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ORIGINAL ARTICLE

A pharmacokinetic and safety study of a novel polymeric paclitaxel formulation for oral application

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Abstract *Purpose*: To investigate the pharmacokinetics, safety, and tolerability of a new oral formulation of paclitaxel containing the polymer polyvinyl acetate phthalate in patients with advanced solid tumors. *Patients and methods*: A total of six patients received oral paclitaxel as single agent given as a single dose of 100 mg on day 1, oral paclitaxel 100 mg in combination with cyclosporin A (CsA) 10 mg/kg both given as a single dose on day 8, and i.v. paclitaxel (Taxol®) 100 mg as a 3-h infusion on day 15. *Results*: The AUC (mean ± standard deviation) values of paclitaxel after oral administration without CsA and with CsA were 476 ± 254 and 967 ± 779 ng/ml h, respectively. T_{max} was 4.0 ± 0.9 h after oral paclitaxel without CsA, and 6.0 ± 3.1 h after oral paclitaxel with CsA. The mean AUC after oral administration as single agent was 13% of the AUC after i.v. administration of paclitaxel, and increased to 26% after co-administration with CsA. No haematological toxicities were observed, and only mild (CTC-grade 1 and 2) non-hematological toxicities occurred after oral intake of paclitaxel with or without CsA. *Conclusion*: The AUC of the new polymeric paclitaxel formulation increased a factor 2 in combination with CsA, which confirms that CsA co-administration can also improve exposure to paclitaxel after oral administration of a polymeric formulation. Because of the delayed release of paclitaxel from this formulation, we hypothesize that a split-dose regimen of CsA where it is administered before and after paclitaxel administration will further increase the systemic exposure to paclitaxel up to therapeutic levels. The formulation was well tolerated at the dose of 100 mg without induction of severe toxicities.

Keywords Paclitaxel · Cremophor-free · Formulation · Pharmacokinetics · Patients

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Introduction

Paclitaxel (Taxol®) is a potent anticancer agent and has antitumor activity against a variety of solid tumors, especially against lung, breast, ovarian, and head and neck tumors [1, 2]. Paclitaxel is a taxane derivative that binds directly to tubulin, causing microtubular stabilization that arrests cell division in the G_2 and M phase of the cell cycle. Currently, Taxol® is only marketed as an intravenous (i.v.) formulation. Paclitaxel is poorly soluble in water, therefore, in the

marketed i.v. formulation it is formulated in a 1:1 combination of the solubilising agent polyoxyethylated caster oil [Cremophor® EL (CrEL)] and dehydrated ethanol. CrEL has been reported to be responsible for severe hypersensitivity reactions [3] and the non-linear pharmacokinetic behavior of i.v. administered paclitaxel [4–6].

Oral administration of paclitaxel is attractive, because it is more convenient for the patient than i.v. administration. Furthermore, oral paclitaxel administration may enable the development of treatment regimens resulting in plasma concentrations above a pharmacologically relevant level for more prolonged periods of time. Previous clinical studies using i.v. paclitaxel as 3-h infusion have suggested that, the time above a paclitaxel concentration of 0.05 μM (43 ng/ml) or 0.1 μM (85 ng/ml) is positively related to the activity of the drug [7, 8]. However, oral treatment with paclitaxel is severely hampered because of its low bioavailability, which is caused by several factors. Firstly, paclitaxel is a high affinity substrate for the efflux multidrug transporter *P*-glycoprotein (*P*-gp), which is highly expressed in the gastro-intestinal tract [9]. Secondly, paclitaxel undergoes first-pass metabolism by the gut and liver cytochrome P450 (CYP) enzymes (CYP 2C8 and CYP 3A4).

Cyclosporin A (CsA) is a potent inhibitor of both *P*-gp and CYP3A4. Preclinical and clinical studies carried out at our institute revealed that co-administration of oral CsA, resulted in a significantly enhanced systemic exposure to oral paclitaxel [10, 11]. As CsA is an inhibitor of *P*-gp and CYP3A4, both an increased absorption and reduced first pass effect may be responsible for the increased systemic exposure. We have shown previously that the effective dose of CsA resulting in a maximal *P*-gp inhibiting effect was reached at a dose of CsA of 10 mg/kg [12].

The i.v. paclitaxel formulation containing CrEL and ethanol was applied orally as a drinking solution diluted with water in previous studies [10, 13–17]. CrEL affect paclitaxel pharmacokinetics by limiting the absorption of paclitaxel from the intestine after oral administration by entrapment of paclitaxel in micelles, thereby reducing the availability of paclitaxel for uptake [4, 18–20]. Furthermore, the drinking solution has a disagreeable bitter taste. Although, many attempts have been undertaken to improve systemic exposure of orally administered paclitaxel, a favorable oral formulation with paclitaxel has not been found yet. The paclitaxel formulation investigated in the current study is a capsule containing the polymer polyvinyl acetate phthalate, but no CrEL and ethanol, possibly leading to an improved systemic exposure and better tolerability.

The purpose of this study was to investigate the pharmacokinetics, safety, and tolerability of an innovative dosage form containing a modified formulation of paclitaxel for oral application in patients with advanced solid tumors. The paclitaxel formulation was administered as a single dose or co-administered with CsA to explore systemic exposure to paclitaxel as a basis for oral therapy in patients with solid tumors.

Patients and methods

Patient population

Patients with a histologic or cytologic proof of cancer, for whom no standard therapy of proven benefit existed, were eligible for the study. Previous radiotherapy or chemotherapy other than taxoid therapy was allowed as long as the last treatment was at least 4 weeks prior to study entry and any resulting toxicities were resolved. Patients had to have acceptable hematological parameters (absolute neutrophil count (ANC) $\geq 1.5 \times 10^9$/l, and platelets $\geq 100 \times 10^9$/l), hepatic function (serum bilirubin ≤ 25 μmol/l; transaminases $\leq 2 \times$ UNL or $\leq 5 \times$ UNL in case of liver metastasis) and renal function (serum creatinine ≤ 160 μmol/l or clearance ≥ 50 ml/min), and a World Health Organization (WHO) performance status ≤ 2. Patients were excluded if they suffered from uncontrolled infectious disease, neurologic disease, bowel obstruction or symptomatic brain metastasis. Further exclusion criteria were concomitant use of known *P*-gp inhibitors 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

Six patients were enrolled in the study and received paclitaxel as a single dose at three different occasions with 7 days between each treatment in the following sequence: (1) p.o. paclitaxel 100 mg, (2) p.o. paclitaxel 100 mg in combination with p.o. CsA 10 mg/kg 30 min before the intake of paclitaxel, and (3) i.v. paclitaxel (Taxol®) 100 mg.

Paclitaxel (Apotex Research Inc., Toronto, ON, Canada) was administered orally as 4 capsules of 25 mg paclitaxel in polyvinyl acetate phthalate each. Cyclosporin A (Neoral®, Novartis, Basel, Switzerland) was administered as capsules of 100 mg each. For patients who had difficulty swallowing the large CsA capsules, use of the drinking solution of CsA (Neoral®

oral solution 100 mg/ml) was allowed instead of the CsA capsules. Paclitaxel [Taxol® i.v. solution 6 mg/ml (Bristol-Myers Squibb)] was administered as a 3-h infusion. The oral and i.v. dosages were administered early in the morning after a fasting period of at least 12 h. The CsA capsules were ingested with 150 ml of tap water and the paclitaxel capsules were taken together with 150 ml of tap water and a cracker. Only 1.5 h after the intake of paclitaxel were patients allowed to have a light breakfast. To prevent possible nausea, vomiting, and hypersensitivity reactions during both the treatment with oral paclitaxel and the combination of paclitaxel with CsA, patients were premedicated with oral granisetron (Kytril®) 1 mg 20 min before the intake of CsA, ranitidine (Zantac®) 50 mg p.o., and clemastine (Tavegil®) 1 mg p.o. 30 min before paclitaxel. To prevent hypersensitivity reactions, all i.v. occasions patients were premedicated with dexamethasone 20 mg orally 12 and 6 h prior to, granisetron 1 mg orally 30 min prior to, i.v. ranitidine 50 mg, and i.v. clemastine 1 mg shortly prior to paclitaxel administration. If considered in their best interest, patients continued on a 3-weekly schedule of i.v. paclitaxel at a dose of 175 mg/m^2.

Sample collection and analysis

Blood samples for pharmacokinetic analysis of paclitaxel were collected via an indwelling catheter in 5 ml heparinized tubes for each treatment. Following oral and i.v. administration samples were obtained predosing, 45 min, and 1.5, 2, 3, 3.5, 4, 4.5, 5, 6, 8, 10, 12, and 24 h after paclitaxel administration. Blood samples were centrifuged, and plasma was separated and immediately transferred into polypropylene tubes and stored at −20°C until analysis. Paclitaxel concentrations in plasma were determined using a validated high performance liquid chromatographic—tandem mass spectrometric (HPLC-MS/MS) method [21].

Pharmacokinetic analysis

Pharmacokinetic parameters were determined by non-compartmental analysis, using Winnonlin™ (version 5.0, Pharsight Corporation, CA, USA). The maximal paclitaxel concentration (C_{max}) and time to maximal concentration (T_{max}) were obtained directly from the experimental data. The terminal rate constant was determined by log-linear regression analysis of the terminal phase of the plasma concentration–time curve. The area under the plasma concentration time curve (AUC) was determined using the trapezoidal method up to the last measured concentration–time point and extrapolated to infinity ($AUC_{0-\infty}$) using the slope of the terminal rate of the logarithmic concentration versus time curve (λ_2). Furthermore, the terminal half-life ($t_{1/2}$) was calculated.

The apparent oral bioavailability (F) of paclitaxel was determined by the ratio of the $AUC_{0-\infty}$ after oral administration and $AUC_{0-\infty}$ after intravenous administration of paclitaxel.

Statistical analysis

The software package Statistical Product and Service Solutions (version 12.0.1 for Windows, SPSS Inc., Chicago, IL, USA) was used for statistical analysis. The a priori level of significance was $P = 0.05$. The paired t-test was applied on logarithmic-transformed values to make a comparison between the pharmacokinetic parameters of paclitaxel after the different study treatments.

Safety

Pretreatment evaluation included a complete medical history and thorough physical examination. Before each course, an interim history including concomitant medication taken, toxicities and performance status were registered and a physical examination was performed.

Non-haematological toxicities and hematology were checked prior to study entry (before the first treatment), 6 days after each oral treatment and 2 weeks after the i.v. treatment. The last assessment was done at the end of the study, which was 2 weeks after the i.v. treatment or after the patient's recovery from toxicities. To evaluate hepatic and renal function, the following parameters for blood chemistry were reported prior to study entry and at the end of study: alanine aminotransferase (ALT), aspartate aminotransferase (AST), gamma glutamyl transpherase (γ-GT), bilirubin, alkaline phosphatase (AP), albumin and serum creatinine. All toxicities observed were graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) version 3.0, 2003 (http://www.ctep.cancer.gov/forms/CTCAEv3.pdf).

Results

Patient characteristics

In total six patients were enrolled in the study. Patient characteristics are outlined in Table 1. All patients had a performance status ≤ 2. All patients received

paclitaxel orally as a single dose on day 1 (first treatment), paclitaxel orally as a single dose combined with oral CsA as a single dose on day 8 (second treatment), and i.v. paclitaxel as a 3-h infusion on day 15 (third and last study treatment). If considered in their best interest, patients continued on a 3 weekly schedule of i.v. paclitaxel at a dose of 175 mg/m^2.

Drug administration

The first patient was administered both CsA as oral drinking solution 100 mg/ml and as capsules, because he experienced problems with swallowing. He received CsA 800 mg; three capsules of 100 mg each and 5 ml of oral solution 100 mg/ml. The second and third patient were given only the oral solution of CsA 100 mg/ml because they had swallowing problems; CsA 760 mg was administered to the second patient as 7,6 ml of the oral solution 100 mg/ml, and the third patient was administered CsA 540 mg as 5,4 ml of the oral solution 100 mg/ml. All other patients ingested the CsA capsules.

Pharmacokinetic and statistical analysis

Figure 1 depicts the plasma pharmacokinetic profiles (semi-logarithmic scale) of paclitaxel after treatment with p.o. paclitaxel as single agent, p.o. paclitaxel in combination with CsA, and i.v. administered paclitaxel ($n = 6$). A relatively large interpatient variability in paclitaxel plasma concentrations was observed after both oral and i.v. administration of paclitaxel.

Figure 2 shows the paclitaxel plasma concentration versus time curves (linear scale) after p.o. paclitaxel given as single agent and p.o. paclitaxel co-administered with CsA. Oral paclitaxel in combination with CsA resulted in a significant increase in systemic exposure to paclitaxel compared to administration of paclitaxel alone.

Table 2 summarizes the pharmacokinetic parameters (T_{max}, C_{max}, $AUC_{0-\infty}$, and $t_{1/2}$) of p.o. paclitaxel without CsA (treatment 1), p.o. paclitaxel + CsA (treatment 2), and i.v. administered paclitaxel (treatment 3). The $AUC_{0-\infty}$ (mean ± standard deviation, SD) of paclitaxel after treatment 2 was 967 ± 779 ng/ml h, which was approximately twofold significantly higher ($P < 0.018$) than the mean $AUC_{0-\infty}$ of 476 ± 254 ng/ml h of paclitaxel after treatment 1. No statistically significant differences were found for T_{max}, C_{max}, and $t_{1/2}$ between treatment 1 and 2. Paclitaxel $AUC_{0-\infty}$ and C_{max} after p.o. administration were substantially lower than after i.v. administration. The apparent F (% coefficient of variation, %CV) for the new oral paclitaxel formulation was 13% (28%), and increased to 26% (54%) after co-administration with CsA. Plasma concentrations of paclitaxel above 0.05 and 0.1 μM were not reached in all patients. The mean duration of plasma levels above 0.05 μM was 3.0 ± 1.4 h in a total of five patients after oral paclitaxel alone and 7.6 ± 8.4 h in a total of four patients after oral paclitaxel with CsA ($P = 0.314$). In only two patients plasma concentrations above 0.1 μM were reached during 1.0–2.7 h after oral paclitaxel alone and 1.6–10.4 h after oral paclitaxel with CsA.

Figure 3 depicts the $AUC_{0-\infty}$ of paclitaxel for each individual patient after treatment with p.o. paclitaxel as single agent and after p.o. paclitaxel in combination with CsA. In five of the six patients co-administration of p.o. paclitaxel with CsA resulted in an increase in $AUC_{0-\infty}$ compared to treatment with p.o. paclitaxel alone.

Table 1 Patient characteristics

Number of patients	6
Male/female	3/3
Median age (range)	50 (35–61)
Tumor type	
Gastric carcinoma	1
Bladder	1
Urothelial cell carcinoma	1
Small cell lung cancer (SCLC)	1
Oesophageal carcinoma	1
Carcinoma of unknown primary site	1

Safety evaluation

In none of the patients any grade 1–4 hematological toxicity (anaemia, leukocytopenia, neutropenia, and thrombocytopenia) was observed 6 days after each oral treatment and 2 weeks after the first i.v. administration. Regarding blood chemistry no clinically significant changes were observed at study end in any of the parameters (see Table 3).

Table 4 summarizes the non-hematological toxicities that were observed 6 days after p.o. paclitaxel (treatment 1), p.o. paclitaxel combined with CsA (treatment 2), and 2 weeks after i.v. paclitaxel (treatment 3). Non-hematological toxicities were mild (CTC-grade 1 and 2) for both oral treatments. The capsules were well tolerated by the premedicated patients, and nausea and vomiting were not reported as drug-related adverse events, except for one patient who had nausea after treatment 2. Stomatitis was seen in one patient after all experimental treatments. Grade 2 fatigue was observed in two patients after oral treatment 2. In one patient constipation occurred after both oral treatments, as loss of appetite and grade 2 low back pain occurred after the

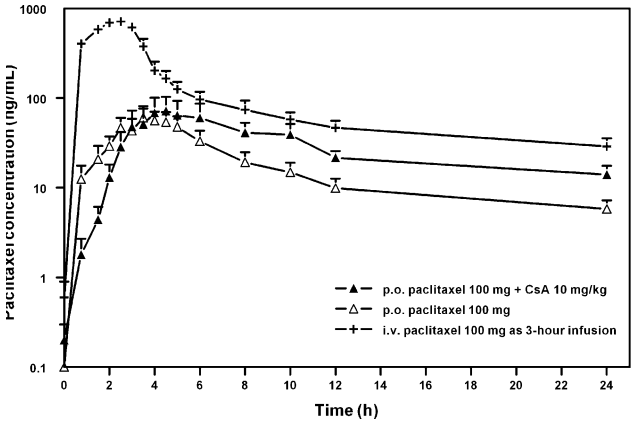

Fig. 1 Plasma concentration versus time curves of p.o. paclitaxel 100 mg, p.o. paclitaxel 100 mg + CsA 10 mg/kg, and i.v. paclitaxel 100 mg as 3-h infusion ($n = 6$). Data are represented as mean ± SEM on a semi-logarithmic scale

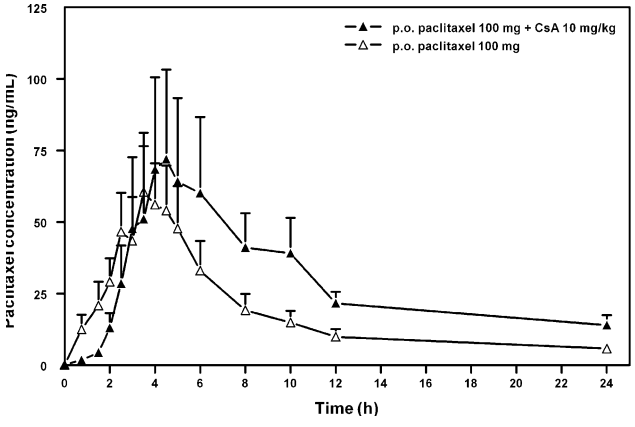

Fig. 2 Plasma concentration versus time curves of p.o. paclitaxel 100 mg and p.o. paclitaxel 100 mg + CsA 10 mg/kg ($n = 6$). Data are represented as mean ± SEM on a linear scale

second oral treatment. Only one patient developed fever, flushing, and sweating and grade 2 diarrhea after the first oral treatment. Neuropathy was reported in one patient after the second oral treatment, and another patient had a tingling feeling of the tongue and sensitive corners of the mouth after all three experimental treatments.

Discussion

In this study we have shown that the apparent bioavailability of the new Cremophor-free formulation of paclitaxel containing the polymer polyvinyl acetate phthalate was 13% after oral administration at a dose of 100 mg in patients with advanced solid tumors. When the novel paclitaxel formulation was given orally in combination with CsA 10 mg/kg, a *P*-gp and CYP3A4 inhibitor, an approximately two-fold increase in $AUC_{0-\infty}$ was achieved resulting in an apparent bioavailability of 26%. Previous studies showed that the orally applied i.v. Taxol® formulation containing CrEL and ethanol resulted in an $AUC_{0-\infty}$ of paclitaxel of 171 ng/ml h and an apparent bioavailability of only 6% compared to i.v. Taxol® administration, but CsA co-administration resulted in an eightfold increase of the $AUC_{0-\infty}$ to 1409 ng/ml h and an apparent bioavailability of 47% [8, 10]. Thus, oral administration of the new paclitaxel formulation without CsA resulted in a higher paclitaxel $AUC_{0-\infty}$ of 476 ng/ml h than was obtained after the orally applied i.v. formulation. However, the twofold increase in $AUC_{0-\infty}$ of paclitaxel (from 476 to 967 ng/ml h) after CsA co-administration in our current study was relatively low compared to the eightfold increase that was observed with the orally applied i.v. formulation of Meerum Terwogt et al. [10].

The term bioavailability, however, should be interpreted with caution due to the non-linear pharmacokinetics of i.v. paclitaxel caused by the presence of CrEL [4, 5]. Entrapment of paclitaxel in CrEL micelles in the

Table 2 Pharmacokinetic parameters of paclitaxel after p.o. paclitaxel (treatment 1), p.o. paclitaxel + CsA (treatment 2), and i.v. paclitaxel (treatment 3)

Parameter	Treatment 1	Treatment 2	Treatment 3
N	6	6	6
T_{max} (h)	4.0 (0.9)	6.0 (3.1)	NA
C_{max} (ng/ml)	73 (35)	79 (72)	726 (230)
$AUC_{0-\infty}$ (ng/ml h)	476 (254)	967 (779)	3,761 (1626)
$t_{1/2}$ (h)	9.4 (3.0)	10.0 (3.1)	14.9 (5.5)
%CV of $AUC_{0-\infty}$	53	81	43
Apparent F (%)	13	26	
%CV of F	28	54	
$T > 0.05$ μM	3.0 (1.4) ($n = 5$)	7.6 (8.4) ($n = 4$)	15.2 (8.4) ($n = 6$)
$T > 0.1$ μM	1.0–2.7 ($n = 2$)	1.6–10.4 ($n = 2$)	6.4 (2.9) ($n = 6$)

Data are represented as mean (± SD)

NA not applicable, *%CV* % coefficient of variation

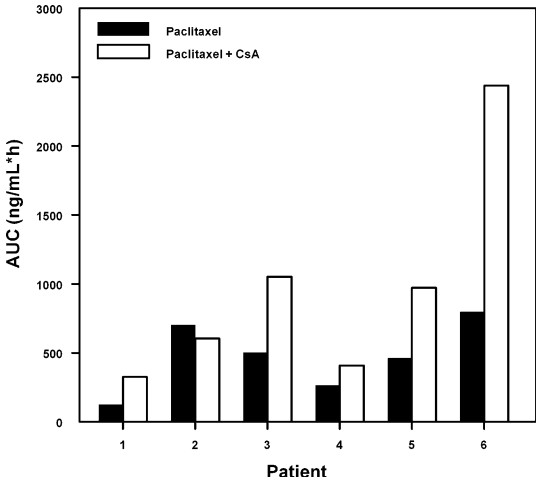

Fig. 3 Individual $AUC_{0-\infty}$ values after treatment with paclitaxel alone and paclitaxel co-administered with CsA

Table 3 Blood chemistry prior to study entry and at study end ($n = 6$)

Maximum severity NCI-CTC grade	CTC-grade	Prior to study entry	Study end
Liver			
γ-GT	1	2	1
	2		1
	3	2	2
AP	1	3	4
	2	1	
	3		1

central compartment causes a more than proportional increase in plasma paclitaxel concentrations with increasing doses. Studies in mice showed that these higher total drug levels in plasma did not result in higher drug levels in tissues [4]. In previous studies it was shown that CrEL is not absorbed after oral administration. This pseudo-non-linearity of i.v. paclitaxel has two important implications for the pharmacology of oral paclitaxel. Firstly, the oral bioavailability of paclitaxel, calculated by comparing the AUC values after oral and i.v. administration, will be underestimated as the affinity of paclitaxel for the plasma compartment is increased after i.v. administration due to the presence of CrEL in the central circulation. Secondly, the pseudo-non-linearity of i.v. paclitaxel implies that after oral administration, when CrEL is not present, plasma levels of paclitaxel represent a higher fraction of free drug, which will result in enhancement of the availability of paclitaxel for the (tumor) tissues [5]. Consequently, threshold values for the paclitaxel concentration established for i.v. paclitaxel [7, 8] can be different for oral administration of paclitaxel. Therefore, we did not use the duration of the paclitaxel plasma concentration above a certain level as a therapeutic endpoint. The pharmacokinetic parameters after i.v. paclitaxel 100 mg (treatment 3) were in line with previous observations [8, 17].

The new polymeric formulation of paclitaxel resulted in a higher T_{max} of 4.0 ± 0.9 h after p.o. paclitaxel alone and 6.0 ± 3.1 h after p.o. paclitaxel plus CsA

Table 4 Non-haematological toxicity profile for all three study treatments ($n = 6$). Toxicities were possibly, probably, or definitely related to study medication. Duration of observation is from start of study until 2 weeks after the first i.v. infusion

Maximum severity NCI-CTC grade	CTC grade[a]	p.o. treatment 1	p.o. treatment 2	i.v. treatment 3	Total
Gastrointestinal disorders					
Stomatitis	1	1	1	1	3
Low back pain	1	–	–	–	–
	2	–	1	–	1
Constipation	1	1	1	–	2
Nausea	1	–	1	–	1
Diarrhea	1	–	–	–	–
	2	1	–	–	1
General disorders and administration site conditions					
Fatigue	1	–	–	1	1
	2	–	2	1	3
Fever	1	1	–	–	1
Sweating	1	1	–	–	1
Flushing	1	1	–	–	1
Central nervous system and other pain disorders					
Neuropathy	1	–	1	1	2
Tingling feeling in tongue	1	1	1	1	3
Sensitive corners of mouth	1	1	1	1	3
Metabolism and nutrition disorders					
Loss of appetite	1	–	1	–	1

[a]No grade 3–4 toxicities were observed

compared to the orally applied i.v. formulation, which had a T_{max} of 2.4 ± 0.6 and 2.4 ± 0.8 h without and with CsA, respectively [10].

It has been shown that in patients who were administered paclitaxel in combination with CsA maximum concentrations of CsA were reached at approximately 1.6–3.3 h after intake [15]. Since the T_{max} values of paclitaxel after oral administration of the new formulation were above 3 h, we hypothesize that during the time period that paclitaxel was released from the formulation and taken up into the systemic circulation, already a large amount of the CsA had been absorbed and metabolized and relatively low concentrations of CsA were present at the site of uptake of paclitaxel. This may have caused less inhibition of *P*-gp in the gastro-intestinal tract leading to a less enhancing effect of CsA on paclitaxel uptake. Since we did not measure CsA concentrations, it remains, however, uncertain whether this was the case.

In summary, we demonstrated that the novel polymeric formulation of paclitaxel in polyvinyl acetate phthalate was well tolerated after oral administration at the given dose of 100 mg also when co-administered with CsA, without inducing severe toxicities. Regarding the almost uneventful oral administration of the 100 mg dose together with the relatively low $AUC_{0-\infty}$ after CsA co-administration, we suggest that new studies should be initiated with this new paclitaxel formulation to explore dose escalation and bi-daily administration in order to increase systemic exposure and to prolong exposure at therapeutic levels. Because of the delayed release profile of paclitaxel from this novel formulation, we hypothesize that a split-dose regimen in which CsA is both given before and after paclitaxel administration will further increase the systemic exposure of paclitaxel from this formulation.

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