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ORIGINAL ARTICLE

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Oral bioavailability of docetaxel in combination with OC144-093 (ONT-093)

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Abstract *Objective*: Docetaxel given orally as monotherapy results in low bioavailability of < 10%. Previous studies have indicated that the intestinal efflux pump P-glycoprotein (P-gp) prevents uptake from the gut resulting in low systemic exposure to docetaxel. The purpose of this study was to determine the degree of enhancement of the oral uptake of docetaxel on combination with orally administered OC144-093, a potent P-gp inhibitor. Furthermore, the safety of combined treatment was determined and whether known functional genetic polymorphisms of the MDR1 gene could be associated with variability in docetaxel pharmacokinetics was also investigated. *Patients and methods*: A proof of concept study was carried out in 12 patients with advanced solid tumors. Patients were randomized to receive one course of 100 mg oral docetaxel combined with 500 mg OC144-093 followed 2 weeks later by a second i.v. course of docetaxel at a flat dose of 100 mg, without OC144-093, or vice versa. This was followed by standard i.v. docetaxel treatment if indicated. *Results*: The apparent relative oral bioavailability of docetaxel was 26 ± 8%. Orally administered docetaxel combined with oral OC144-093 resulted in a C_{max} of 415 ± 255 ng ml^{-1}, an $AUC_{0-\infty}$ of 844 ± 753 ng h ml^{-1} and k_{el} of 0.810 ± 0.296 h^{-1}. These values differed significantly from those following i.v. administration of docetaxel, with a C_{max} of 2124 ± 1054 ng ml^{-1}, an $AUC_{0-\infty}$ of 2571 ± 1598 ng h ml^{-1} and a k_{el} of 1.318 ± 0.785 h^{-1} ($P = 0.003$, $P = 0.006$, $P = 0.016$). The study medication was well tolerated and most of the adverse events possibly or probably related to OC144-093 and docetaxel were of CTC grade 1 and 2. One patient had a homozygous 3435T/T mutation, which is associated with low intestinal P-gp expression, and two other patients had a homozygous mutation on exon 21. *Conclusion*: The relative apparent bioavailability of 26% was most likely caused by a significant effect of OC144-093 on the oral uptake of docetaxel. Large intrapatient and interpatient (pharmacokinetic) variation was found after oral as well as after i.v. administration of docetaxel. Higher plasma levels were observed after 100 mg i.v. docetaxel than after 100 mg oral docetaxel plus 500 mg oral OC144-093. The safety of the oral combination was good. More patients should be evaluated to determine the effect of P-gp single nucleotide polymorphisms on oral pharmacokinetic values of docetaxel.

Keywords Docetaxel · Oral administration · P-glycoprotein · OC144-093 · Pharmacogenetics · Pharmacokinetics · Bioavailability

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Introduction

Docetaxel (Taxotere) as a single agent is registered for anthracycline-resistant breast cancer and second-line treatment of non-small-cell lung cancer (NSCLC). Recently it has been registered for first-line treatment for advanced NSCLC in combination with cisplatin. Furthermore, docetaxel has shown activity in head and neck cancer [12]. To enhance patient's convenience, facilitate

combined treatment with other antineoplastic agents and to facilitate the use of more chronic treatment regimens, oral therapy has received increasing interest in the last few years [4, 5, 7, 16, 18]. However, docetaxel has poor bioavailability when given orally in humans. Docetaxel is a substrate with high affinity for the MDR1 efflux protein P-glycoprotein (P-gp) [27]. P-gp is highly expressed in the mucosa of the gastrointestinal tract directed towards the gut lumen and in the liver, where it is oriented towards the bile canaliculi [25]. High expression of P-gp combined with high affinity of docetaxel for the efflux pump is the most plausible explanation for the low systemic availability upon oral administration.

Studies conducted in our institute have revealed that the oral bioavailability of docetaxel in wild-type mice is very low (<5%). Furthermore, in *mdr1*(*a*/*b*)(−/−) knockout mice, which lack functional P-gp activity, the oral bioavailability of docetaxel is more than sixfold higher than in wild-type mice with proficient P-gp. When docetaxel is combined with cyclosporin A (CsA), a P-gp inhibitor, in wild type mice a similar bioavailability is observed as in *mdr1*(*a*/*b*)(−/−) knockout mice, indicating that functional blockade of P-gp might contribute to an enhanced oral bioavailability [1, 24]. These results gave rise to a proof of concept study in patients [19], in which the bioavailability of oral docetaxel (75 mg m^{-2}), given as an oral drinking solution of the i.v. formulation, increased from 8 ± 6% (monotherapy) to 90 ± 44% when combined with 15 mg kg^{-1} CsA. Notably, CsA is metabolized in the liver by CYP3A4 enzymes, which are also involved in the metabolism of docetaxel in mice and humans. The increased oral bioavailability of docetaxel seen after combination with CsA could therefore also be explained by a decreased metabolism of docetaxel in the gastrointestinal tract.

These results formed the rationale for investigating whether the P-gp inhibitor OC144-093, which has little effect on CYP3A, is able to increase the oral bioavailability of docetaxel [11]. Furthermore, the safety of combined treatment of docetaxel plus OC144-093 was determined. In addition, whether genetic functional single nucleotide polymorphisms (SNPs) of MDR1 could be associated with the variability of docetaxel pharmacokinetics was also explored.

Patients and methods

Patient population

Patients for whom no standard therapy of proven benefit existed and who were considered to be able to benefit from treatment with docetaxel, e.g., advanced breast, gastric, esophagus, bladder or ovarian cancer, NSCLC and carcinoma of unknown primary site, were eligible for the study. Previous radiotherapy, chemotherapy or hormonal therapy was allowed, provided that the last treatment was at least 3 or 1 week respectively, prior to study entry. Eligibility criteria included a life expectancy of more than 3 months, acceptable bone marrow function (white blood cell count $>3.0\times10^9$ l^{-1}; platelets $>100\times10^9$ l^{-1}) and a WHO performance status ≤ 2. Patients were excluded if they suffered from uncontrolled infectious disease, bowel obstruction, neurologic disease, symptomatic brain or leptomeningeal metastases, or unresolved (grade 1 or more) toxicities of previous chemotherapy. Other exclusion criteria were concomitant use of MDR- and CYP3A-modulating drugs, such as Ca^+ entry blockers (verapamil, dihydropyridines), CsA or grapefruit juice, impaired renal function (serum creatinine >160 mmol l^{-1}, or clearance <50 ml min^{-1}), serum bilirubin >20 μmol l^{-1}, ASAT and ALAT more than 1.5 times the upper limit of normal (ULN), unless related to liver metastases, then more then three times ULN, serum albumin <25 g l^{-1}, and chronic use of H2-receptor antagonists or proton pump inhibitors. The study protocol was approved by the medical ethics committee of the Institute and all patients gave written informed consent.

Study design

Twelve patients were randomized to receive docetaxel on two occasions. In treatment arm A patients received 500 mg OC144-093 orally combined with docetaxel 100 mg orally administered as a drinking solution of the i.v. formulation of Taxotere, after which patients drank 100 ml tap water. The dose of docetaxel when combined with OC144-093 was chosen at 100 mg based on prior experience using the combination of docetaxel and CsA [17, 19]. Also docetaxel was given orally as 100 mg for safety reasons, because coadministration of a P-gp inhibitor and oral docetaxel might result in higher systemic exposure than docetaxel oral monotherapy. An oral dose of 500 mg OC144-093 was selected based on earlier studies [20]. Two weeks later patients received 100 mg docetaxel i.v. as a 1-h infusion, without OC144-093. In treatment arm B patients received the same treatment in the reverse order. Patients received oral OC144-093 followed 30 min later by oral docetaxel; however this time interval was altered to simultaneous administration after examination of the plasma docetaxel levels of the first six patients. If it was considered to be in the patient's best interest, docetaxel i.v. treatment was continued on a standard 3-weekly schedule of 100 mg m^{-2}. The first standard i.v. course of docetaxel was given 2 weeks after the end of treatment A or B.

Drug administration

The i.v. formulation of docetaxel (Taxotere; Rhône Aventis, Antony, France) was used for both i.v. and oral administration. The commercially available Taxotere formulation was diluted with 95% ethanol/water (13:87) to provide a 10 mg ml^{-1} docetaxel solution.

Patients were given 10 ml of this solution using a syringe after which they drank 100 ml of tap water. OC144-093 (ONT-093, IRIX Pharmaceuticals, Florence, SC; 500 mg free base equivalent) was administered as two hard gelatin capsules each containing 425 mg mesylate salt 30 min prior to docetaxel or at the same time. Patients were fasted from midnight the night before dosing until 1.5 h after drug intake, at which time they received a nonstandardized breakfast. Two hours before oral docetaxel administration, patients received 1 mg oral granisetron (Kytril; GlaxoSmithKline, London, UK) and 4 mg oral dexamethasone (Centrapharm) 4 mg. Dexamethasone administration was repeated after 12 h. For i.v. docetaxel treatment patients received standard i.v. therapy, two times 8 mg dexamethasone (Centrapharm), as per the institute's protocol.

Patient evaluation

Pretreatment evaluation included a complete medical history, physical examination and before each course an interim history including concomitant medications, toxicities, and performance status were registered. Blood chemistry, including serum electrolytes, liver and renal function, total protein and albumin levels and hematology were checked every week. Toxicity was evaluated on every course and graded according to National Cancer Institute Common Toxicity Criteria [10]. Dose-limiting toxicities were defined as grade 4 granulocytopenia lasting more than 5 days, grade 4 thrombocytopenia of any duration or any grade 3 or 4 nonhematologic toxicity except alopecia and untreated nausea and vomiting. Tumor measurements were performed when clinically indicated, but at least after the first two standard i.v. courses. Responses were evaluated according to the WHO criteria, however they were not a study endpoint.

Sample collection and analysis

Blood samples of two times 5-ml for pharmacokinetic analyses were collected during course 1 and 2 at 0 (predose), 15, 30, 45, 60, 75, 90 min and 2, 3, 4, 6, 8, 12, 24, 36 and 48 h after oral intake and one 5-ml blood sample was taken at the same time points after the start of the 1 h i.v. infusion given either during treatment course arm A or arm B.

Blood samples were centrifuged, plasma was separated, and samples were immediately stored at −20°C until analysis. Docetaxel and OC144-093 concentrations were determined using validated high-performance liquid chromatography assays [21]. From every patient 3 ml extra blood was taken before the start of the first course to determine pharmacogenetic polymorphisms of the MDR1 gene.

Pharmacokinetics

Noncompartmental pharmacokinetic methods were applied to process the results. For docetaxel and OC144-093 the AUC (area under the concentration–time curve) was calculated by the trapezoidal rule up to the last measured concentration–time point (AUC_t) and extrapolated to infinity using the terminal rate constant k_{el} ($AUC_{0-\infty}$) using WinNonlin (version 3.0, Pharsight Corporation, Calif.). The maximal drug concentration (C_{max}) and time to maximal drug concentration were obtained directly from the experimental data. Apparent bioavailability of oral docetaxel was calculated as the ratio of the $AUC_{0-\infty}$ after oral and after i.v. administration. Statistical analysis of the data was performed on the C_{max}, k_{el} and $AUC_{0-\infty}$ values, using a nonparametric unpaired Mann–Whitney test for testing the two groups, that is coadministration of the drugs and the group with 30 min between administrations. A signed ranks test was performed for the two different administration routes, that is for the i.v. and the oral data for C_{max}, $AUC_{0-\infty}$ and k_{el}. The a priori level of significance was $P < 0.05$.

Pharmacogenetics

MDR1 gene polymorphisms on exon 12 (C1236T), exon 21 (G2677T) and exon 26 (C3435T) were determined. Blood samples (3 ml) were taken before the start of treatment. Genomic DNA was isolated using the method of Boom et al. [2]. DNA was amplified by PCR according to the method of Kim et al. with modification [15] for exon 12 and 21 and the method of Hoffmeyer et al. [13] for exon 26. The PCR products were sequenced on a 3100-Avant (Applied Biosystems) and the polymorphisms were determined using Seqscape software (Applied Biosystems) [13, 15].

Results

A total of 12 patients were enrolled into the study. At study entry, the median age of the patients was 63 years (range 46–73 years) and the median WHO performance status was 1 (range 0–2). All patients were of Caucasian origin. The primary tumor types included bladder ($n = 2$), esophageal ($n = 1$), gastric ($n = 3$), breast ($n = 2$), NSCLC ($n = 2$) and ovarian ($n = 2$). All patients had received prior surgical therapy and chemotherapy; six of the patients had also received radiotherapy (Table 1).

Patient nos. 1–6 received docetaxel 30 min after intake of OC144-093. Patient nos. 7–12 received docetaxel and OC144-093 at the same time. Patient nos. 1, 4, 8, 9 and 12 were randomized to receive oral medication on the first treatment day followed by i.v. infusion on day 14. The other patients (nos. 2, 3, 5, 6, 10 and 11) received treatment in the reverse order.

Table 1 Patient characteristics

No. of patients	12
Sex	
Female	6
Male	6
Age (years)	
Median	63
Range	47–73
WHO performance status	
Median	1
Range	0–2
Tumor type	
Bladder carcinoma	2
Esophageal carcinoma	1
Gastric carcinoma	3
Breast carcinoma	2
NSCLC	2
Ovarian adenocarcinoma	2
Prior treatment	
Surgical therapy and chemotherapy	12
Surgical therapy, radiotherapy, and chemotherapy	6

Pharmacokinetics

Individual plasma pharmacokinetic parameters of orally and i.v. administered docetaxel are presented in Table 2. In Fig. 1, average plasma time concentrations of docetaxel administered i.v. and orally are shown. One patient did not receive oral treatment, because of worsening of pneumonia developed after i.v. treatment, during course 1. The apparent relative oral bioavailability of docetaxel was $26 \pm 8\%$. Oral docetaxel combined with oral OC144-093 resulted in a C_{max} of 415 ± 255 ng ml^{-1}, an $AUC_{0-\infty}$ of 844 ± 753 ng h ml^{-1} and k_{el} of 0.810 ± 0.296 h^{-1}. These values differed significantly from those following i.v. docetaxel which resulted in a C_{max} of 2124 ± 1054 ng ml^{-1}, an $AUC_{0-\infty}$ of 2571 ± 1598 ng h ml^{-1} and a k_{el} of 1.318 ± 0.785 h^{-1} ($P = 0.003$, $P = 0.006$, $P = 0.016$). The mean oral $AUC_{0-\infty}$ value in the patients who were randomized to be treated with oral medication at first was not significantly different from the mean oral $AUC_{0-\infty}$ in the patients who received oral treatment at the second occasion. The average C_{max}, $AUC_{0-\infty}$ and k_{el} interpatient (pharmacokinetic) data for i.v. docetaxel administration were in agreement with data from previous studies [17, 22].

Pharmacogenetics

MDR1 polymorphisms in exon 12 (C1236T), exon 21 (G2677T) and exon 26 (C3435T) were determined. One patient (no. 5) had a homozygous T/T allele expressed in exon 26 and the same patient had also in exon 12 and 21 homozygous SNPs. In our study, 8 of 12 patients (67%) had heterozygous T/C allele expression, and only 1 patient (8%) showed homozygosity.

Table 2 Main pharmacokinetic parameters of docetaxel after oral administration (100 mg combined with 500 mg OC144-093). The apparent bioavailability (F) was determined by dividing the $AUC_{0-\infty}$ following oral administration by the $AUC_{0-\infty}$ following i.v. administration

Cohort[a]	Patient	Docetaxel oral				Docetaxel i.v.				Apparent bioavailability F
		C_{max} (ng ml^{-1})	T_{max} (h)	$AUC_{0-\infty}$ (ng h ml^{-1})	k_{el} (h^{-1})	C_{max} (ng ml^{-1})	T_{max} (h)	$AUC_{0-\infty}$ (ng h ml^{-1})	k_{el} (h^{-1})	
A	1	123	0.58	187	0.9873	933	0.97	984	3.1367	0.19
B	2	917	1.58	1695	0.5836	4965	1.00	6923	0.7976	0.24
B	3	No data available[b]				1624	0.75	1937	0.9732	Not available
A	4	275	1.25	323	1.0773	1623	0.77	1564	2.0044	0.21
B	5	187	2.02	350	0.3902	1731	0.50	1882	1.3943	0.19
B	6	120	3.0	405	0.6632	1486	0.78	2292	0.6357	0.18
B	7	827	1.5	2654	0.5491	1908	0.77	2216	0.8528	1.20[c]
A	8	422	1.18	749	1.3339	2601	0.77	2905	1.7437	0.26
A	9	518	2.03	1103	1.1137	2871	0.75	2670	1.3174	0.41
B	10	460	0.55	460	0.7929	2281	0.50	1995	1.7972	0.23
B	11	235	0.83	327	0.8935	1226	0.77	1328	1.0473	0.25
A	12	481	1.25	1031	0.5266	2257	0.75	2658	0.1175	0.39
Number		11	11	11	11	12	12	12	12	10[c]
Mean		415*	1.25	844*	0.810	2124	0.77	2571	1.318	0.26
SD		255	2.5	753	0.296	1054	0.50	1598	0.785	0.08
Median		422	1.25	460	0.793	1820	0.77	2106	1.182	0.24
Range		797	2.45	2467	0.944	4032	0.50	5939	3.019	0.23

*$P < 0.01$ docetaxel oral compared with i.v.

[a]Group I (patient nos. 1–6) received docetaxel 30 min after intake of OC144-093, group II (patient nos. 7–12) received docetaxel and OC144-093 at the same time. Patient nos. 1, 4, 8, 9 and 12 were randomized to receive oral medication on the first treatment day followed by i.v. infusion on day 14 (cohort A). The other patients (nos. 2, 3, 5, 6, 10 and 11) received treatment in the reverse order (cohort B).

[b]Patient number 3 did not receive oral medication; therefore no oral data are available.

[c]The oral bioavailability of patient number 7 was omitted in the calculation. This value was an outlier, as this patient had a high apparent oral bioavailability, probably due to the disease, gastric adenocarcinoma, which was also metastasized to the paraesophageal lymph nodes and to the liver.

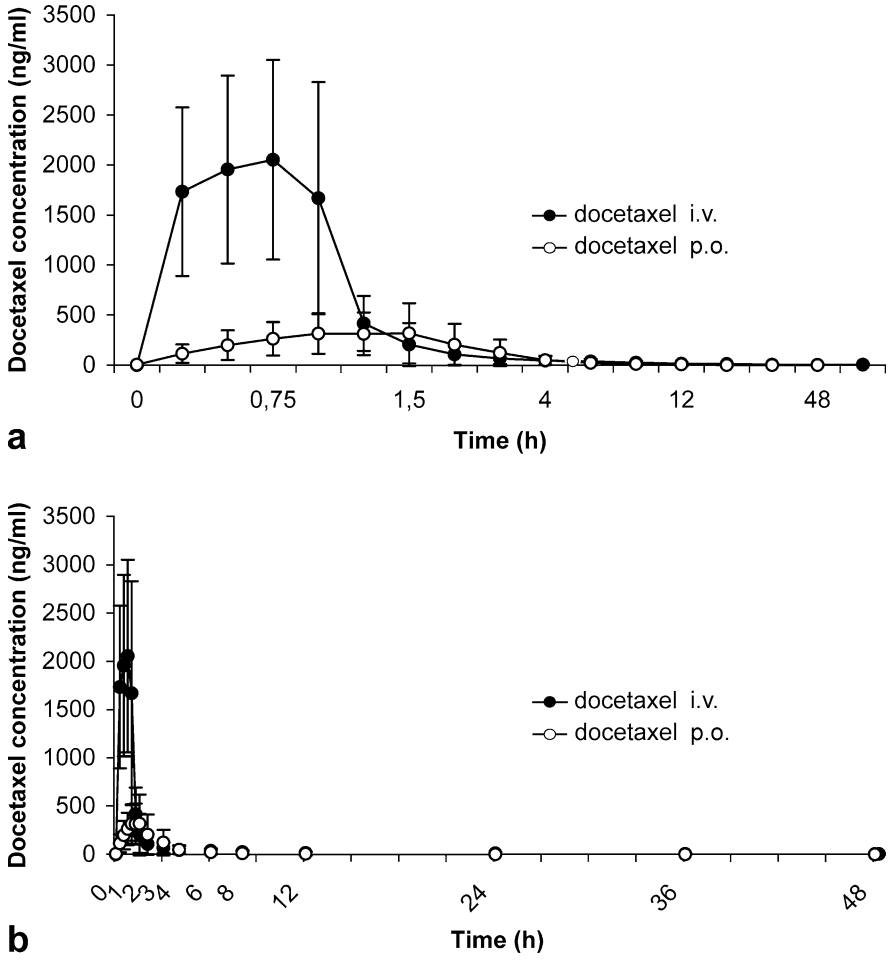

Fig. 1 **a** Average plasma time curve of docetaxel administered orally and intravenously. **b** Average plasma time curve of docetaxel administered orally and intravenously

Table 3 Toxicities following trial medication possibly, probably or definitely related to trial medication in cohort A and B

Toxicity	Number of patients with CTC	
	Grade 1 and 2	Grade 3
Gastrointestinal		
Anorexia		1
Diarrhea	1	2
Nausea	2	
Stomatitis	4	
Vomiting	1	
Neurologic	1	
Light-headedness	1	
Neuropathy/sensory	1	
Bone marrow toxicity		
Anemia	1	1
Neutropenia	1	1
Skin, redness of skin	1	
Alopecia	3	
Other		
Fatigue	1	
Malaise		2
Fever	1	
Flu-like symptoms	1	

No grade 4 toxicities were noted. No significant hematologic toxicity was observed

Safety results

Most of the adverse events possibly or probably related to OC144-093 and docetaxel, which included gastrointestinal symptoms, neutropenia and neurologic symptoms, were CTC grade 1 and 2 (Table 3). However, also CTC grade 3 related adverse events were reported: anorexia, malaise, anemia and neutropenia. Three patients developed a drug-related serious adverse event during administration of trial medication (i.v. and oral). These serious adverse events were all CTC grade 3 except for neutropenia, which was grade 4 combined with fever. The two other related serious adverse events were diarrhea combined with rectal blood loss and fever with malaise. Toxicities clearly associated with OC144-093 were not observed.

Discussion

The P-gp blocker OC144-093 was added to oral docetaxel to increase the systemic exposure of docetaxel and improve its oral bioavailability. A mean apparent

oral bioavailability of 26% was observed, which demonstrates a relevant increase in the uptake of docetaxel from the gastrointestinal tract in the presence of OC144-093. In earlier studies an oral bioavailability of docetaxel as monotherapy of only 8% was found when docetaxel was administered as an oral drinking solution without a P-gp blocker [19]. In that study, docetaxel was also combined with oral CsA in another cohort of patients, which resulted in an apparent oral bioavailability of $90 \pm 44\%$. The results of our study are consistent with OC144-093 increasing the bioavailability of docetaxel. [19]. Bardelmeijer et al. discussed the possibility that the increased systemic exposure, seen after coadministration of CsA and docetaxel is caused by inhibition of docetaxel metabolism in the gut wall and/or liver, as both CsA and docetaxel are CYP3A4 substrates [1, 24]. Here, we tried to enhance the systemic exposure of orally administered docetaxel through coadministration of a third-generation P-gp inhibitor, OC144-093. Third-generation inhibitors have high potency and selectivity for P-gp. No appreciable impact on the CYP3A4 drug metabolism and no clinically significant drug interactions with common chemotherapeutic agents have been observed with OC144-093 [26]. The more modest effects observed with OC144-093 are in accord with the more specific mechanism of action of OC144-093. Of note, patient no. 7 showed a high apparent oral bioavailability of 120%, which was due to the high area under the curve after administration of the oral regimen. This patient did not use, as far as we know, comedication that could have affected drug absorption or elimination. The results obtained in patient no. 7 were omitted from the calculation of the mean and median bioavailability as we considered the dataset an outlier.

The combination of oral docetaxel and OC144-093 showed a good safety profile. The major adverse events included mild gastrointestinal symptoms, neutropenia and neurologic symptoms. The toxicity profile is in agreement with that seen in an earlier phase II study, in which oral docetaxel was combined with CsA in metastatic breast cancer patients [17].

MDR1 polymorphisms in exon 12, 21 and 26 were determined to exclude the possibility that major deviations from the mean pharmacokinetic values could be attributed to genetic polymorphism in the expression or functional activity of P-gp. One patient (no. 5) had a homozygous T/T allele expressed in exon 26, while 8 of 12 patients (67%) had heterozygous T/C allele expression, and 3 patients (8%) had a homozygous C/C allele expression. Although several studies have been performed to elucidate the relationship between MDR polymorphism, focusing on exon 26 with drug kinetics, thus far no consensus has been reached. Hoffmeyer et al. described a significant impact of a polymorphism in exon 26 (C3435T) of MDR1 [13] on the pharmacokinetics of digoxin. In that study, C/C homozygosity was associated with more than twofold lower duodenal P-gp protein expression levels and fourfold higher digoxin plasma levels. It was expected that the uptake of orally administered P-gp substrates would be influenced in these individuals [9, 13, 14]. However, Drescher et al. found that C3435T is independent of digoxin plasma levels, and this is in line with the results of Gerloff et al. [6, 8], whereas Sakaeda et al. have described lower digoxin serum concentrations in subjects with a TT allele [23]. Cascorbi et al. have determined that the three most frequent SNPs in the Caucasian population are located in exons 12, 21 and 26 [3]. Studies in healthy volunteers have shown that these changes are in linkage disequilibrium [15].

In our study with a limited number of patients we were unable to identify a clear relationship between exon 26 polymorphism and the pharmacokinetics of docetaxel. The only patient with homozygous C3435T SNP was patient no. 5. This patient was also homozygous for G2677T on exon 21 and C1236T on exon 12. The pharmacokinetics observed in this patient were not different from those in the other patients. One may argue whether a difference could have been found as we combined oral docetaxel with OC144-093 with the aim of blocking P-gp completely. It would be of interest to determine these SNPs in future studies in larger patient cohorts and with orally administered drugs that are to some extent substrates for P-gp, but that do not need enhancement of bioavailability by coadministration of a P-gp blocker.

In summary, coadministration of OC144-093 enhanced oral bioavailability of docetaxel, although to a limited extent. The magnitude is considered insignificant for further development of this combination. However, our data are important in the interpretation of mechanisms involved in affecting oral bioavailability of docetaxel. Furthermore, combined oral treatment of docetaxel and OC144-093 had a good safety profile. Extended studies are needed to determine the influence of SNPs in MDR1 exon 12, 21 and 26 on the pharmacokinetics of orally and i.v. administered docetaxel.

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