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PHASE I STUDIES

Quantification of the pharmacokinetic-toxicodynamic relationship of oral docetaxel co-administered with ritonavir

Huixin Yu[1] · Julie M. Janssen[1] · Vincent A. de Weger[2] · Bastiaan Nuijen[1] · Rik E. Stuurman[1,3] · Serena Marchetti[2] · Jan H. M. Schellens[2,4,5] · Jos H. Beijnen[1,4,5] · Thomas P. C. Dorlo[1] · Alwin D. R. Huitema[1,6]

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Summary
Introduction Oral formulations of docetaxel have successfully been developed as an alternative for intravenous administration. Co-administration with the enzyme inhibitor ritonavir boosts the docetaxel plasma exposure. In dose-escalation trials, the maximum tolerated doses for two different dosing regimens were established and dose-limiting toxicities (DLTs) were recorded. The aim of current analysis was to develop a pharmacokinetic (PK)-toxicodynamic (TOX) model to quantify the relationship between docetaxel plasma exposure and DLTs. *Methods* A total of 85 patients was included in the current analysis, 18 patients showed a DLT in the four-week observation period. A PK-TOX model was developed and simulations based on the PK-TOX model were performed. *Results* The final PK-TOX model was characterized by an effect compartment representing the toxic effect of docetaxel, which was linked to the probability of developing a DLT. Simulations of once-weekly, once-daily 60 mg and once-weekly, twice-daily 30 mg followed by 20 mg of oral docetaxel suggested that 14% and 34% of patients, respectively, would have a probability >25% to develop a DLT in a four-week period. *Conclusions* A PK-TOX model was successfully developed. This model can be used to evaluate the probability of developing a DLT following treatment with oral docetaxel and ritonavir in different dosing regimens.

Keywords Docetaxel · Oral formulation · Ritonavir · Pharmacokinetics · Toxicodynamics

Introduction

Oral administration of docetaxel is currently in clinical development as a convenient alternative for intravenous administration [1]. Firstly, a solid dispersion capsule formulation (ModraDoc001) was developed which showed improved dissolution characteristics compared to crystalline docetaxel. Secondly, a further improved solid dispersion tablet formulation (ModraDoc006) was developed [2–4]. A major limitation for oral administration of docetaxel is low bioavailability due to transport by P-glycoprotein (Pgp) and metabolism by Cytochrome P450 3A4 (CYP3A4) [5–7]. In order to boost docetaxel exposure after oral administration, co-administration of ritonavir was added to the treatment regimen, which resulted in a strong boost of the oral bioavailability of docetaxel as a result of CYP3A4 inhibition [8, 9].

The ModraDoc capsules and tablets were studied in two dose-escalation trials with co-administration of ritonavir [10, 11]. The maximum tolerated doses (MTDs) of ModraDoc006/r (r refers to a 100 mg ritonavir tablet) were explored. Similar to intravenous docetaxel, neutropenia and fatigue were observed as dose-limiting toxicities (DLTs), but the most frequently observed DLTs were gastrointestinal toxicities, such as diarrhoea, vomiting, nausea, and anorexia [10–12].

Pharmacokinetic (PK)-pharmacodynamic (PD) modelling and simulation has proved to be useful to study relationships

✉ Julie M. Janssen
ju.janssen@nki.nl

1 Department of Pharmacy & Pharmacology, The Netherlands Cancer Institute, Plesmanlaan 121, 1066, CX Amsterdam, The Netherlands

2 Department of Clinical Pharmacology, The Netherlands Cancer Institute, Amsterdam, The Netherlands

3 Centre for Human Drug Research, Leiden, The Netherlands

4 Department of Medical Oncology, The Netherlands Cancer Institute, Amsterdam, The Netherlands

5 Utrecht Institute of Pharmaceutical Sciences, Utrecht University, Utrecht, The Netherlands

6 Department of Clinical Pharmacy, University Medical Center Utrecht, Utrecht University, Utrecht, The Netherlands

between PK and toxicodynamics (TOX) [13]. In PK-TOX models, the relationship between drug exposure and toxicity is quantified. These models can be used to further evaluate dosing regimens and to predict toxicity of alternative dosing regimens by performing simulation studies [14, 15].

The aims of the current study were: 1) to establish a PK-TOX model for oral docetaxel co-administered with ritonavir based on the accumulated data from two phase I clinical trials; 2) to optimise the dosing schedules of ModraDoc/r formulations and to support clinical drug development.

Methods

Clinical studies

ModraDoc capsules or tablets were given weekly once- or twice-daily in combination with ritonavir in two phase I studies in a classical 3 + 3 dose escalating scheme [10, 11]. DLTs were evaluated during the first treatment cycle (i.e. the first four weeks of treatment). In total, 85 patients were evaluable for DLT assessment, among which 50 patients received a weekly once-daily dose and 35 patients received a weekly twice-daily dose. The studies were approved by institutional review boards and independent ethics committees, and were carried out in accordance with the ethical principles of the Declaration of Helsinki. Informed consent was obtained from all individual patients participating in the studies. In total, 18 (21.2%) patients developed a DLT during the first treatment cycle, of which 11 patients showed a DLT within the first two weeks. Detailed information on the number of patients and DLTs included in the current analysis is shown in Table **1**.

Model development

Sequential modelling of PK and TOX was used to establish the full PK-TOX model [16]. Firstly, an integrated PK model of oral docetaxel and ritonavir was used in this analysis [17]. Ritonavir PK was described by a two-compartment model with first-order elimination and inverse gaussian absorption. The oral docetaxel PK was described by a two-compartment model with a transit compartment representing the metabolism of docetaxel in the liver. Docetaxel liver clearance was influenced by the individual predicted ritonavir concentrations. The individual parameter estimates of docetaxel and ritonavir from the final PK model were used as input in the subsequent PK-TOX modelling.

The probability of the occurrence of DLTs was estimated by logistic regression. Several measures for drug exposure, such as absolute dose, area under the plasma concentration-time curve until 48 h after dose (AUC_{0-48}) and cumulative AUC over the dosing interval in both the central and gastrointestinal compartment originating from the population PK model, were considered as predictors for TOX in the logistic regression model. An effect compartment model relating drug exposure in the effect compartment to the probability of DLT was also considered.

Model evaluation

The models were required to reach successful minimisation with plausible and precise parameter estimates. For hierarchical models, the significance level related to the difference of objective function values (dOFV) was defined as $p < 0.01$ (degree of freedom = 1, dOFV = −6.6).

Simulations

In the simulation study the following posterior outcome measures were evaluated: 1) the simulated probability of DLT was compared to the observed DLT incidence; 2) the time course of the probability of DLT was

Table 1 Overview of the information on the dose levels and dose-limiting toxicity included in the model development

	Once-daily dosing [11]		**Twice-daily dosing** [10]	
	ModraDoc001 capsule	ModraDoc006 tablet	ModraDoc001 capsule	ModraDoc006 tablet
ModraDoc dose levels (mg/day)	40, 60, 80	60, 80	40, 60, 80	40, 50, 60
Ritonavir dose levels (mg/day)	100	100	200	100, 200
Number of patients				
total	37	13	17	18
Dose-limiting toxicity	9		9	
Dose-limiting toxicity at week 1	1		1	
Dose-limiting toxicity at week 2	5		4	
Dose-limiting toxicity at week 3	2		2	
Dose-limiting toxicity at week 4	1		2	

investigated for both once-daily and twice-daily regimens; 3) the differences in the probability of DLT were shown between once-daily and twice-daily regimens.

Simulations of the probability of DLT were performed based on simulations for 1000 patients per dosing regimen for a treatment period of four weeks using the final PK-TOX model. The ModraDoc006 tablet was assumed for all simulations, since this is the formulation of choice for future clinical trials. The simulated dosing regimens included: weekly once-daily 60 mg and 80 mg; weekly twice-daily 20 mg (20/20 mg), 30 mg followed by 20 mg (30/20 mg), and 30 mg (30/30 mg). A 100 mg ritonavir tablet was co-administered at each drug intake. The commonly defined MTD in rule-based designs of dose-escalation studies is the dose at which the probability of DLT is <33%. Therefore, this value was used as a cut-off value in the simulations to compare with the observed DLT incidences. In addition, model-based designs of dose-escalation studies typically use a pre-defined target toxicity rate of 10–33% [18]. Accordingly, an additional target probability of 25% for DLT was chosen to further evaluate the recommended phase II dose.

Software

Model estimations and simulations were performed using NONMEM (version 7.3.0, ICON Development Solutions, Ellicott City, MD, USA) together with a gfortran compiler and Pirana was used as graphical interface [19, 20]. For model estimation, the second-order conditional (Laplacian) estimation method was used. R (version 3.0.3) was used for preprocessing of the data, plotting and calculating the significance of the DLT predictor [21].

Results

Model development

In total, 18 DLTs were observed (Table 1), most of which were gastro-intestinal related (nausea, diarrhoea, vomiting and mucositis). The structure of the final PK-TOX model that best described the occurrence of DLTs in patients treated with ModraDoc/r is shown in Fig. 1. Final parameter estimates for this model are listed in Table 2.

Inclusion of cumulative docetaxel AUC until the end of the dosing interval as a predictor for the probability of DLT did not result in a significant improvement of the PK-TOX model. Particularly, the probability of DLT in weeks 3 and 4 of the DLT period was overpredicted. Therefore, an effect compartment representing the site of harmful effect was introduced. The input of this effect compartment was the docetaxel concentration in the central compartment, the output was modelled as a first order recovery rate. Subsequently, the log-transformed docetaxel amount in the effect compartment ($A_{effect,doc}$) was related to the probability of DLT. $A_{effect,doc}$ was a significant predictor of the probability of DLT ($p < 0.01$). Compared to the model using the cumulative AUC as a predictor for DLT, the final model showed a substantially improved fit (dOFV of −10.6 points). Introduction of inter-individual variability (IIV) did not improve model fit and was thus not included in the model.

The differential equation of the effect compartment and the logistic regression function are shown in Eq. 1–3:

$$\frac{dA_{effect,doc}}{dt} = C_{central,doc} - KR \cdot A_{effect,doc} \quad (1)$$

$$t = B_0 + B_1 \cdot \log\left(A_{effect,doc}\right) \quad (2)$$

$$\Pr = \frac{\exp(t)}{1 + \exp(t)} \quad (3)$$

where $A_{effect,doc}$ represents the amount in the docetaxel effect compartment, $C_{central,doc}$ represents the concentration of docetaxel in the central compartment, KR represents the recovery rate of the effect compartment, t is a linear function of log-transformed $A_{effect,doc}$, with B_0 and B_1 as intercept and slope, respectively, Pr is the logistic function representing the probability of DLT.

The KR was estimated as 0.21 day^{-1} (RSE 39%), translating into a recovery half-life of 3.3 days. Based on the estimated B_0 and B_1 (Table 2), the $A_{effect,doc}$ when Pr is 33% and 25%, respectively, was calculated as 511 μg·h/L and 435 μg·h/L. Figure 2 shows that the predicted Pr curve with corresponding $A_{effect,doc}$ provides an adequate description of the observed DLTs. 98% of patients without DLT, and 81% patients with DLT have a Pr < 33% during the first treatment cycle; 96% of patients without DLT, and 69% patients with DLT have a Pr < 25%. The final PK-TOX minimised successfully and the parameters were estimated with acceptable precision (RSE < 40%, Table 2).

Simulations

Figure 3 shows the simulated Pr with a cut-off of 33% versus the observed DLT incidence in patients treated with the ModraDoc006 tablet. For the weekly once-daily 60 mg dose-level, 10% of simulated patients showed Pr > 33%, while one DLT was observed in 9 patients (1/9); for the once-daily 80 mg dose-level, 19% of simulated patients had a Pr > 33%, while 2 DLTs were observed in 4 patients (2/4). For the weekly twice-daily 20/20 mg dose-level, 18% of patients had a Pr > 33% while zero DLTs were observed in 3 patients (0/3); for the 30/20 mg dose-level, the simulated fraction of patients with a Pr > 33% increased to 27%, while one DLT was observed in nine patients (1/9); for the 30/30 mg dose-

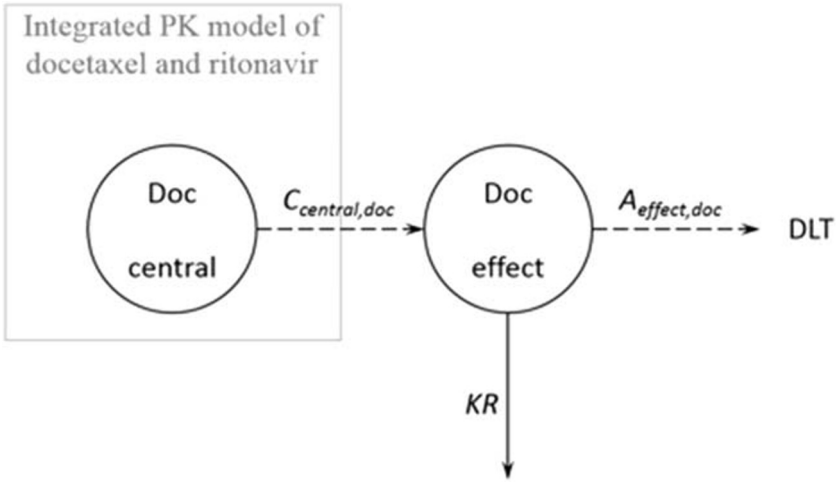

Fig. 1 Schematic representation of the pharmacokinetic-toxicodynamic model for oral docetaxel. $A_{effect,doc}$, amount in the effect compartment of docetaxel; $C_{central,doc}$, concentration levels of docetaxel in central compartment; DLT, dose-limiting toxicity; Doc, docetaxel; *KR*, recovery rate constant

level, the simulated fraction of patients with Pr > 33% further increased to 37%, while two DLTs were observed in six patients (2/6).

In order to visualise the change of the $A_{effect,doc}$ over time, Fig. 4 shows the median and 10%–90% percentile of simulated $A_{effect,doc}$ for weekly once-daily 60 mg and weekly twice-daily 30/20 mg dosing for a period of four weeks. In both dosing regimens, the $A_{effect,doc}$ increased within the first two weeks, followed by a steady-state situation (with limited further accumulation in $A_{effect,doc}$ of 3% and 5% for once-daily dose and twice-daily dose, respectively). By week 4, the median of $A_{effect,doc}$ for weekly twice-daily dosing was 53% higher than for once-daily dosing, which translated into a higher Pr for this regimen. In the twice-daily dosing regimen, ritonavir was also dosed twice-daily instead of once-daily. This resulted in higher docetaxel plasma concentrations, and higher $A_{effect,doc}$ despite the slightly lower total daily dose.

Quantitatively, Fig. 5 shows the cumulative percentage of simulated patients with a Pr > 25% at each week for once-daily 60 mg and twice-daily 30/20 mg doses. The newly occurred incidence of DLTs lowered gradually over treatment time. The majority of DLTs, i.e. 67% for 60 mg and 73% for 30/20 mg, developed within the first two weeks. This was supported by the dynamic change in $A_{effect,doc}$, and the DLTs observed in these weeks (Table 1).

Table 2 Parameter estimates of pharmacokinetic-toxicodynamic model of oral docetaxel co-administered with ritonavir

Parameters	Units	Estimate	RSE (%)
Recovery rate constant (*KR*)	day^{-1}	0.21	39
Intercept (B_0)	–	−15.8	23
Slope (B_1)	–	2.42	22

Abbreviations: RSE, relative standard error

Discussion

A PK-TOX model relating the docetaxel exposure following oral administration of two ModraDoc formulations to the probability of DLT was developed. This model was developed using data from two dose-escalation trials in which only a few patients were evaluated at each dose level. Therefore, the different types of DLTs were grouped into one variable and analysed as such. Furthermore, docetaxel PK showed wide inter-patient variability [17]. These two issues pose challenges for dose finding studies of oral docetaxel. The currently developed model enabled the in silico evaluation of the different dose-levels that were tested in clinical trials.

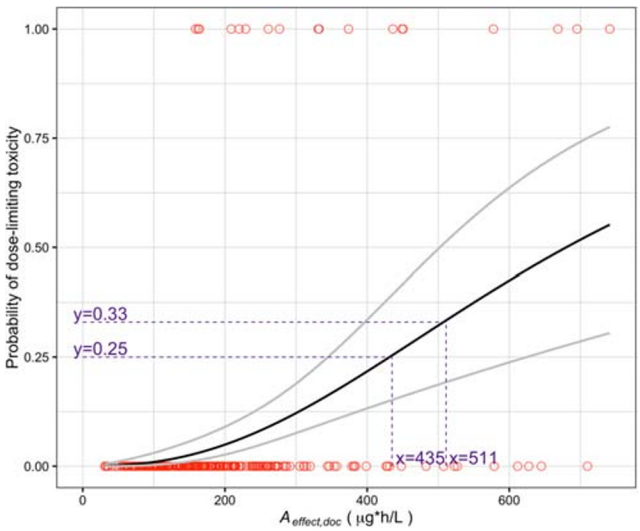

Fig. 2 Probability of dose-limiting toxicity predicted by the amount in the effect compartment of docetaxel. $A_{effect,doc}$, amount in the effect compartment of docetaxel. The solid black curve represents the Pr of dose-limiting toxicity (DLT) predicted by $A_{effect,doc}$; the solid grey lines represent the 95% confidence interval; the empty circles present the observed DLT events corresponding to $A_{effect,doc}$; the dashed lines show the $A_{effect,doc}$ when the Pr is predicted at 0.25 and 0.33

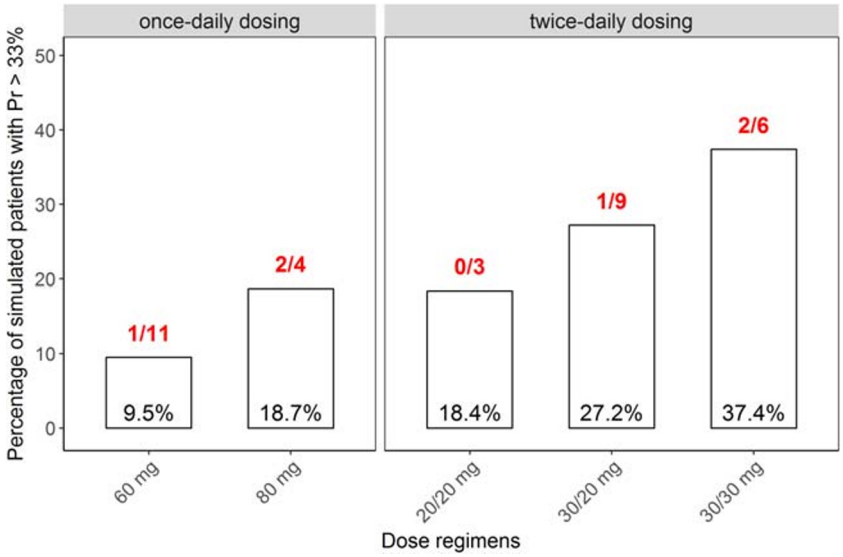

Fig. 3 Percentage of simulated patients with >33% of probability of dose-limiting toxicity at different ModraDoc006/r (100 mg ritonavir with every ModraDoc006 administration) dose regimens and the observed incidence of dose-limiting toxicity. Pr, probability of dose-limiting toxicity. The bars and the numbers inside the bars show the percentage of simulated patients with Pr > 33% at different dose regimens; the numbers above the bars indicate the observed number of patients with dose-limiting toxicity out of the total evaluable patients treated at that dose

The model can additionally be used to evaluate alternative dosing regimens and to predict DLTs that might be observed in future clinical trials, although extrapolations outside the conditions on which the model was developed should be interpreted with caution. It should additionally be noted that the docetaxel PK is characterized by large IIV. This could result in differences in response between individual patients.

The $A_{effect,doc}$ proved to predict the probability of DLT better than cumulative docetaxel AUC in plasma, cumulative dose and local exposure in the gastrointestinal tract. In Fig. 4, it can be seen that the amount in the effect compartment, representing hypothetical site of the harmful effect, reached steady-state at approximately 2 weeks after start of treatment and accordingly, the probability of DLT reached steady-state at the same time. This is in agreement with the clinical observation that 70% of DLTs occurred within the first two weeks. The recovery half-life of DLT was estimated at 3.3 days, with relatively good precision given the limited dataset. In the final model, an additional direct effect of ritonavir exposure on the probability of DLT was not included. Ritonavir was administered at a relatively low dose in the clinical studies that were included in our analysis compared to the application in the treatment of human immunodeficiency virus (HIV). Patients with HIV are treated with ritonavir in a continuous twice-daily 600 mg regimen without major gastrointestinal toxicities. We therefore assumed that the DLTs observed in our study were mainly caused by docetaxel exposure.

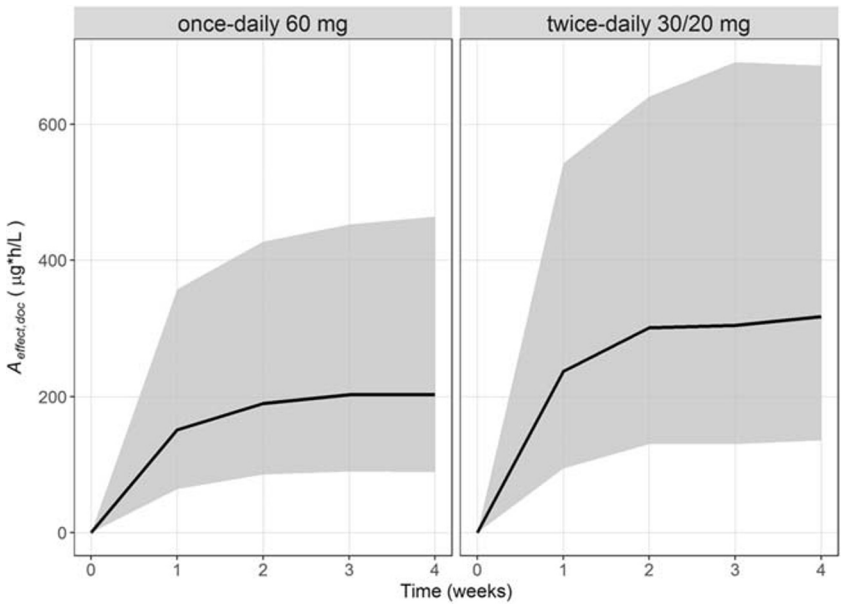

Fig. 4 Simulated amount in the effect compartment of docetaxel over four weeks at weekly once-daily and weekly twice-daily dose regimens ($n = 1000$). $A_{effect,doc}$, amount in the effect compartment of docetaxel. The solid curve represents the simulated median of $A_{effect,doc}$ over time; the grey areas show the simulated $A_{effect,doc}$ between 10% and 90% percentiles

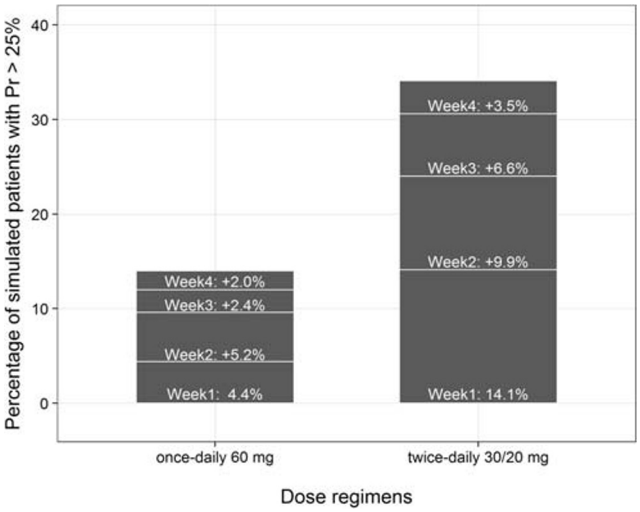

Fig. 5 Cumulative percentage of simulated patients with >25% of probability of dose-limiting toxicity at each treatment week with once-daily and twice-daily dose regimens ($n = 1000$). Pr, probability of dose-limiting toxicity. This figure shows the cumulative percentage of patients with Pr > 25%. The increment of patients at each week was indicated. In total, 14% of patients receiving once-daily 60 mg, and 34.1% of patients receiving twice-daily 30/20 mg of docetaxel with Pr > 25%

The simulations with the PK-TOX model supported the MTDs found in dose-escalation trials. Among the evaluated dose regimens, the MTD of interest for ModraDoc006/r for the weekly once-daily dose was 60 mg, and for the twice-daily dose it was 30/20 mg (both regimens in combination with 100 mg ritonavir). For once-daily dose regimens, the model simulation agreed with the percentage of DLTs that occurred at 60 mg (9.5% vs. 1/9), but suggested a much lower incidence of DLTs at 80 mg (19% vs. 2/4), which is lower than the model predicted Pr at the 30/20 mg twice daily regimen. For twice-daily dose regimens, the simulations were in line with the findings for 20/20 mg (18% vs. 0/3) and 30/30 mg (37% vs. 2/6), while indicated a slightly higher incidence of DLTs at 30/20 mg (27% vs. 1/9). This inconsistency can be explained by the low number of patients that were included in these dose levels. Therefore, this comparison should be interpreted with caution.

Conclusion

A PK-TOX model was developed for the prediction of the probability of DLTs for oral docetaxel co-administered with ritonavir. Simulations using the final PK-TOX model suggested that the model adequately predicted the DLTs that were observed in the phase I trials. Therefore, this model is suitable to be used to predict the toxicity of dosing regimens for future phase II trials. In addition, data from these future trials can be used to validate the performance of the here proposed PK-TOX model.

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Compliance with ethical standards

Conflict of interest BN, JB and JS are inventors and hold a patent on oral ModraDoc formulations. JB and JS are part-time employees and shareholders in Modra Pharmaceuticals, a spinout company developing oral taxane formulations. HY, JJ, VW, RS, SM, TD and AH declare that they have no conflict of interest.

Ethical approval All procedures performed in the studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed consent Informed consent was obtained from all individual participants included in the clinical studies.

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