaxel in this study was 13.7 ± 2.3 L/h/m² compared with the reported clearance of 34 ± 3.2 and 22.6 ± 3.4 L/h/m² for the whites and Japanese women, respectively.

Initially, the main predictors of total docetaxel clearance variability were BSA, AAG, hepatic function and age, more recently hepatic CYP450 3A4 activity [14]. Although some studies found correlation between DXC clearance and CYP450 3A4 activity [7,13,15], such type of relation was absent in our study which may be due to the presence of other metabolic pathways which might have been involved in the metabolism of the excess amount of exogenous cortisol [16], or due to an excess amount of substrate over enzyme capacity [7]. However, this apparent difference is inconclusive and need further investigation and may be accounted for the small sample size, assay variation, differences in methods of assay and sampling time points.

In this work, after exogenous cortisol administration, the total amount of 24-hr urinary 6β-OHF was 19.9 ± 10.4 mg/d (mean ± SD), urinary FC was 16.8 ± 10.3 mg/d and the 6β-OH /FC ratio was 1.8 ± 1.9 compared to 12.2 ± 4.0, 13.6 ± 5.7 mg/d and 1.02 ± 0.45 for the amount of 24-hr urinary 6β-OH, FC and 6β-OH/FC ratio respectively in Japanese [13]. Although marked interpatient heterogeneity in the activity of CYP34A is known to exist, the clinical implications of having a high or low CYP3A4 activity were not necessarily known. In this study low CYP34A activity (6β-OH/FC ratio <1) appears to be associated with the higher response. It implies that consideration should be given to modifying the dose for patients with high CYP3A4 activity (6β-OH/FC ratio >1) because they are at risk of getting sub-therapeutic doses of docetaxel.

The time-serum concentration represented by prolonged AUC and the decrease in the volume of distribution Vd may reflect the decrease in clearance of DXC and the higher incidence of neutropenia in our
Hematological and non-hematological toxicities in breast cancer patients

Table 7:

<table>
<thead>
<tr>
<th>Side effects</th>
<th>No. of Patients</th>
<th>Percent (%)</th>
<th>Severity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hematologic toxicities</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Neutropenia</td>
<td>10</td>
<td>71</td>
<td>3-4</td>
</tr>
<tr>
<td>Febrile neutropenia</td>
<td>1</td>
<td>7.1</td>
<td>4</td>
</tr>
<tr>
<td>Non-hematologic toxicities</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Alopecia</td>
<td>12</td>
<td>85.7</td>
<td>Moderate</td>
</tr>
<tr>
<td>Nausea</td>
<td>3</td>
<td>21.4</td>
<td>Mild</td>
</tr>
<tr>
<td>Vomiting</td>
<td>3</td>
<td>28.5</td>
<td>Mild</td>
</tr>
<tr>
<td>Mucositis</td>
<td>3</td>
<td>21.4</td>
<td>Mild</td>
</tr>
<tr>
<td>Neuropathy</td>
<td>6</td>
<td>42.8</td>
<td>Mild</td>
</tr>
</tbody>
</table>

10 One patient may have more than one toxicity

Table 7: Hematological and non-hematological toxicities in breast cancer patients receiving 100mg/m² of docetaxel and degree of severity according to NCI toxicity criteria.

results. In our study a negative correlation between AUC and the clearance was detected, however, the established relationship between the docetaxel AUC and the percentage decrease in ANC was not confirmed. This may have been due to the large heterogeneity of patient population (decrease in ANC ranged from 23.3% to 86.9%) and the small number of patients in this study. The AUC in our study was almost doubled (7.2 ± 1.1) (µg/ml/hr) while, it was (3.1 ± 0.9) and (2.6 ± 0.9) (µg/ml/hr) in the whites and Japanese respectively. Our data showed Vₐ = 65.6 ± 28.6 L (mean ± SD), Cₚmax ranged 1.1-3.4 µg/ml, Tₚmax 8.8 minute and Tₛₕₜ 4.5 hr compared to Vₐ = 84.0 ± 66.1, Cₚmax 0.99-2.41 µg/ml, Tₚmax 5 minute and Tₛₕₜ 51 minute for European population [12] and VD 75.0 ± 20.6, C₀ 0.36-2.7µg/ml, Tₚₜ 9.2 minute and Tₛₜ 5 hr for Japanese patients [13]. Our patients presented by the high incidence of toxicity especially neutropenia which is the dose limiting toxicity of docetaxel. The toxicities namely, grade 3 or4 neutropenia was seen in virtually in most of our patients (78% percentage, incidence 11/14), it appeared to be more significant than in Western patients (58% percentage, the incidence of 14/24) [12]. However, reported an incidence of neutropenia was 25out of 29 patients, with the total percentage of patients was 86% [16]. The absolute neutrophil count decreased with the administration of DCX, reached a nadir at approximately 1 week after the treatment, and increased thereafter to a level higher than the basal ANC value 3 weeks after DCX dosage. A similar pattern for neutropenia was also reported by Friberg et al. [17]. A recent study find that severe hematological toxicities are more frequently experienced in the Japanese compared to the US and European patients. This difference in toxicity profiles was possibly caused by other unknown genetic factors, and differences in unbound docetaxel concentrations or baseline counts of white blood cells. However, mechanistic insights are not yet elucidated for different sensitivity to docetaxel toxicity between Japanese and Western populations [18].

Moreover, a significant relationship between CYP activity represented by 6β-OHF/FC ratio and the percentage decrease in neutrophil count in our study was observed (p=0.04). A result which may be attributed to the presence of pathway which results in a metabolite that is toxic to neutrophils. Interestingly, [12] reported high concentrations of oxazolidinedione metabolite in the plasma of patients who suffered from the most edema and weight gain. In addition, the occurrence of neurotoxicity was significantly more frequent in patients homozygous for GSTP1105 Ile allele [19]. It was found that docetaxel is mainly metabolized in the liver by the cytochrome P450 CYP3A4 and CYP3A5 subfamilies of isoenzymes. Metabolism is principally oxidative and at the start-butyl propionate side chain, resulting first in an alcohol docetaxel, which is then cyclised to three further metabolites two diastereomeric hydroxy oxazolidinones and oxazolidinedione [2].

α-1-acid glycoprotein is the main determinant of docetaxel serum binding variability. High AAG level have been associated with a decrease in the free fraction of docetaxel with reduced total clearance. In this study, AAG and the 6β-OHF/FC ratio do not appear to be correlated which may be due to the Polyisorbate 80 which was reported to increases the unbound drug fraction by 16-24% and resulted in lower unbound docetaxel clearance.

Finally recent studies have disclosed that human breast cancer tissues express CYP 3A4 [20] suggesting that docetaxel may be metabolized to its inactive forms in tumor tissues and that CYP3A4 activity in tumor tissues may, therefore, affect the antitumor activity of docetaxel. CYP3A4 mRNA expression levels in tumors showed no association with their relationship with the response to docetaxel were studied. The authors reported breast tumors with low expression of CYP3A4 mRNA a significantly higher response rate (71%) than those with high expression of CYP3A4 mRNA (11%) [21]. Interestingly, CYP3A4 mRNA expression in tumor tissues showed no association with response to epirubicin based regimens [20]. These results are taken together suggest that intratumoral expression of CYP3A4 mRNA or CYP3A4 protein determined by immunohistochemistry could serve as a predictor of resistance to docetaxel. The role of CYP3A4 in the acquisition of such resistance thus appears to merit further basic and clinical studies.

In conclusion, the significant correlation observed between 6β-OHF/FC ratio and percentage decrease in absolute neutrophil count (ANC) was needed to be confirmed with further studies with larger sample size. The interpatient variability of CYP3A4 activity in
each patient could be predicted by measuring the total amount of 24-hour urinary 63-OHF after cortisol administration. Individualized dosing to optimize drug exposure for each patient could be performed based on this method.

References


