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A phase I clinical and pharmacokinetic study of paclitaxel and docetaxel given in combination in patients with solid tumours

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ABSTRACT

The aim of this study was to determine the safety and feasibility profile of paclitaxel (PTX) and docetaxel (DTX) in combination and the pharmacokinetic and pharmacodynamic interaction between these two drugs in two different alternated sequences of administration. The starting dose was PTX (100 mg/m^2) as a 3-h IV infusion followed by DTX (50 mg/m^2) as 1-h IV infusion or the alternative sequence in every other patient. The sequence was alternated in the second course in each patient treated. Cycle duration was 21 days. Twenty patients received 103 cycles of treatment through three dose levels. Febrile neutropenia and grade 4 neutropenia lasting longer than 7 days were dose-limiting and defined the toxic dose of DTX (50 mg/m^2) and PTX (135 mg/m^2) in patients with prior treatment and the recommended dose in patients without prior treatment. Non-hematological toxicities included asthenia, neuropathy, arthralgia/myalgia and stomatitis. Pharmacokinetics of DTX were significantly affected by the sequence. Nadir ANC was more profound when DTX was administered first ($P = 0.022$). There were one complete response and six partial responses, giving an overall response rate of 35%. DTX (50 mg/m^2) followed by PTX (135 mg/m^2) can be administered safely and it is an active regimen. The pharmacokinetics of PTX are not influenced by DTX but DTX pharmacokinetics depend on the sequence of administration, which influences its haematological toxicity profile.

1. Introduction

Paclitaxel (PTX) and docetaxel (DTX) remain two of the most active agents in cancer treatment. Accumulative evidence suggests that they are not-near identical agents.[1] DTX and PTX both bind to the same site of tubulin, but the affinity of DTX is 1.9-fold higher than that of PTX. DTX is slightly more active as a tubulin assembly promoter and

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as a microtubule stabiliser, and a 2-fold more potent inhibitor of microtubule depolymerization; PTX alters the number of protofilaments per microtubule, whereas DTX does not.[2] DTX is active mainly during S phase; PTX during late G_2/M phase.[3] Preclinical data show some distinct PTX effects on gene induction,[4] apoptosis, proliferation and inflammation govern,[5] and significantly superior activity of DTX against MRP (multidrug resistant protein)-expressing tumour xenografts.[6] DTX is a more potent cytotoxic agent than PTX when the two drugs are compared using a variety of murine and human tumour cell lines.[7] Additionally, *in vivo* cloning assay studies have indicated that there is incomplete cross-resistance between the two taxoids.[1,8] DTX has antitumour activity in metastatic breast cancer patients that have primary or secondary resistance to PTX.[1] Distinct pharmacokinetic properties have been described: DTX is extensively metabolised through the action of the cytochrome P450-3A subfamily of isoenzymes whereas the 6α hydroxylation of PTX is catalysed by CYP 2C8.[9] PTX's disposition is distinctly nonlinear (especially when administered by short infusion), while DTX's disposition appears to be linear.[9,10] In addition, a statistically significant relationship between the AUC (area under the curve) and a decrease in neutrophil count has been observed with DTX,[11] but not with PTX.

Data from phase I and II studies established that both taxoid compounds share many of the same toxic effects.[12] Neutropenia limits the dose of both drugs and stomatitis is observed with both agents, although stomatitis is more common when prolonged administration schedules are used. Skin toxicity, such as rash and nail changes, is seen in up to two-thirds of patients treated with DTX. However, skin toxicity is an uncommon reported event with PTX. A syndrome of cumulative fluid retention is also an effect unique to DTX. The characteristic adverse events due to PTX are cardiac and dose-related myalgia/arthralgia effects. Neurosensory symptoms are also frequently noted with PTX, but they are not a prominent toxicity at the usual dose and schedule of DTX.

The common, though not completely identical, novel mechanism of action along with the lack of pre-clinical and clinical cross-resistance, the different toxicity profile and pharmacokinetic behaviour, and the high clinical activity of each drug as single agent supports the evaluation of the combination of PTX and DTX in patients with cancer.[13–15]

The pharmacokinetics and pharmacodynamics of drugs given in combination may depend on the sequence and/or schedule of administration. Interactions when the taxanes are given concurrently with other drugs have been widely described and these sometimes include sequence dependency.[16]

We present the results of a clinical and pharmacological study evaluating the safety and feasibility profile of the combination of PTX and DTX in patients with solid tumours. In this study, we also explored the pharmacokinetic and pharmacodynamic interaction between the two drugs by measuring the plasma concentrations of the drugs and their metabolites and the toxicity profile in two different alternated sequences of administration.

2. Patients and methods

2.1. Patients

Twenty patients were enrolled onto the study. All patients had measurable or non-measurable metastasic cancer. Patients could have received one prior chemotherapy regimen for metastasic disease. Inclusion criteria were histological proof of cancer, age 18–70 years, performance status 0–2 (Eastern Cooperative Oncology Group [ECOG] scale), absolute neutrophil count (ANC) greater than or equal to 1500/μL, platelet count greater than or equal to 100,000/μL, normal function of the liver (bilirubin level < the upper limits of normal [ULN], AST/ALT level ⩽1.5 times the ULN, alkaline phosphatase level <2.5 times the ULN) and kidneys (creatinine level ⩽1.25 times the ULN), and absence of neuropathy greater or equal to grade 1. The trial was approved by the Ethical Committee of Ciutat Sanitària i Universitària de Bellvitge. All patients provided informed consent.

2.2. Study design, treatment plan and dose modifications

The study was conducted using a standard escalating phase I design with cohorts of 3–6 patients. At least three patients were to be treated at each dose level to evaluate toxicity. An interval of 3 weeks was planned before the entry of the first patient at the next dose level. If one out of three patients experienced a DLT (dose limiting toxicity) during the first cycle, at least one more additional patient was to be treated at this dose level. The maximum tolerated dose (MTD) was defined as the dose level at which two of the three to six treated patients experienced DLT, and the recommended dose (RD) was determined at one level below. In the absence of DLT at the first cycle, treatment could be continued up to six cycles. Beyond six cycles, the patient could receive further cycles at the discretion of the treating oncologist. No dose escalation was allowed on the same patient, and dose reductions were allowed in patients who experienced DLT and for whom treatment seemed to be of clinical benefit. The treatment continued at the level just below the dose at which the serious adverse event was observed.

To prevent hypersensitivity reactions to chremophor, all patients received premedication with dexamethasone (20 mg), desclorphenhiramine (5 mg) and ranitidine (50 mg), IV (intravenous) 30 min before treatment administration. Premedication for DTX was oral dexamethasone (8 mg twice a day) for 4 d, beginning 24-h before administration of DTX. Chemotherapy consisted of either DTX administered as 1-h IV infusion followed by PTX as a 3-h IV infusion or the reverse sequence in every other patient. For each patient, the sequence was alternated for course 2. From the third cycle on, each patient received the drugs in the order of administration of the first cycle. The two-drug combination was administered to the patients in the outpatient clinic every 21 d. The starting dose was PTX (100 mg/m^2) and DTX (50 mg/m^2); Dose level II was: PTX (135 mg/m^2), DTX (50 mg/m^2); dose level III was PTX (150 mg/m^2), DTX (60 mg/m^2) and further escalations were to be implemented if definition of MTD was not reached. Toxicities were evaluated according to the National Cancer Institute Common Toxicity Criteria. DLT was defined as fol-

lows: (1) grade 4 neutropenia (absolute neutrophil count $\leqslant$500/μL) for 7 d or more; (2) febrile neutropenia (fever $\geqslant$grade 2 with grade 3 or 4 neutropenia and requiring IV antibiotics); (3) thrombocytopenia grade 4 for seven days or more; (4) any other non-haematological toxicity $\geqslant$grade 3, except inadequately treated vomiting; (5) vomiting grade 4 regardless of adequate treatment; (6) more than 2 weeks delay in the recovery of toxicities.

2.3. Study assessments

All patients were initially evaluated by history, physical examination, chest X-ray, complete blood cell (CBC) count, liver and kidney function tests, pregnancy test if female and ECG. Computed tomography (CT) or magnetic resonance imaging (MRI) of the chest, liver and abdomen and bone scan with X-ray if hot spots were observed. Other evaluations were performed when clinically indicated. While on therapy, complete blood cell and platelet counts were performed weekly (or every 2 d in case of febrile neutropenia, until solution of all infectious symptoms). Biochemistry and liver and renal function tests were performed before each cycle. Specific neurological examination was performed at the baseline and before every other cycle. Tumour measurements were performed every two cycles. World Health Organization response criteria were used.

2.4. Pharmacokinetic study design

Blood samples were collected during the first and second cycles from every patient starting just before the first drug infusion. PTX levels were measured at 90 min, at the end of infusion and 5, 15, 30 min and 1, 2, 3, 6, 12, 24 and 48 h after the end of infusion. DTX levels were measured at 30 min, at the end of infusion and 5, 15, 30, 60, 90 min and 2, 3, 4, 6, 8, 12 and 24 h after the end of infusion. Blood samples were immediately centrifuged at 4 °C, and the plasma was separated and stored in aliquots at −20 °C until analysis. Samples were analysed by reversed-phase high-performance liquid chromatography (HPLC) validated in our laboratory. The limit of quantification was 10 ng/mL, the linear range 10–10,000 ng/mL and the coefficients of variation and accuracy for controls were lower than 15% and 20% (LOQ: 10 ng/mL), respectively.

The samples preparation consisted of a solid phase extraction (Oasis® 30 mg cartridge, Waters Chromatography) of 1 mL plasma to 200 μL mobile phase. The chromatographic system included a separations module (2690 Separations Module, Waters Chromatography), a programmable multiple-wavelength ultraviolet light detector (996 Photodiode Array Detector, Waters Chromatography) and a C_{18} reverse-phase HPLC column (Nova-Pak C18, 4.6 × 250 mm HPLC Cartridge Column, 4-mm particle size, Waters Chromatography). The mobile phase was prepared with 42.5% acetonitrile and 57.5% water. Isocratic flow rate was 1 mL/min at 30 °C, volume injected was 75 μL and detection was performed at 230 nm. The retention time for docetaxel and paclitaxel was about 19 and 24 min.

Non-compartimental pharmacokinetic data analysis was performed. The following plasma pharmacokinetic parameters were calculated for both drugs: maximum concentration (C_{max}), time to C_{max} (T_{max}), elimination half-life ($t_{1/2}$), area under the curve (AUC: trapezoidal rule method), volume of distribution (V_d), and systemic clearance (CI).

2.5. Statistical analysis

The pre-treatment to nadir ANC ratios was analysed to determine the effects of treatment sequence on haematological toxicity. A linear regression was calculated between ANC ratios and treatment sequence, which was adjusted for the multiple courses of treatment given per patient. Intention-to-treat analysis was performed for response rate.

Descriptive parameters of both compounds are reported as mean values ± SD. The difference in pharmacokinetic parameters between patient cohorts was evaluated statistically using a non-parametric Kruscal–Wallis test. The effect of drug administration sequence on the pharmacokinetic parameter values was evaluated by calculation of the 90% confidence interval for the ratio of the respective parameter values. The relation between the sequence and nadir was analysed using the non-parametric Wilcoxon test. The Chi-Squared test or Fisher exact 2-tailed tests were used, as appropriate, for comparative analysis between categorical variables.

The relation between the pharmacokinetic parameters and nadir was analysed using the Kendall correlation Tau coefficient. All calculations were done with the SPSS software package.

3. Results

3.1. Clinical study

Twenty patients were enrolled in the study and treated at three dose levels. All patients were evaluable for toxicity. Patients' characteristics are listed in Table 1. The median age was 53 (range 36–70) and the median ECOG performance status was 0. All patients had evaluable or measurable disease, 15 (75%) had received one prior chemotherapy regimen for metastasic disease, and four others in the adjuvant setting. Primary tumours were breast (eight patients), gastric (five patients), lung (five patients), renal (one patient), CUP (Cancer of Unknown Primary) (one patient). The majority of the patients (75%) had less than three involved sites of disease (Table 1).

A total of 103 cycles of the combination were administered. All patients received at least two cycles (at different sequences of treatment administration), except for one who received only one cycle, due to early progression. Therefore ten patients were treated with DTX followed by PTX at the first cycle, and PTX followed by DTX at the second cycle. The other ten patients received PTX followed by DTX at the first cycle and the reverse sequence at the second cycle (except one patient who received only one cycle). From the third cycle on, each patient received the drugs in the order of administration of the first cycle.

Fifteen patients received six cycles of treatment, as planned. The reasons for treatment discontinuation in the other patients were disease progression (three patients; 15% [after four, three and one cycles]), and death due to progressive disease (two patients; 10% [after four and two cycles]). Dose reduction was required in 12 cycles (12%) distributed

Table 1 – Patient characteristics

Characteristic	No.	Range	%
No.	20		
Evaluable for toxicity	20		
Evaluable for antitumor activity	20		
Sex			
Male	11		55
Female	9		45
Age (years)			
Median	53		
Range		36–70	
ECOG performance status			
0	13		65
1	7		35
Median prior chemotherapy regimens	1		100
Prior therapy			
Chemotherapy (metastatic setting)	15		75
Chemotherapy (adjuvant setting)	4		20
Radiotherapy	5		25
Surgery	11		55
Hormonotherapy	4		20
Inmunotherapy	1		5
Tumor type			
Breast	8		40
NSCLC	5		25
Gastric cancer	5		25
Kidney	1		5
Unknown primary	1		5
Metastatic lesions			
1	6		30
2	9		45
$\geqslant 3$	5		25

Abbreviations: NSCLC, non-small cell lung cancer.

as follows: PTX at ten cycles and DTX at six (at all dose levels). The reason for dose reduction was mainly neutropenia (11 cycles, 11%). Reduction was required at the sixth cycle in one patient, due to peripheral neuropathy. Delays were required in only three cycles (3%).

At dose level I (PTX 100 and DTX 50) one out of the initial three patients had a DLT during the first course, which consisted of febrile neutropenia. The level was then expanded up to six patients and no more DLTs were encountered. Other significant toxicities at this dose level included: grade 4 neutropenia in three more patients (two during first or second cycle), and grade 3 anaemia in one patient. Dose levels and DLTs are described in Table 2.

At dose level II (PTX 135 and DTX 50) one out of the three initial patients experienced a grade 4 neutropenia of more than 7 days duration. After expanding the level with two more patients, the second one experienced febrile neutropenia. All these patients had received prior chemotherapy for metastasic disease. After these two DLTs this level was declared the maximum tolerated dose for this patient population (previously treated). We then went on to further explore this level by entering patients with no prior chemotherapy for metastasic disease. Four patients were entered (two of them had received adjuvant treatment with chemotherapy). None of them suffered a DLT. Level III was then opened in patients with no prior treatment (PTX 150 mg/m^2 and DTX 60 mg/m^2). One out of the three initial patients at this level III experienced a DLT (febrile neutropenia). Two out of these three patients had received adjuvant chemotherapy. Then two more patients were included sequentially, the second one experiencing febrile neutropenia, and the study recruitment was closed because MTD and RD criteria were met. Three more patients presented grade 4 neutropenia without fever at this dose level, which lasted less than 7 d. Grade 3 anaemia was observed in one patient. The highest grade for thrombocytopenia was 1, which was observed in eight patients across all dose levels. Neutrophil toxicity at the different treatment sequences is summarized in Table 3. No prophylactic G-CSF (granulocyte colony-stimulating factor) was administered, and no treatment with G-CSF was necessary.

Table 4 lists the most significant all-cycle non-haematological toxicities observed in the study. Asthenia was the most frequent toxic effect observed (in 18 patients [90% of the patients]). Seventeen patients experienced grade 1–2 peripheral neuropathy. As expected, neurotoxicity increased with the increasing cumulative dose of PTX. Alopecia was complete and almost universal. Only one patient suffered a hypersensitivity reaction (moderate bronchospasm) that was successfully treated on an outpatient basis. Grade 3 hypertension was observed in one patient at dose level I, related to concomitant treatment. PTX-related grade 3 arthralgia/myalgia was observed in one patient, while 14 patients experienced mild and moderate arthralgia/myalgia. They were treated with analgesics and it was usually self-limited. Other mild to moderate (grade 1 or 2) non-haematological toxic effects reported across the three dose levels were stomatitis (80% of patients),

Table 2 – Dose levels and DLTs

Level	PTX dose (mg/m^2)	DTX dose (mg/m^2)	No. of patients	No. of cycles	DLTs (No.)	Febrile neutropenia (all cycles)	
						No. of patients	No. of cycles
I	100	50	6	28	Febrile neutropenia (1)	2	2
II	135	50	9	45	Febrile neutropenia (1), grade 4 ANC > 7 days (1)	2	3
III	150	60	5	30	Febrile neutropenia (2)	2	3
Total			20	103		6	8

DLT, dose limiting toxicity; PTX, paclitaxel; DTX, docetaxel; ANC, absolute neutrophil count.

Table 3 – Incidence of neutrophil toxicity with different sequences

Level (P/D dose mg/m^2)	Sequence at first cycle (no. of patients)	No. cycles	No. of patients with ANC < 500 μL				No. of cycles with ANC < 500 μL	
			Cycle 1	Cycle 2[a]	Cycles 1 and 2	All cycles	Cycles 1 and 2	All cycles
I	PD (3)	14	1	1	1	2	2	4
(100/50)	DP (3)	14	2	2	2	2	4	5
II	PD (5)	25	4	2	5	5	6	15
(135/50)	DP (4)	20	3	3	3	3	5	9
III	PD (3)	18	3	2	3	3	5	16
(150/60)	DP (2)	12	2	2	2	2	4	5
Total		103			16	17		54

P, paclitaxel; D, docetaxel; ANC, absolute neutrophil count.
a Reverse sequence.

Table 4 – Nonhematologic toxicity

Toxicity	Grade (no. of patients)			
	1	2	3	4
Stomatitis	12	6	0	0
Myalgia/arthralgia	7	8	1	0
Asthenia	3	8	6	1
Peripheral neuropathy	4	13	0	–
Allergia (bronchospasm)	1	1	0	0
Hypertension	0	0	1	0
Alopecia	0	18	–	–
Nausea	8	0	0	0
Vomiting	4	0	0	0

Worst grade per patient ($n = 20$).

skin alterations (65%) nausea and vomiting (55%), anorexia (45%), and phlebitis (30%). Nail alterations (20%) and fluid retention (15%) were noted across the entire dose range.

3.2. *Antitumour activity*

All 20 eligible patients were evaluable for the efficacy analysis. One patient with previously treated gastric cancer treated at dose level I obtained a complete response that lasted 4 months. Six patients with metastasic breast cancer treated at dose levels I, II and III obtained a partial response, with median response duration of 5 months (mean: 7, range [4–10]). Two of them had received adjuvant chemotherapy. The other four had not been previously treated. Stable disease was observed in ten patients and three patients were evaluated as progression. The overall response rate was therefore 35% (95% confidence interval, 15.4–59.2). Median time to progression was 5.47 months, range (4.13–10.9 months).

3.3. *Pharmacokinetic analysis*

The pharmacokinetics of PTX and DTX were analysed in all 20 patients. The pharmacokinetics of DTX were not evaluable in one patient because of technical reasons. Paired plasma samples were available for 19 of 20 patients, because one patient received only one cycle, as described before. One other patient who showed an abnormal high ANC at the beginning of the study was excluded from PK-PD analysis and the relation between the sequence and nadir was analysed in the remaining 18 patients.

No effect of sequence of administration was observed on the PK of PTX (Tables 5 and 6). However, the Cmax, $t_{1/2}$, AUC of DTX were significantly higher and the CI lower when DTX was given after PTX (Table 5). Accordingly, nadir ANC significantly correlated with sequence (mean 0.39×10^9/L for PTX/DTX vs. 0.65×10^9/L for DTX/PTX [$p = 0.022$]) (Non-parametric Wilcoxon test).

Table 5 – Impact of sequence effect on pharmacokinetics of paclitaxel

PK concept	Paclitaxel PK parameters				Correlation with sequence
	DTX/PTX		PTX/DTX		
	Mean	SD	Mean	SD	
$t_{1/2}$	8.66	0.21	9.03	0.24	NS
C_{max}	2077.29	172.52	2268.12	209.32	NS
AUC	7.19	0.51	7.83	0.58	NS
MRTI	4.71	0.16	4.99	0.21	NS
CI (kg)	0.47	0.028	0.45	0.031	NS
V_d (kg)	2.22	0.16	2.28	0.2	NS

C_{max}, maximum concentration; $t_{1/2}$, elimination half-life; AUC, area under the curve; V_d, volume of distribution; CI, systemic clearance; SD, standard deviation; NS, non-significant.

Table 6 – Impact of sequence effect on pharmacokinetics of docetaxel

PK concept	Docetaxel PK parameters				Correlation with sequence
	DTX/PTX		PTX/DTX		
	Mean	SD	Mean	SD	
$t_{1/2}$	6.423	0.535	10.685	1.642	NS
C_{max}	1524.94	83.191	1961.151	108.721	$p = 0.000$
AUC	1.9398	0.1133	2.8277	0.1973	$p = 0.000$
MRTI	2.7962	0.293	4.3598	0.9857	NS
CI (kg)	0.72032	0.04847	0.52397	0.0348	$p = 0.001$
V_d (kg)	1.86898	0.15067	2.17112	0.49365	NS

C_{max}, maximum concentration; $t_{1/2}$, elimination half-life; AUC, area under the curve; V_d, volume of distribution; CI, systemic clearance; SD, standard deviation; NS, non-significant.

4. Discussion

PTX and DTX are two of the most widely used established drugs in cancer treatment. Novel agents, including new taxane analogues and new drug combinations, are being developed. An alternative strategy remains to test the most rational combinations of the drugs already available in the cancer treatment armamentarium. In this study we have analysed the feasibility, optimal sequence and recommended dose of the doublet DTX–PTX, and we were able to achieve clinically relevant doses of both drugs.

In this study, DLT was febrile neutropenia and grade 4 ANC > 7 d, which precluded dose escalation of PTX and DTX further than 150 and 60 mg/m^2, respectively, and defines the recommended phase II schedule for this drug combination in patients without prior chemotherapy for metastasic disease as DTX 50 mg/m^2 followed by PTX 135 mg/m^2. In the previously treated patient population, the RD was one dose level below, at 50/100, respectively.

Neutropenia is the DLT for single-agents PTX and DTX. Grade 4 neutropenia was observed in 80% of the patients treated in this trial, in 30% of them associated with fever. Neutropenia was brief and non-cumulative, and was rarely associated with treatment delays. No treatment with G-CSF was necessary.

The most important non-haematological toxicity was asthenia reported in 90% of the patients, though it did not preclude the administration of the planned six cycles in the majority of patients. Gastrointestinal toxicity was frequent but usually mild. The incidence of PTX specific toxicities like hypersensitivity was low and did not constitute a major clinical problem. Fluid retention, which is characteristic of DTX, was not seen, probably because all patients received corticosteroid pre-medication. Neurotoxicity occurred in 65% of the patients but was usually mild, and led to dose reduction in one patient only, despite a median number of cycles of 6. Delays were required in only 3% of cycles.

The overall response rate was 35%, observed across all dose levels. Interestingly six of eight patients with breast cancer showed a partial response (75%). In the literature, response rates in patients with minimally pre-treated breast cancer range from 50% to 78%. Therefore, the current study results lie in the highest range of therapeutic activity in this patient population and deserves further evaluation.

The combination of these two drugs has been explored by Lokich, who published a phase I study testing this combination.[17] There are some important differences to the present study: only the sequence DTX/PTX was explored, no PK analysis was performed, G-CSF was used for leukopenia treatment and a weekly schedule was elected. Probably because of this schedule, he observed a cutaneous toxicity syndrome consisting of erythema on the foot, which was associated with vesicles and blister formation. No similar toxicities were observed in our study. Their RD was: DTX, 35 mg/m^2/week, plus PTX, 65 mg/m^2/week. This study showed that the combination is feasible and active with this schedule.

One of the main objectives of the trial was to explore the sequence of this combination. A sequence effect both with PTX and DTX has been previously reported when combined with other drugs. Rowinski and colleagues showed that the order of administration of PTX in combination with cisplatin was associated with significantly better tolerability when the taxane was given first.[18] A similar sequence effect is observed with carboplatin.[19] This was not observed when PTX was administered with cyclophosphamide or doxorubicin.[16] Venturini and colleagues[20] treated 39 consecutive stage II breast cancer patients, 21 with epirubicine (EPI) followed by PTX and 18 with the opposite sequence. The second group was associated with an increase in the EPI plasma concentrations compared with the reverse sequence. A higher total plasma exposure to EPI, as measured by AUC, was correlated with a lower percentage of neutrophil recovering on day 21 ($p = 0.012$). In a second study, Itoh and colleagues[21] observed in a randomised cross-over trial with DTX and doxorubicine in which the sequence of drug administration was switched for the second course, that the duration of grade 4 neutropenia was significantly longer in patients treated with the DTX-doxorubicine sequence than in the patients treated with the opposite sequence ($P = 0.0062$). In both studies, the sequence of PTX or DTX followed by the other drug was more toxic, possibly because of pharmacokinetic interference leading to higher concentrations of the second drug. In the present study, the pharmacokinetic behaviour of the two sequences was explored in the same patient, minimising the interpatient variability. Interestingly, we observed significantly higher severity of neutropenia with the sequence PTX/DTX compared with DTX/PXT. PTX significantly altered the pharmacokinetics of DTX when administered first by increasing

the $t_{1/2}$, Cmax and AUC of DTX, thus leading to a clinically significant increase of haematological toxicity. However, no effect on the PK of PTX was observed when DTX was given first.

The presence of complex pharmacological interactions between PTX or DTX and other drugs has been well documented. Some explanations have been proposed, such as the known inhibition induced by some drugs on other drugs' metabolism, through the cytochrome-P450 enzymes. Pharmacokinetic studies have shown that the systemic elimination of PTX predominantly involves hepatic metabolism by the CYP isozymes, CYP2C8 and CYP3A4[22] and they are the subject of polymorphisms and high phenotypic variability.[23] CYP3A4 is also the major elimination route of DTX, which is also subject to large variability and can be modified by typical CYP3A substrates and/or inhibitors such as erythromycin, ketoconazole, nifedipine, midazolam, and troleandomycin. Some Vinca alkaloids and doxorubicin were shown to inhibit DTX metabolism in human hepatocytes and liver microsomes.[24] Some in vitro interactions have been described between these two agents showing that PTX reduced significantly the hydroxylation of DTX.[25] It may well be that CYP3A4 is rate limiting for DTX and not for PTX metabolism, which would account for the sequence dependency seen in this trial, but this should be confirmed with appropriate preclinical models.

To summarise, our data show that the combination of PTX and DTX is feasible, active and well tolerated. The recommended schedule for this combination in patients without prior treatment is 50 mg/m^2 of DTX followed by 135 mg/m^2 of PTX, given on day 1, on a 3-week schedule. Our data also show a pharmacokinetic interaction between these two drugs. In addition, the response rate of this combination of agents in breast cancer patients warrants further phase II evaluation.

Conflict of interest statement

None declared.

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