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Original Research

A dose-escalation study of bi-daily once weekly oral docetaxel either as ModraDoc001 or ModraDoc006 combined with ritonavir

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Abstract ***Introduction:*** Two solid dispersions of docetaxel (denoted ModraDoc001 capsule and ModraDoc006 tablet (both 10 mg)) were co-administered with 100 mg ritonavir (/r) and investigated in a bi-daily once weekly (BIDW) schedule. Safety, maximum tolerated dose (MTD), pharmacokinetics (PK) and preliminary activity were explored.
Methods: Adult patients with metastatic solid tumours were included in two dose-escalation arms. PK sampling was performed during the first week and the second or third week. Safety was evaluated using US National Cancer Institute's Common Terminology Criteria for Adverse Events (NCI-CTCAE) version 3.0. Antitumour activity was assessed every 6 weeks according to Response Evaluation Criteria in Solid Tumours (RECIST) version 1.0.
Results: ModraDoc001 capsule/r and ModraDoc006 tablet/r were administered to 17 and 28 patients, respectively. The most common adverse events were nausea, vomiting, diarrhoea and

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fatigue, mostly of grade 1–2 severity. Grade 3/4 neutropenia/neutropenic fever was observed in 2 patients (4%). The MTD was determined as 20/20 mg ModraDoc001/r and 30/20 mg ModraDoc006/r (morning/afternoon dose) once weekly. The mean area under the plasma concentration–time curve (AUC_{0-48}) ± standard deviation at the MTD for ModraDoc001/r and ModraDoc006/r were 686 ± 388 ng/ml*h and 1126 ± 382 ng/ml*h, respectively. Five partial responses were reported as best response to treatment.

Conclusion: Oral administration of BIDW ModraDoc001/r or ModraDoc006/r is feasible. The once weekly 30/20 mg ModraDoc006 tablet/r dose-level was selected for future clinical development. Antitumour activity is promising.

1. Introduction

The anticancer agent docetaxel has proven antitumour activity and has been approved for the treatment of advanced solid tumours at an intravenous (iv) dose of 75 mg/m^2 or 100 mg/m^2 every 3 weeks [1].

Oral administration of taxanes is hampered by two factors: (1) poor water solubility and (2) high first-pass effect due to high affinity for drug transporters (e.g. P-glycoprotein (P-gp), multidrug resistance-associated protein 2 (MRP2)) and metabolism by the cytochrome P450 enzyme (CYP) CYP3A4, all abundantly present in the intestine and the liver [2]. The poor water solubility has been improved by the development of two solid dispersion formulations for oral use ModraDoc001 capsule (10 mg docetaxel, freeze dried) and the ModraDoc006 tablet (10 mg docetaxel, spray dried) [3,4]. The first pass-effect of docetaxel can be decreased by co-administration of an inhibitor of P-gp and/or CYP3A4 [3,5,6]. The protease inhibitor ritonavir could be an ideal booster drug as it is a strong inhibitor of CYP3A4 and a moderate inhibitor of P-glycoprotein (P-gp). Furthermore, it has been used for many years as a booster drug to increase plasma levels of other protease inhibitors [7].

The aim of the current study was to investigate safety and feasibility of the co-administration of oral docetaxel as ModraDoc001 capsule or as ModraDoc006 tablet, both in combination with ritonavir in a bi-daily once weekly (BIDW) schedule. Secondary objectives included pharmacokinetics (PK) and preliminary antitumour activity.

2. Patients and methods

2.1. Study design and treatment schedule

In this phase I, open-label, dose-escalation study two oral docetaxel formulations, ModraDoc001 capsule [3] and ModraDoc006 tablet [4] were investigated. Dosing of patients occurred in a BIDW schedule. A dose of 100 mg ritonavir (Norvir®, Abbott, Illinois, United States of America (USA)) was co-administered with ModraDoc formulations. Study drug administration occurred in a fasted condition (2 h prior and 1 h after administration). The dose-levels investigated are presented in Fig. 1.

The study started with dose-escalation with the ModraDoc001 capsule formulation, starting from a BIDW 40/40 mg (morning/afternoon dose) ModraDoc001 capsule with BIDW 100 mg ritonavir (r) (ModraDoc001 capsule/r). The starting dose was based on the results of another phase I trial exploring a once daily-once weekly (QW) administration of ModraDoc001 capsule/r [8]. However, the starting dose proved to be intolerable, due to dose-limiting toxicities (DLTs), after which a dose de-escalation was applied until the MTD was reached.

Subsequently, the ModraDoc006 tablet formulation became available for clinical testing and was implemented in a new dose-escalation cohort. The starting dose for this cohort corresponded to the MTD observed for the capsule formulation: BIDW 20/20 mg ModraDoc006 tablet with BIDW 100 mg ritonavir (ModraDoc006 tablet/r).

The BIDW administrations of study drugs were performed with a 7–12 h interval. Premedication consisted of 1 mg granisetron 1 h prior to both administrations. If patients did not experience nausea or vomiting during the first few weeks of treatment, administration of granisetron was omitted after week 3. Patients were allowed to continue study treatment until disease progression or intolerable toxicity.

Dose-escalation in both cohorts was performed according to a classic 3 + 3 design [9]. Patients who received at least one dose of study drug were considered evaluable for safety. The DLT period was defined as the first 4 weeks of treatment. Patients who did not complete the first 4 weeks of treatment due to reasons not related to ModraDoc/r toxicity were replaced. The MTD was expanded to a maximum of 12 patients.

DLT was defined as any of the following events occurring within the first 4 weeks of treatment and considered to be possibly, probably or definitely related to ModraDoc/r: grade 3 or 4 non-haematological

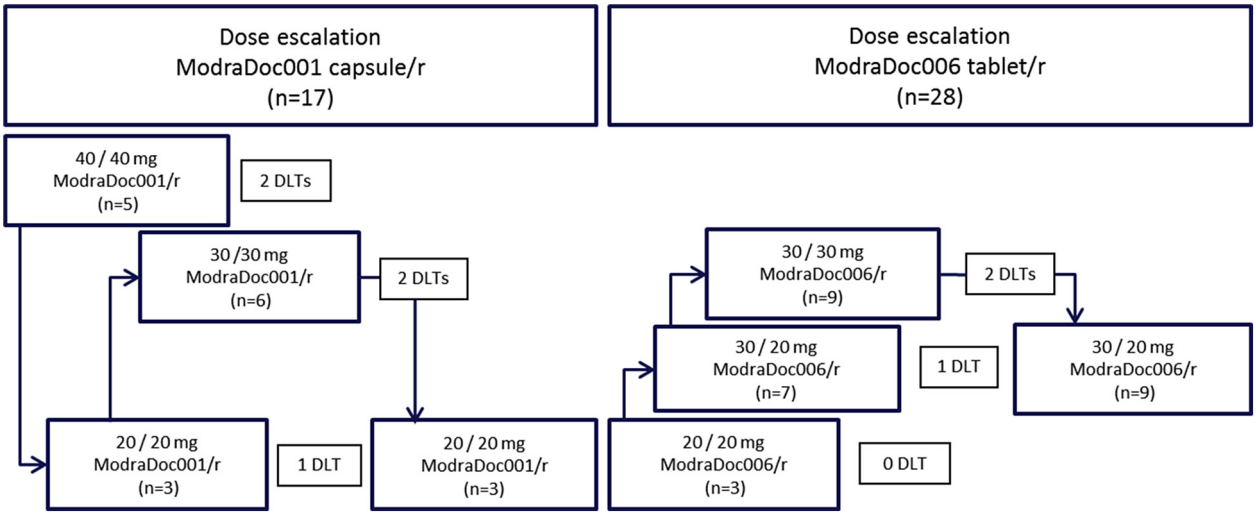

Fig. 1. Dose-escalation as performed for ModraDoc001 and ModraDoc006; n = number of patients included, r = ritonavir, DLT = dose-limiting toxicity, BIDW = bi-daily weekly, QW = once weekly.

toxicity, grade 3 and 4 nausea, vomiting and/or diarrhoea despite maximum support, grade 4 thrombocytopenia or grade 4 neutropenia for more than 7 consecutive days, febrile neutropenia and/or inability to begin the next course of treatment within 7 days of scheduled dosing due to toxicity other than stated above.

2.2. Patient eligibility

Adult patients with advanced solid tumours and World Health Organization (WHO) performance status (PS) of $\leq$2 and adequate bone marrow, renal and hepatic functions were included. The use of concomitant medication being a strong P-gp or CYP3A4 inhibitor was not allowed. Patients with symptomatic cerebral or leptomeningeal metastases were also excluded. The study protocol was approved by the Medical Ethical Committee of the Netherlands Cancer Institute and all patients had to provide written informed consent prior to start of study procedures. The study was registered in clinicaltrial.gov under identifier: NCT01173913.

2.3. Study procedures

A complete medical history including concomitant medication, physical examination, laboratory evaluation and a radiological tumour assessment were performed at baseline. Patients were seen weekly at the outpatient clinic during the first 6 weeks of treatment and subsequently every 2 weeks. Adverse events (AEs) were collected according to the National Cancer Institute's Common Terminology Criteria for AEs version 3.0 (NCI-CTCAE v3.0) [10]. tumour response evaluation was performed every 6 weeks according to Response Evaluation Criteria in Solid Tumour (RECIST) version 1.0 [11].

2.4. Pharmacokinetics

Pharmacokinetic (PK) blood sampling was performed on day 1 and 15 of treatment for the capsule formulations and on day 1 and 8 for the tablet formulation. Samples were drawn pre-dose, 0.5, 1, 1.5, 2, 3, 4, 6, 7, 7.5, 8, 8.5, 9, 10, 11, 24 and 48 h after the first administration. The second administration of the study drug was performed 7 h after the first administration. Samples were collected in lithium heparin tubes of 4 ml and centrifuged within 1 h at 1500 g, for 10 min at 4 °C. Plasma was stored in a pre-labelled 2 ml eppendorf tubes at −20 °C until quantification. Docetaxel concentrations were determined in plasma by a liquid chromatography coupled with tandem mass spectrometry (LC-MS/MS) method as described by Hendrikx *et al.* [12]. Stable isotopically labelled docetaxel was used as internal standard. The lower limit of quantification of the assay was 0.5 ng/ml docetaxel. The assay fulfills current US Food and Drug Administration (US FDA) guidelines for bioanalytical validation [13].

2.5. Data analysis

The individual non-compartmental pharmacokinetic parameters were determined using validated scripts in the R software package (version 3.01) [14]. The mean, standard deviation (SDev) and coefficient of variation (CV) for the following PK parameters were calculated: maximum concentration (C_{max}) after the first and second dose of oral docetaxel (C_{max} 1 and C_{max} 2), time to reach C_{max} 1 and 2 (T_{max} 1 and 2, respectively), the area under the plasma concentration−time curve between t = 0 and the last PK time point at 48 h (AUC_{0-48h}), and if possible with extrapolation to infinity (AUC_{0-inf}) and the terminal half-life ($t_{1/2}$).

3. Results

3.1. Patients characteristics

Table 1 shows the characteristics of the included patients. In the dose-escalation cohort of the ModraDoc001 capsule, a total of 17 patients were enrolled, 9 (53%) male and 8 (47%) female patients. The median age was 60 years (range 41–77). The majority of patients had a WHO PS $\leq$ 1 (94%). All patients had received prior chemotherapy, and 53% and 41% had received prior radiotherapy and/or surgery, respectively (Table 1). Patients were treated at three dose-levels ranging from BIDW 20/20 mg ModraDoc001/r to BIDW 40/40 mg ModraDoc001/r (Fig. 1).

In the dose-escalation cohort of the ModraDoc006 tablet formulation a total of 28 patients were enrolled, 17 (61%) male and 11 (39%) female patients. The median age was 58 years (range 47–76). The majority of patients had an WHO PS $\leq$ 1 (97%). Previous treatments included chemotherapy (93%), radiotherapy (64%) and surgery (36%) (Table 1). Three dose-levels were investigated ranging from BIDW 20/20 mg ModraDoc006/r to BIDW 30/30 mg ModraDoc006/r (Fig. 1).

3.2. Safety and tolerability

An overview of adverse events considered to be (possibly, probably or definitely) related to the study medication is presented in Table 2 for ModraDoc001 capsule/r and ModraDoc006 tablet/r, respectively.

The most common adverse events reported with ModraDoc001 capsule/r were fatigue (82%), diarrhoea (65%), anorexia (47%) and nausea (47%), mostly being of grade 1 or 2 severity. Fatigue grade 3 occurred in 3 patients while grade 3 diarrhoea, anorexia and nausea were all seen in 1 patient.

The most common adverse events observed with ModraDoc006 tablet/r were diarrhoea (64%), nausea (61%), vomiting (43%) and fatigue (39%), mostly of grade 1 and 2 severity. Mucositis grade 3 was observed in 3 of 16 (19%) patients treated at the 30/20 mg docetaxel dose.

Table 1
Patient demographic and baseline characteristics.

Number of patients	ModraDoc001 capsule/r	ModraDoc006 tablet/r
	n = 17	n = 28
Gender		
Male	9 (53%)	17 (61%)
Female	8 (47%)	11 (39%)
Age		
Median (range), years	60 (41–77)	58 (47–76)
WHO performance status		
0	8 (47%)	13 (47%)
1	8 (47%)	14 (50%)
2	1 (6%)	1 (3%)
Primary tumour type		
NSCLC	11	10
Neuro endocrine carcinoma	0	4
Urogenital	3	3
Head and neck	0	3
Anal	1	1
Ovarian	1	1
Other	1	6
Prior therapy		
- Chemotherapy	17 (100%)	26 (93%)
- Radiotherapy	9 (53%)	18 (64%)
- Surgery	7 (41%)	10 (36%)

Abbreviations: n = number of patients, NSCLC = non-small cell lung cancer.

3.3. Dose-limiting toxicity

Overall 8 patients experienced dose-limiting toxicities (Table 3). A total of 5 patients treated with the ModraDoc001 capsule/r reported 13 AEs that were considered as dose-limiting: grade 4 neutropenic fever, grade 3 nausea (2x), dehydration (2x), diarrhoea, mucositis, elevated alanine transaminase (ALT), epistaxis and upper gastro-intestinal tract bleeding, fatigue and hyponatraemia. All AEs occurred in 1 patient except for nausea and dehydration. Three patients treated with the ModraDoc006 tablet/r reported 9 AEs that were considered as dose-limiting: grade 3 mucositis (2x), dehydration (2x), diarrhoea, nausea, vomiting, anorexia and neutropenic fever. All AEs occurred in 1 patient except for mucositis and dehydration. Based on the observed DLTs, the MTD was BIDW 20/20 mg ModraDoc001 capsule/r and 30 mg (morning dose) and 20 mg (afternoon dose) once weekly ModraDoc006 tablet/r.

3.4. Serious adverse events (SAEs)

A total of 21 SAEs were reported in the ModraDoc001 capsule/r cohort, of which 18 (86%) were considered related to study treatment. The most common treatment-related SAEs were dehydration, nausea and mucositis, all occurring in 2 patients.

A total of 65 SAEs were reported in the ModraDoc006 tablet/r cohort, of which 23 (42%) were considered related to study treatment. The most common treatment-related SAEs were mucositis and vomiting, both occurring in 4 patients. Other common treatment-related SAEs were diarrhoea, nausea and dehydration, all occurring in 2 patients.

3.5. Treatment discontinuations – dose modifications

In the ModraDoc001 capsule cohort, the most common reason for permanent discontinuation of study treatment was progression of disease (PD) (11 patients, 65%), followed by adverse events (5 patients, 29%), and withdrawn by the principal investigator (1 patient, 6%). Dose-reductions were reported in 2 patients (12%).

Table 2
Treatment-related adverse events.

Name of AE	ModraDoc001/r 40/40 mg (n = 5)			ModraDoc001/r 20/20 mg (n = 6)		ModraDoc001/r 30/30 mg (n = 6)		ModraDoc006/r 20/20 mg (n = 3)		ModraDoc006/r 30/20 mg (n = 16)		ModraDoc006/r 30/30 mg (n = 9)			n = 45	
	Gr 1–2	Gr 3	Gr 4	Gr 1–2	Gr 3	Gr 1–2	Gr 3	Gr 1–2	Gr 3	Gr 1–2	Gr 3	Gr 1–2	Gr 3	Gr 4	Total	%
Diarrhoea	3	0	0	3	0	4	1	2	0	12	0	3	1	0	29	64%
Fatigue	4	1	0	4	0	3	2	1	1	4	2	3	0	0	25	56%
Nausea	2	0	0	1	1	3	1	2	0	9	1	4	1	0	25	56%
Vomiting	1	0	0	2	0	3	0	1	0	7	0	3	1	0	18	40%
Anorexia	3	0	0	0	0	4	1	0	0	1	1	2	2	0	14	31%
Mucositis	1	1	0	0	0	1	0	0	0	4	3	0	2	0	12	27%
Alopecia	1	0	0	1	0	1	0	0	0	3	0	3	0	0	9	20%
Weight loss	1	0	0	2	0	2	0	0	0	2	0	2	0	0	9	20%
AST increased	0	0	0	1	0	2	0	0	0	1	0	3	0	0	7	16%
Dysgeusia	0	0	0	0	0	1	0	0	0	4	0	2	0	0	7	16%
ALT increased	0	0	0	0	1	1	0	0	0	1	0	3	0	0	6	13%
Constipation	0	0	0	2	0	0	0	0	0	3	0	1	0	0	6	13%
Anaemia	1	1	0	0	0	2	0	0	0	2	0	0	0	0	6	13%
Pain, abdomen	1	0	0	2	0	1	0	0	0	2	0	0	0	0	6	13%
Nail toxicity	0	0	0	0	0	0	0	0	0	2	1	3	0	0	6	13%
Abdominal cramps	0	0	0	0	0	1	0	0	0	2	0	2	0	0	5	11%
Dehydration	0	1	0	0	0	0	1	0	0	0	0	0	2	0	4	9%
Leucocytopenia	1	0	1	0	0	0	0	0	0	0	0	0	0	1	3	7%
Neutropenia	1	0	1	0	0	0	0	0	0	0	0	0	0	1	3	7%
Epistaxis	0	0	0	0	0	0	1	0	0	0	0	1	0	0	2	4%
Febrile neutropenia	0	0	1	0	0	0	0	0	0	0	0	0	1	0	2	4%
Hyponatraemia	0	1	0	0	0	0	0	0	0	0	0	0	1	0	2	4%
Hypoalbuminaemia	0	0	0	0	0	0	0	0	0	0	0	1	1	0	2	4%
Hypokalaemia	0	0	0	0	0	0	0	0	0	0	1	1	0	0	2	4%
Haemorrhage, upper GI	0	0	0	0	0	0	1	0	0	0	1	0	0	0	1	2%
INR increased	0	0	0	0	0	0	1	0	0	0	0	0	0	0	1	2%
Lymphocytopenia	0	1	0	0	0	0	0	0	0	0	0	0	0	0	1	2%
Oedema peripheral	0	0	0	0	0	0	0	0	0	0	0	1	1	0	1	2%
Gastritis	0	0	0	0	0	0	0	0	0	1	0	0	0	0	1	2%
Pneumonia	0	0	0	0	0	0	0	0	1	0	0	0	0	0	1	2%
Rash	0	0	0	0	0	0	0	0	0	0	1	0	0	0	1	2%

Treatment-related adverse events observed in ≥10% of patients treated with ModraDoc001 capsule or ModraDoc006 tablet formulations in combination with ritonavir or ≥ grade 3. Abbreviations: n = number of patients, BIDW = bi-daily once weekly, AST = aspartate aminotransferase, ALT = alanine transaminase, GI = gastro-intestinal tract, INR = international normalised ratio.

Table 3
Dose-limiting toxicities (every line represents 1 patient).

Dose-level	Dose-limiting toxicity (CTCAE v3.0)	SAE
Capsule dose-escalation		
20/20 mg ModraDoc001/r	Grade 3 nausea, elevated ALT	No
30/30 mg ModraDoc001/r	Grade 3 anorexia, epistaxis and haemorrhage upper gastro-intestinal tract	Yes
30/30 mg ModraDoc001/r	Grade 3 diarrhoea, nausea, dehydration	Yes
40/40 mg ModraDoc001/r	Grade 4 febrile neutropenia, grade 3 mucositis (oral cavity), dehydration, hyponatraemia	Yes
40/40 mg ModraDoc001/r	Grade 3 fatigue	No
Tablet dose-escalation		
30/20 mg ModraDoc006/r	Grade 3 nausea and mucositis	Yes
30/30 mg ModraDoc006/r	Grade 3 diarrhoea, vomiting, dehydration and anorexia	Yes
30/30 mg ModraDoc006/r	Grade 3 neutropenic fever, dehydration, mucositis	Yes

Abbreviations: SAE = serious adverse event, BIDW = bi-daily once weekly, QW = once weekly, r = ritonavir, ALT = alanine transaminase.

In the ModraDoc006 tablet cohort, the most common reason for permanent discontinuation of study treatment was PD (21 patients, 75%), followed by adverse events (6 patients, 22%). Dose reductions were reported in 3 patients (11%), 1 patient required 2 dose reductions because of prolonged grade 1 thrombocytopenia.

3.6. Pharmacokinetics

PK parameters are presented in Table 4 (both formulations) and plasma concentration–time curves are presented in Fig. 2A and B for the capsule and tablet dose-levels, respectively. The mean C_{max} for the ModraDoc001 capsule was reached after 2.33 and 9.42 h after the first and second dose in cycle 1, respectively (T_{max}) independently of dose. C_{max} and AUC_{0-inf} increased with dose. C_{max} at the MTD of 20/20 mg ModraDoc001/r was 35.7 (coefficient of variation (CV) 62%) and 78.2 (CV 79%) ng/ml after the first and second dose in cycle 1, respectively and AUC_{0-48h} at the MTD in cycle 1 was 686 ng/ml*h (CV 57%).

The mean C_{max} for the ModraDoc006 tablet was reached after 2.76 and 9.33 h after the first and second dose in cycle 1, respectively (T_{max}) independently of dose. C_{max} and AUC_{0-inf} increased with dose. C_{max} at the MTD of 30/20 mg ModraDoc006/r was 69.4 (CV 66%) and 102 (CV 45%) ng/ml after the first and second dose in cycle 1, respectively and AUC_{0-48h} at the MTD in cycle 1 was 1126 ng/ml*h (CV 34%). The AUC_{0-48h} at the MTD for the ModraDoc006 tablet/r in cycle 2 was 1537 ng/ml*h (CV 40%), a significant increase of 36% in comparison to cycle 1 (paired *T* test (for patients for whom PK data of cycle 1 and 2 was available; $p = 0.0049$)).

3.7. Antitumour activity

A total of 14 out of the 17 patients treated with ModraDoc001 capsule/r were evaluabe for efficacy. One patient with NSCLC had a partial response (PR), 5 patients had stable disease (SD) and 8 patients had PD as best response to treatment. Median time on study in patients experiencing clinical benefit (SD + PR at 6 weeks) was 10 (range 3–21) weeks. A total of 17 out of the 28 patients trealted with ModraDoc006 tablet/r were evaluable for efficacy. Four patients had a PR (2 patients with a SCCHN and 2 with a NSCLC), 5 patients had SD and 7 patients had PD as best response to treatment. Median time on study in patients experiencing clinical benefit (SD + PR at 6 weeks) was 18 (range 11–54) weeks. In Supplementary Figs. 1 and 2 the time on study and best change in tumour volume per patient is presented, respectively.

4. Discussion

In this dose-finding study, the BIDW administration of oral docetaxel as the ModraDoc001 capsule or as the ModraDoc006 tablet formulation co-administered with ritonavir was explored according to a classical 3 + 3 dose-escalation design. Based on the observed dose-limiting toxicities, the MTD was BIDW 20/20 mg ModraDoc001 capsule/r, and BIDW 30/20 mg ModraDoc006 tablet/r. Treatment related-toxicity was mostly of grade 1 and 2 severity and was manageable with dose modifications and interruptions. No unexpected safety signals were observed considering the known safety profile of the registered iv docetaxel formulation. Of note, no hypersensitivity reactions and in addition only 1 event (2%) of grade 3 fluid retention (well-known adverse events reported for the docetaxel iv formulation) were observed despite the lack of premedication with corticosteroids. This is probably due to the fact that ModraDoc001 capsule and ModraDoc006 tablet do not contain polysorbate-80, the excipient used in the iv formulation which causes hypersensitivity reactions [15,16]. Also no grade 3 peripheral sensory

Table 4
Pharmacokinetic parameters on docetaxel exposure (cycle 1). C_{max} 1 = maximum concentration measured after the first dose; C_{max} 2 = maximum concentration measured after the second dose; AUC_{0-48} = Area under the plasma concentration–time curve from 0 to the last time point at 48 h; AUC_{0-inf} = Area under the plasma concentration–time curve from 0 to infinity; T_{max} 1 = time at which C_{max} 1 was measured; T_{max} 2 = time at which C_{max} 2 was measured t1/2 = terminal half-life; BIDW = bi-daily once weekly, QW = once weekly.

	ModraDoc001 capsule/r 20/20 mg (n = 6)	ModraDoc001 capsule/r 30/30 mg (n = 6)	ModraDoc001 capsule/r 40/40 mg (n = 5)	ModraDoc006 tablet/r 20/20 mg (n = 3)	ModraDoc006 tablet/r 30/20 mg (n = 16)	ModraDoc006 tablet/r 30/30 mg (n = 9)
C_{max} 1 ng/ml	35.7 ± 22.1 (62%)	75.8 ± 43.8 (58%)	102 ± 97.0 (95%)	33.0 ± 7.79 (24%)	69.4 ± 46.0 (66%)	98.9 ± 50.4 (51%)
C_{max} 2 ng/ml	78.2 ± 61.9 (79%)	150 ± 78.7 (53%)	151 ± 169 (112%)	83.8 ± 13.5 (16%)	102 ± 46.4 (45%)	197 ± 104 (53%)
AUC_{0-48} ng/ml*h	686 ± 388 (57%)	1508 ± 874 (58%)	1818 ± 1799 (99%)	702 ± 187 (27%)	1126 ± 382 (34%)	1598 ± 834 (52%)
AUC_{0-inf}[a] ng/ml*h	791 ± 500[a] (63%)	1367 ± 155[a] (11%)	2799 ± 3107[a] (111%)	781 ± 188[a] (24%)	1418 ± 429[a] (30%)	1602 ± 814[a] (51%)
T_{max} 1 h	1.99 ± 1.04 (52%)	2.59 ± 1.68 (65%)	2.46 ± 1.05 (43%)	3.03 ± 1.04 (34%)	2.84 ± 1.49 (52%)	2.52 ± 1.02 (40%)
T_{max} 2 h	9.02 ± 0.545 (6.0%)	9.08 ± 0.990 (11%)	10.3 ± 0.417 (4.0%)	9.20 ± 0778 (8.5%)	9.48 ± 1.27 (13%)	9.11 ± 0.856 (9.4%)
$t_{1/2}$[a] h	14.6 ± 1.30[a] (8.9%)	18.4 ± 4.93[a] (27%)	12.9 ± 1.37[a] (11%)	14.8 ± 5.23[a] (35%)	17.8 ± 4.79[a] (27%)	15.6 ± 2.22[a] (14%)

[a] Patients with unreliable regression were removed from the analyses for AUC_{0-inf} and $T_{1/2}$: n = 5, 5, 2, 3, 10, 8 for the columns 1 to 6, respectively.

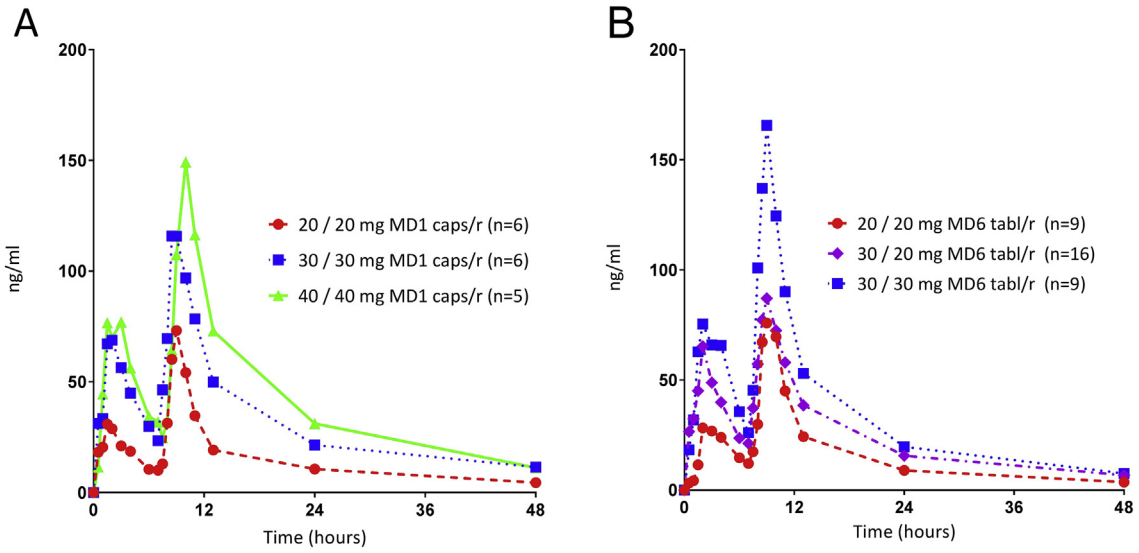

Fig. 2. Plasma concentration–time curves of ModraDoc001 capsule with ritonavir (fig. A) and ModraDoc006 tablet with ritonavir (fig. B) at all dose-levels evaluated. MD1 caps = ModraDoc001 capsule, MD6 tabl = ModraDoc006 tablet, r = ritonavir.

neuropathy was observed. Alopecia was reported in about 20% of patients. The most commonly reported treatment-related adverse events consisted of non-haematological toxicities, with mucositis, diarrhoea and nausea being dose-limiting. The incidence of severe neutropenia and neutropenic fever was limited to one event in both cohorts (4% of all patients). These findings are in line with a meta-analysis published by di Miao and colleagues showing a reduction in bone marrow suppression and a slight increase in non-haematological toxicity when a weekly iv docetaxel schedule was compared with a 3-weekly iv administration [17].

The exposure to docetaxel in terms of AUC_{0-inf} at the MTD for the ModraDoc006 tablet formulation was in the same range as once weekly iv docetaxel of 30–36 mg/m^2 [18–20]. Furthermore the observed inter-patient variability for ModraDoc006 tablet/r is in line with those previously reported for iv docetaxel [20,21]. Antitumour activity of ModraDoc001 capsule/r and ModraDoc006 tablet/r was reported in known docetaxel-sensitive tumours: partial responses were observed in 3 out of 21 patients with NSCLC (14%) and in 2 out of 3 patients with SCCHN (66%). This preliminary activity is considered promising [22,23].

Finally, from a pharmaceutical point of view the ModraDoc006 tablet formulation is preferable over the ModraDoc001 capsule formulation for three reasons, as was described by Sawicki *et al.* [4]. It is therefore likely that the ModraDoc006 tablet formulation will be developed further.

5. Conclusion

Oral administration of docetaxel either as ModraDoc001 capsule or asModraDoc006 tablet co-administered with ritonavir according to a continuous BIDW schedule appears feasible. The MTD was determined as BIDW 30/20 mg ModraDoc006 tablet/r (morning/afternoon dose). Toxicity was manageable. Antitumour activity is considered promising. Further investigation in the clinic is warranted.

Conflict of interest statement

J.H. Beijnen and J.H.M. Schellens have received a grant for translational research (ZonMw code 40-41200-98-004).

J.H. Beijnen and J.H.M. Schellens are (part-time) employees and shareholders of Modra Pharmaceuticals BV, a spin-out of the Netherlands Cancer Institute, developing oral taxane formulations.

M. Keessen and E. Sawicki are current employees of Modra Pharmaceuticals BV.

B. Nuijen, J.J. Moes, J.H. Beijnen and J.H.M. Schellens are patent holders on oral taxane formulations.

The other authors declare that they have no conflict of interest.

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Appendix A. Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.ejca.2017.09.010.

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