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ORIGINAL ARTICLE

A. Felici · W. J. Loos · J. Verweij · I. Cirillo
P. de Bruijn · K. Nooter · R. H. J. Mathijssen
M. J. A. de Jonge

A pharmacokinetic interaction study of docetaxel and cisplatin plus or minus 5-fluorouracil in the treatment of patients with recurrent or metastatic solid tumors

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Abstract *Background*: The purpose of this study was to look at the pharmacokinetics of docetaxel, cisplatin-derived platinum and 5-fluorouracil (5-FU), when used in combination, to exclude potential clinically relevant pharmacokinetic interactions. *Methods*: Fifteen patients with recurrent or metastatic solid tumors were randomized to receive docetaxel 75 mg/m^2 and cisplatin 75 mg/m^2 in the first treatment course on day 1 and the same combination plus 5-FU 750 mg/m^2/day on days 1–5 in the second course, or the two treatment courses in reversed order. Cycles were repeated every 3 weeks. A pharmacokinetic analysis was performed during the first two cycles. *Results*: Full pharmacokinetic data was available for 12 of the 15 patients. Treatment was tolerated well, with frequency of toxicity consistent with the safety profile known for docetaxel, cisplatin and 5-FU. Mean clearance values for docetaxel and cisplatin showed no statistically significant difference across the "triple" and the "double" combination treatments, and the mean pharmacokinetic parameters of all agents were within the ranges for previously reported single agent treatment. *Conclusion*: No clinically relevant pharmacokinetic interactions between docetaxel, cisplatin and 5-FU used in combination were noticed in this study.

A. Felici (✉) · W. J. Loos · J. Verweij · P. de Bruijn
K. Nooter · R. H. J. Mathijssen · M. J. A. de Jonge
Department of Medical Oncology, Erasmus University Medical Center/Daniel den Hoed, Groene Hilledijk 301,
3075 Rotterdam, The Netherlands

A. Felici
Department of Medical Oncology, Regina Elena National Cancer Institute, Via Elio Chianesi, 53, 00144 Rome, Italy
E-mail: alefelici@yahoo.it
Tel.: +39-06-52666916
Fax: +39-06-52665637

I. Cirillo
Sanofi Aventis, Metabolism & Pharmacokinetics,
Bridgewater, NJ, USA

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Introduction

Interactions between drugs were first recognized over 100 years ago. For various reasons chemotherapy mostly consists of a combination of drugs introducing the possibility of both pharmacokinetic (PK) and pharmacodynamic interactions. Therefore it is essential to study the pharmacokinetic interactions of any new combination regimen prior to introduction in the clinic. The combination of docetaxel, cisplatin and 5-fluorouracil (5-FU) was studied in several phase I/II trials in patients with head and neck cancer and gastric cancer indicating that the combination is feasible and highly active [1–7].

Docetaxel (Taxotere®, Sanofi Aventis) is a semi-synthetic drug derived from a precursor (10-deacetyl baccatin III) isolated from the needles of the European tree *Taxus Baccata*. Docetaxel promotes tubulin assembly into microtubules, stabilizes the microtubules and inhibits de-polymerization to free tubulin [8, 9]. This leads to the formation of bundles of microtubules in the cell, thus blocking cells in the M-phase of the cell cycle and resulting in cell death.

In blood, docetaxel is mainly located in the plasma compartment, extensively bound to serum proteins: albumin, lipoproteins and α_1-acid glycoprotein. Some drugs, including cisplatin, administered in combination with docetaxel do not modify its plasma binding [10]. After a single administration, docetaxel is metabolized and excreted primarily through the feces via biliary excretion.

Cisplatin is one of the most active and widely used cytotoxic drugs in solid tumors, and its major mechanism of action is the formation of adducts or intra-strand cross-links at the DNA level [11]. After

intravenous administration, cisplatin is rapidly and irreversibly bound to plasma proteins and only the unbound fraction remains biologically active. Approximately 25% of cisplatin is excreted, predominantly renally, during the first 24 h.

5-Fluorouracil is a cell cycle phase-specific agent. Basically, 5-FU acts as a "false" pyrimidine or antimetabolite to ultimately inhibit the formation of the DNA-specific nucleoside base thymidine. Currently 5-FU is mostly given as (semi-)continuous intravenous (i.v.) infusion, given its short plasma half-life and the increased dose intensity that can be achieved as compared to bolus injection [12]. Up to 80% of the dose of 5-FU is detoxified through metabolic liver degradation, with significant renal excretion occurring after the first few hours.

Considering the different mechanisms of action, the only partial overlap of toxicity profiles and the activity of all drugs as single agent, the combination of docetaxel, cisplatin and 5-FU (TCF) may be interesting for patients with several advanced solid tumors. To date, several phase I–II studies have shown an acceptable toxicity profile and high overall response rate in patients with solid tumors [1–7]. However, the possible pharmacokinetic interaction between the three agents has not yet been investigated. The hypothetic docetaxel interactions with cisplatin or 5-FU were studied only as "doublet" combinations: when docetaxel was administered in combination with cisplatin no pharmacokinetic interaction independent from the sequence of administration was revealed [13]; when docetaxel was combined with 5-FU, PK of both drugs appeared to be consistent with those from single agent studies [14, 15].

In order to evaluate the possible interaction of 5-FU on docetaxel and cisplatin PK parameters, we performed a study in which patients were treated with docetaxel and cisplatin with or without 5-FU.

Patients and methods

Patient selection

The study was conducted in accordance with good clinical practice (GCP) and was approved by the Ethical Committee of the Erasmus Medical Center. Patients with recurrent or metastatic solid tumors were eligible for the study respecting the following inclusion criteria: (1) signed informed consent; (2) age ≥18 years; (3) histologically or cytologically confirmed solid tumor for which docetaxel–cisplatin or docetaxel-cisplatin-5-FU was considered an adequate therapy; (4) WHO Performance Status ≤ 1; (5) no major fluid effusions; (6) no irradiation to ≥25% of the bone marrow area prior to study entry; (7) no participation in clinical trials of experimental agents within 4 weeks of study entry; and (8) adequate hematopoietic (hemoglobin ≥6.0 mmol/l, absolute peripheral granulocyte count $\geq 1.5\times10^9$ L^{-1} and platelet count $\geq 100\times10^9$ L^{-1}), hepatic (bilirubin < 1.0 times the upper normal limit, alkaline phosphatase ≤ 5 times the upper normal limit and serum aspartate aminotransferase and alanine aminotransferase ≤ 2.5 times the upper normal limit) and renal (serum creatinine concentration < 1.0 times the upper normal limit) functions. Patients with symptomatic brain or leptomeningeal metastases and/or peripheral neuropathy ≥ grade 2 or who received major surgical therapy within 2 weeks of study entry were excluded. Patients with a known dihydropyrimidine-dehydrogenase (DPD) deficiency were ineligible as well.

Drug administration

In this single center, open-label, randomized crossover study, patients were randomly assigned at study entry to one of two treatment groups.

Group A In the first treatment course, patients received docetaxel 75 mg/m^2 as an 1 h infusion in 250 ml of normal saline solution, followed, after a 15 min interval to administer anti-emetics, by cisplatin 75 mg/m^2 as a 3 h infusion, diluted in 250 ml of hypertonic saline [3% (w/v) sodium chloride] on day 1. In the second course, the "triplet" was administered with the additional administration of 5-FU at a dose of 750 mg/m^2/day as a continuous infusion from day 1 to day 5 following the administration of cisplatin. Courses were to be repeated every 3 weeks.

Group B Patients received the two treatment courses in reversed order.

The third and following courses were administered at the discretion of the treating physician. Dexamethasone premedication was administered orally at the dose of 8 mg b.i.d., beginning the night before therapy for a total of six doses. For prevention of cisplatin-induced renal damage, the administration of cisplatin was preceded by the infusion of 1,000 ml of a mixture of 5% (w/v) dextrose and 0.9% (w/v) sodium chloride over 4 h and followed by another 3,000 ml with the addition of 20 mM potassium chloride and 2 g/l magnesium sulfate applied over 16 h. Adequate anti-emetic regimens, consisting of granisetron in combination with dexamethasone, were administered according to institutional practice. G-CSF administration was not allowed for the first two cycles, while permitted at the following cycles, if clinically indicated. No dose modifications were planned for cycles 1 and 2. A total of 12 subjects had to be enrolled and treated in this study, 6 in each of the two treatment arms. Subjects for which PK samples were not evaluable were replaced, so that a total of 12 patients would be evaluable for PK analysis.

Cisplatin (Platosin®) was purchased as a powder from Pharmachemie (Haarlem, the Netherlands). Docetaxel was provided by Aventis Pharmaceuticals (Sanofi Aventis, Antony Cedex, France) as a solution containing 40 mg/ml docetaxel in polysorbate 80. The

solvent for docetaxel is a 13% w/w solution of ethanol in water for injection. 5-FU was purchased from TAVA as an aqueous solution containing 500 mg/10 ml of the drug in glass ampoules.

Treatment assessment

Before therapy, a complete medical history was taken and a physical examination was performed. A complete blood cell count (CBC) including white blood cell count and differential, and serum biochemistry [which included sodium, potassium, calcium, creatinine, total protein, albumin, total bilirubin, alkaline phosphatase, aspartate aminotransferase (ASAT), alanine transferase (ALAT) and magnesium] if clinically indicated were performed, as was creatinine clearance. Weekly evaluations included history, physical examination, toxicity assessment according to the NCIC-CTC criteria (Version 2.0) and hematology and serum chemistry.

Pharmacokinetic sampling procedure and analysis

Blood samples for pharmacokinetic analysis were collected for each patient at cycles 1 and 2. Samples were drawn from the arm opposite to the infusion arm and collected in heparinized glass tubes.

To characterize docetaxel pharmacokinetics, samples were collected before the start of infusion, during infusion at 30 and 55 min, at the end of the infusion and at 15 and 30 min, 1, 2, 4, 7, 11 and 24 h after the end of the infusion. Immediately after collection, samples were centrifuged at 3,000 *g* for 10 min to obtain the plasma fraction, which was stored at $T < -70$°C until analysis. Docetaxel concentrations were analyzed according to a slightly modified high-performance liquid chromatographic (HPLC) method [16]. In brief, the sample preparation involved a liquid–liquid extraction of 1,000 µl of plasma with a mixture of acetonitrile:*n*-bulylchloride (1:4, v/v), using the structurally related compound, paclitaxel, as internal standard. Chromatographic separations of the dried and re-dissolved residue were achieved on a Zorbax Exlipse XDB-C8 column (150×4.6 mm^2, 5 µm particle size) using the Agilent 1100 series HPLC system. The column effluent was monitored at a wavelength of 230 nm. The lower limit of quantitation of the method was validated at 15.0 ng/ml.

A full sampling schedule was also implemented for cisplatin, consisting of blood collection immediately prior to cisplatin administration, at 1 and 2 h during the infusion, 5 min before the end of infusion and at 0.5, 1, 2, 4 and 21 h after the end of drug infusion. Immediately after collection, plasma was separated by centrifugation at 3,000 *g* for 10 min, after which 500 µl aliquots of the plasma supernatant were mixed with 1.0 ml of ice-cold (−20°C) ethanol. The ethanolic samples were stored at $T < -20$°C for at least 5 h and a maximum of 24 h, after which the ethanolic supernatant was collected by centrifugation of the samples at 23,000 *g* for 5 min, which was subsequently stored at $T < -70$°C until analysis, as was the remaining plasma. For measurement of unbound platinum, aliquots of 1,000 µl of the ethanolic supernatant was evaporated to dryness under nitrogen at $T \sim 80$°C and the residue reconstituted in 200 µl water containing 0.2% (v/v) Triton X-100 and 0.06% (w/v) cesium chloride (i.e., diluent). A volume of 20 µl, in duplicate, was injected onto the graphite furnace of a Perkin Elmer Model 4110 ZL atomic absorption spectrophotometer (AAS). Platinum peak areas were measured at 265.9 nm. The lower limit of quantitation of this assay was established at 0.0300 µg/ml platinum in plasma. For the determination of total platinum concentrations in plasma, a 100 µl volume of plasma was added to 500 µl diluent. Also, 20 µl of this solution, run in duplicate, was injected into the AAS. The lower limit of quantitation for total platinum in plasma was set at 0.200 µg/ml [17].

In cycles comprising 5-FU infusion, samples for 5-FU pharmacokinetics were collected before the start of infusion, at 2, 4, 24, 48 and 96 h after the start of infusion, at the end of infusion and at 15, 30 and 45 min and 1 and 2 h after the end of the drug infusion. To obtain the plasma fraction, blood samples were centrifuged at 3,000 *g* for 10 min immediately after collection. The plasma was stored at $T < -70$°C until analysis according to a slightly modified HPLC method as published by Loos et al. [18]. In brief, aliquots of 100 µl plasma were extracted, after the addition of 5-chlorouracil as internal standard, with 5 ml ethyl acetate. Chromatographic separations of the dried and re-dissolved residue were achieved on an Inertsil ODS-3 Column (250×4.6 mm^2, 5 µm particle size) using the Agilent 1100 series HPLC system. The column effluent was monitored at a wavelength of 266 nm. The lower limit of quantitation of the method was established at 50.0 ng/ml.

Pharmacokinetic and statistical procedures

Pharmacokinetic parameters were calculated from plasma concentrations of docetaxel, cisplatin-derived platinum and 5-FU in cycles 1 and 2. Docetaxel PK were estimated by non-linear mixed effects modeling, and platinum and 5-FU PK were estimated via non-compartmental analysis. The choice of PK analysis methods was based on previous PK studies for the single agent characterization of drug distribution [19–21].

The analysis of docetaxel PK focused on docetaxel total body clearance (CL), calculated by Bayesian estimation using individual concentration–time data for each patient as posterior information and the previously defined population model as prior information [22]. A three-compartmental structural model with first order elimination was used and individual pharmacokinetic analysis was performed with the NONMEM program (double precision, Version V, level 1.1).

A non-compartmental PK analysis was also performed on docetaxel plasma concentration data using validated WinNonlin® software Version 3.3 (Pharsight Corporation). The area under the plasma concentration–time curve (AUC) to the last measured concentration point was calculated via a linear trapezoidal method and then extrapolated to infinity to generate AUC(0–∞). Clearance was calculated as dose/AUC(0–∞). The terminal half-life ($t_{1/2}$) was estimated by linear regression of the log-transformed data and the volume of distribution at steady state (V_{ss}) was calculated as CL × MRT (mean residence time).

For the characterization of total and unbound platinum and of 5-FU PK, non-compartmental analysis was conducted using a validated WinNonlin® Version 3.3 (Pharsight Corporation). The maximum platinum and 5-FU concentration in plasma (C_{max}) after drug administration were determined directly from the concentration–time data. The following parameters were calculated: AUC(0–∞), AUC, $t_{1/2}$, CL and V_{ss}, as done for the non-compartmental analysis used for docetaxel. The pharmacokinetic for unbound platinum has been calculated using time points up to 7 h after the start of infusion. Due to the insufficient number of sample points, the concentration–time profile was not adequately captured to estimate half-life, and subsequently AUC(0–∞) of 5-FU. To calculate CL and V_{ss}, the terminal observation, below the quantification limit, was set to 0 and the AUC_{last} and MRT_{last} estimates were used in the following equations:

$$CL\ (ml/h) = 10^6 \times Dose/AUC_{last},$$
$$V_{ss}(ml) = CL \times MRT_{last}.$$

Descriptive statistics of the pharmacokinetic parameters was used. Continuous variables were summarized with the mean, standard deviation (SD), median, minimum, maximum and number of observations. The geometric mean and geometric SD were additionally calculated for PK parameters. For docetaxel and unbound platinum, the log-transformed data were applied to an analysis of variance (ANOVA) with the factor treatment individually for each comparison. The mean square error obtained in these models was then used to calculate the 90% confidence intervals (CI). For docetaxel, the mean CL values from this study were also compared to historical mean docetaxel CL values. Individual comparison of the data from the current studies' triple and double combination treatments were combined with the historical control by taking the logarithm of the CL values and comparing these values with the analysis of variance. The mean square error of this treatment difference was used to construct the 90% CI for the ratio between the treatments.

Results

Patient characteristics

A total of 15 patients were screened and randomized to one of the two treatment arms: 8 patients to arm A and 7 patients to arm B. Three patients were not evaluable for PK analysis and were replaced. Two of these subjects had improper sample storage and one subject discontinued the triple combination treatment due to myocardial ischemia. Of the 15 randomized patients, 14 received study medication in their respective treatment sequence for each treatment cycle and all were analyzed for safety. Seven males and eight females were enrolled, with a median age of 54 years and a median WHO performance status of 1; all patients were Caucasians with a median body surface area (BSA) of 1.87 and 1.93 m^2 for arms A and B, respectively. Only 4 patients received prior chemotherapy regimens and 13 had metastatic disease. As described in Table 1, there were no differences in terms of WHO performance status, extent of disease and number of prior chemotherapy regimens between the two arms.

Table 1 Patient characteristics

	Arm A, $N=8$	Arm B, $N=7$	Total, $N=15$
Age (years)			
Median	54.5	54	54
Range	23–58	43–63	23–63
Male, *N* (%)	3 (37.5)	4 (57.1)	7 (46.7)
Female, *N* (%)	5 (62.5)	3 (42.9)	8 (53.3)
Race white, *N* (%)	8 (100)	7 (100)	15 (100)
Body surface area (m^2)			
Median	1.87	1.93	1.92
Range	1.42–2.18	1.81–2.15	1.42–2.18
WHO PS 0, *N* (%)	3 (37.5)	0	3 (20)
WHO PS 1, *N* (%)	5 (62.5)	7 (100)	12 (80)
Metastatic disease, *N* (%)	7 (87.5)	6 (85.7)	13 (86.7)
Locoregional recurrence, *N* (%)	1 (12.5)	1(14.3)	2(13.3)
Prior chemotherapy regimen			
0, *N* (%)	5 (62.5)	6 (85.7)	11 (73.3)
1, *N* (%)	2 (25)	0	2 (13.3)
2, *N* (%)	1 (12.5)	1 (14.3)	2 (13.3)

Safety

The most frequent and severe chemotherapy side effects are listed in Table 2. Grade 3–4 neutropenia was reported in all patients. Three patients experienced grade 2 febrile neutropenia on triple therapy, not requiring hospitalization. Grade 3–4 anemia or thrombocytopenia was not observed. One patient was discontinued from the study due to myocardial ischemia grade 2 occurring during TCF infusion, which turned out to be reversible. Administration of docetaxel and cisplatin (TC) in cycle 2 was delayed by 4 days in one patient due to grade 2 nausea; there were no further cycle delays. After the two study cycles, 14 patients continued on TC, one of whom additionally received TCF during follow-up therapy.

PK results

Pharmacokinetics were fully evaluable in 12 patients: 6 in arm A and 6 in arm B.

As shown in Fig. 1, the mean (±SD) docetaxel plasma concentration–time curves were similar in the two arms.

Descriptive analysis for docetaxel PK parameters following non-compartmental analysis is listed in Table 3. The overall mean (±SD) clearance of docetaxel was 22.2 (±5.6) and 23.2 (±6.0) l/h/m^2 in TC and TCF, respectively, with an interpatient variability as expected. After the end of the 1 h i.v. infusion, docetaxel plasma concentration decreased in a tri-phasic manner with a mean terminal $t_{1/2}$ of 11.7±7.1 and 11.8±11.5 h for the TC and TCF arms, respectively. With or without 5-FU, the mean area under the curve extrapolated to infinity [AUC(0–∞)] was similar. The compartmental analysis of docetaxel yielded mean docetaxel CL of 20.6±6.7 and 22.4±6.8 l/h/m^2 for TC and TCF, respectively. The geometric mean of the Bayesian CL (TC arm: 19.6±6.7 l/h/m^2; TCF arm: 21.6±6.8 l/h/m^2) were used to generate 90% CI for the ratio of docetaxel CL from TCF treatment (test) versus docetaxel CL from TC treatment (reference). This analysis of variance yielded a

Table 2 Grade 3 and 4 toxicities reported during treatment

	TC, $N=14$		TCF, $N=15$	
	Gr 3, n (%)	Gr 4, n (%)	Gr 3, n (%)	Gr 4, n (%)
Hematological				
Leucopenia	5 (36)	0	4 (27)	2 (13)
Neutropenia	4 (28)	4 (28)	2 (13)	6 (40)
Flu-like symptoms				
Lethargy	1 (7)	0	1 (7)	0
Gastrointestinal				
Anorexia	1 (7)	0	1 (7)	0
Diarrhea	0	0	2 (13)	0
Pain/cramping	0	0	1 (7)	0
Nausea	1 (7)	0	1 (7)	0
Stomatitis	0	0	1 (7)	0
Vomiting	1 (7)	1 (7)	1 (7)	0
Cardiovascular				
Venous	0	0	1 (7)	0
Neurologic				
Constipation	0	0	1 (7)	0
Cortical, somnolence	0	0	1 (7)	0

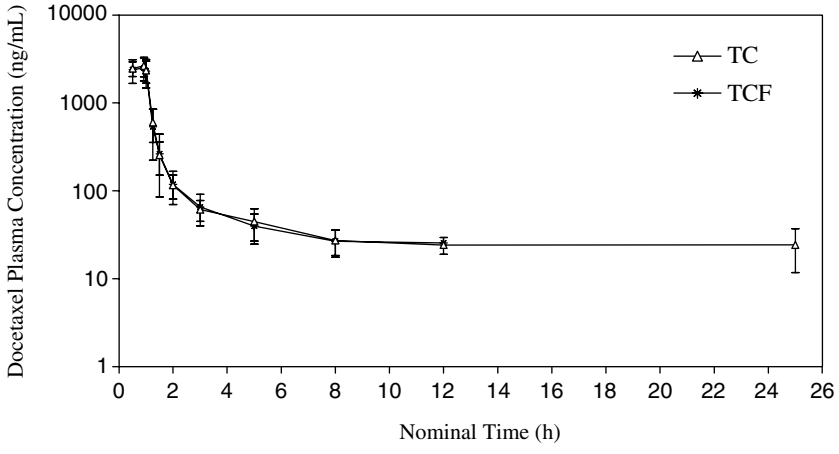

Fig. 1 Mean (± SD) docetaxel plasma concentration–time curves (log-linear scale). *TC* double combination of docetaxel + cisplatin, *TCF* triple combination of docetaxel + cisplatin + 5-FU

Table 3 Mean docetaxel (following a non-compartmental analysis), unbound cisplatin and 5-fluorouracil pharmacokinetics parameters

Treatment	Statistic	C_{max}–C_{ss} (5-FU)			$t_{1/2}$ (h)			AUC(0 → ∞)			CL[a] (l/h/m^2)			V_{ss} (l)		
		T (ng/ml)	C (μg/ml)	F (ng/ml)	T	C	F	T (ng·h/ml)	C (μg·h/ml)	F	T	C	F	T	C	F
TC	*N*	12	12		9	12		9	12		9	12		9	12	
	Mean	2,717.7	1.22		11.7	1.10		3,518.6	3.72		22.2	39.2		197.4	83.67	
	Range	1,479.1–3,573.1	0.85–1.53		4.0–24.0	0.95–1.44		2,114.5–4,550.7	2.96–4.79		16–34.9	29.2–49.1		66.3–544.7	51.9–123.5	
	SD	591.2	0.194		7.1	0.157		733.3	0.523		5.6	6.35		155	19.25	
	CV%	21.8	15.9		60.4	14.3		20.8	14.0		25.1	16.2		78.5	23	
TCF	*N*	12	12	12	10	12	–	10	12	–	10	12	12	10	12	12
	Mean	2,706.6	1.18	265.2	11.8	1.26		3,442.7	3.67		23.2	39.9	234.2	218.2	84.25	1,505.5
	Range	1,397.5–4,061.6	0.96–1.46	158.2–402.6	1.3–36.8	0.90–2.21		2,196–5,277	3.02–4.54		14.0–33.6	30.8–50.1	140–418.8	30.0–708.5	57.4–121	235.4–4,655.2
	SD	715.1	0.172	60.8	11.5	0.382		970.3	0.533		6	6.63	75.8	241.3	17.20	1,147.5
	CV%	26.4	14.6	22.9	97.2	30.3		28.2	14.5		26	16.6	32.4	110.6	20.4	76.2

T docetaxel, *C* cisplatin, *F* 5-fluorouracil, *N* number of patients, *SD* standard deviation, *CV* coefficient of variation, C_{max} maximal concentration, C_{ss} concentration at steady state, $t_{1/2}$ half-life, $AUC(0 \rightarrow \infty)$ area under the curve extrapolated to infinity, *CL* clearance, V_{ss} steady-state volume

[a]Normalized to body surface area

point estimate of 110% (90% CI: 98.3–123.1%). An additional comparison was made to historical docetaxel single agent data, involving 30 gastric cancer patients administered 100 mg/m^2 docetaxel [23]. The geometric mean of the Bayesian docetaxel CL of 21.6 l/h/m^2 for the TCF arm and 19.6 l/h/m^2 for the TC arm were compared with the same value previously reported for single agent docetaxel (mean CL of 19.3 l/h/m^2), and no statistical difference was observed. The point estimated ratio calculated was 111.3% (90% CI: 94.6–131.1%) and 101% (90% CI: 85.1–120.4%) for the triplet and the doublet combinations, respectively.

Concentration of unbound platinum was measured and PK parameters were estimated via non-compartmental analysis methods. Platinum peak plasma concentrations of 1.2 μg/ml were reached at approximately the same time of 2.9 h for unbound platinum in both the TC and TCF arms and the mean (±SD) plasma concentration–time profiles for unbound platinum are similar for the doublet and triplet combinations (Fig. 2). No statistical difference was detected for unbound platinum clearances between treatments; the analysis of variance comparing the unbound platinum clearance in treatment TCF versus TC yielded a *P* value of 0.5990. The point estimate was 105.3% (90% CI: 88.7–125.1%). Similar results were obtained for total platinum pharmacokinetics.

The observed 5-FU plasma concentration curves did not meet the requirements for intended non-compartmental analysis because many patients had too few sample points. As already mentioned, 5-FU half-life and AUC(0–∞) were not calculated due to the insufficient number of sample points. Overall, the comparison of the data obtained in patients given TCF and TC in both arms provides evidence of the lack of clinically relevant pharmacokinetics interference by 5-FU on the disposition of docetaxel and cisplatin.

Discussion

The pharmacokinetics of cytotoxic agents have been related to both their toxic and therapeutic effects. Therefore, when assessing new combinations of drugs, possible clinically relevant PK interactions need to be excluded.

Among new agents active in several cancer models, docetaxel showed a potential synergy with cisplatin and 5-FU, respectively [24]. On this basis, the combination of docetaxel, cisplatin and 5-FU (TCF) was already studied in patients with head and neck, esophageal and gastric cancers. Several phase I–II studies were conducted to evaluate the feasibility and the clinical outcome in neoadjuvant chemotherapy for locally advanced previously untreated squamous cell carcinoma of the head and neck (SCCHN) [1–6]. While all studies tested different combination doses, they indicated a manageable and reversible toxicity and suggested interesting activity. Obviously a phase III study comparing TCF to the

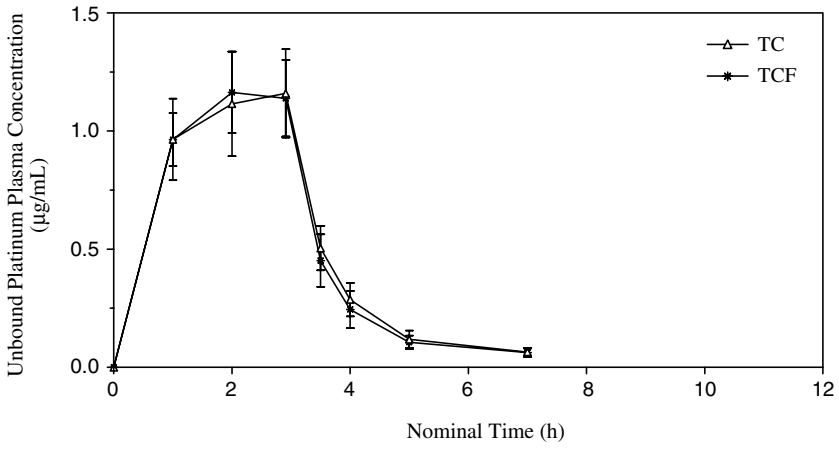

Fig. 2 Mean (± SD) unbound platinum plasma concentration–time curves. *TC* double combination of docetaxel + cisplatin, *TCF* triple combination of docetaxel + cisplatin + 5-FU

standard regimen CF is required, for induction chemotherapy in locally advanced SCCHN, to study a potential improvement in overall response rate and survival in patients with a good performance status for whom such aggressive therapy can be the best option.

The addition of 5-FU to TC combination was suggested in a randomized phase II study to possibly produce a higher overall response rate when compared with TC alone in patients with advanced gastric or gastro-esophageal adenocarcinoma [25]. On this basis the triplet combination was employed as experimental arm and compared with the reference regimen in the USA, cisplatin-5-FU [26], and in Europe, epirubicin-cisplatin-5-FU (ECF) [27]. The preliminary results of these two trials report a significant benefit in overall response rate and time to progression in favor of TCF. Thus, the TCF combination may impact on the future clinical practice in the management of advanced gastric cancer. Recently, the triplet combination was also tested as first-line chemotherapy in patients with advanced esophageal cancer with a high response rate and acceptable toxicities [28]. None of the mentioned studies have assessed the pharmacokinetic interaction between docetaxel, cisplatin and 5-FU.

Although no clinical study was performed to evaluate the pharmacokinetic interaction between cisplatin and 5-FU, several in vitro and in vivo models reported a synergistic effect of the two drugs [29, 30]. This effect was attributed to a reduction in the removal of DNA adducts and to the 5-FU capacity to modulate the repair of platinum–DNA adduct [31]. Docetaxel pharmacokinetic parameters were investigated only when used in combination with cisplatin or 5-FU as doublet combination, and no PK interactions were observed [13–15]. Actually, pharmacokinetic parameters reported for drugs in combination were in the same range observed for single administration. Even if no pharmacokinetic interaction was reported between docetaxel and cisplatin, a pharmacodynamic correlation was found for platinum agent and taxanes. In leukocytes obtained from patients treated with taxanes, a reduction of intracellular accumulation of cisplatin, as well as a reduction in DNA adduct level, was observed with each taxane when compared to non-treated control [32]. Studies of the influence of drug sequence on toxicity and activity found that docetaxel followed by cisplatin led to a lower platinum–DNA adduct than the reversed sequence [33].

The purpose of the current study was to assess the pharmacokinetics of docetaxel, cisplatin-derived platinum and 5-FU, when used in combination to exclude potential and clinically relevant PK interactions. Overall, using a compartmental analysis for docetaxel and a non-compartmental analysis for cisplatin and 5-FU, this study demonstrates there is no PK interaction between the three drugs when used in combination. Mean clearance values for cisplatin and docetaxel were not statistically significantly different between the triplet and doublet combination treatments. Mean PK parameters of all agents were in ranges previously reported for single agent treatment, and docetaxel clearance values obtained in this study were not statistically different from historical single agent data.

In general, treatment with docetaxel in combination therapy was manageable, and the frequency of toxicities reported was consistent with the known safety profile for docetaxel, cisplatin and 5-FU. Only one patient discontinued treatment due to an adverse event of myocardial ischemia during TCF treatment and, as expected, gastrointestinal toxicity was more pronounced in cycles containing 5-FU. Frequencies of hematological and biochemistry toxicities on treatment were consistent with the known safety profiles for the three drugs.

In summary, we can exclude a clinically relevant pharmacokinetic interaction between docetaxel, cisplatin and 5-FU when administered in combination, maintaining an acceptable toxicity profile.

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References

1. Colevas AD, Busse PM, Norris CM et al (1998) Induction chemotherapy with docetaxel, cisplatin, fluorouracil, and leucovorin for squamous cell carcinoma of the head and neck: a phase I/II trial. J Clin Oncol 16:1331–1339
2. Colevas AD, Norris CM, Tisheler RB et al (1999) Phase II of docetaxel, cisplatin, fluorouracil, and leucovorin as induction for squamous cell carcinoma of the head and neck. J Clin Oncol 17:3503–3511
3. Posner MR, Glisson B, Frenette G et al (2001) Multicenter phase I–II trial of docetaxel, cisplatin, and fluorouracil induction chemotherapy for patients with locally advanced squamous cell cancer of the head and neck. J Clin Oncol 19:1096–1104
4. Janinis J, Papadakou M, Panagos G et al (2001) Sequential chemotherapy with docetaxel, cisplatin, and 5-fluorouracil in patients with locally advanced head and neck cancer. Am J Clin Oncol 24:227–231
5. Haddad R, Tishler RB, Norris CM et al (2003) Docetaxel, cisplatin, 5-fluorouracil (tpf)-based induction chemotherapy for head and neck cancer and the case for sequential, combined-modality treatment. Oncologist 8:35–44
6. Schrijvers D, Van Herpen C, Kerger J et al (2004) Docetaxel, cisplatin and 5-fluorouracil in patients with locally advanced unresectable head and neck cancer: a phase I–II feasibility study. Ann Oncol 15:638–645
7. Roth AD, Maibach R, Fazio N et al (2004) 5-Fluorouracil as protracted continuous intravenous infusion can be added to full-dose docetaxel (Taxotere)-cisplatin in advanced gastric carcinoma: a phase I–II trial. Ann Oncol 15:759–764
8. Ringel I, Horowitz S (1991) Studies with RP 56976 (Taxotere): a semisynthetic analog of taxol. J Natl Cancer Inst 83:288–291
9. Bissery MC (1995) Preclinical pharmacology of docetaxel. Eur J Cancer 31A(Suppl 4):S1–S6
10. Urien S, Barrè J, Morin C (1996) Docetaxel serum protein binding with high affinity to alpha$_1$-acid glycoprotein. Invest New Drugs 14:1547–1551
11. Schellens JHM, Ma J, Planting ASTh et al (1996) Relationship between the exposure to cisplatin, DNA-adduct formation in leucocytes and tumour response in patients with solid tumours. Br J Cancer 74:323–326
12. Leichman CG, Fleming TR, Muggia F et al (1995) Phase II study of fluorouracil and its modulation in advanced colorectal cancer: a Southwest Oncology Group Study. J Clin Oncol 13:1303–1311
13. Pronk LC, Schellens JHM, Planting ASTh et al (1997) Phase I and pharmacologic study of docetaxel and cisplatin in patients with advanced solid tumors. J Clin Oncol 15:1071–1079
14. Van Den Neste E, de Valeriola D, Kerger J et al (2000) A phase I and pharmacokinetic study of docetaxel administered in combination with continuous intravenous infusion of 5-fluorouracil in patients with advanced solid tumors. Clin Cancer Res 6:64–71
15. Ando M, Watanabe T, Sasaki Y et al (1998) A phase I trial of docetaxel and 5-day continuous infusion of 5-fluorouracil in patients with advanced or recurrent breast cancer. Br J Cancer 77:1937–1943
16. Loos WJ, Verweij J, Nooter K et al (1997) Sensitive determination of docetaxel in human plasma by liquid–liquid extraction and reverse-phase high-performance liquid chromatography. J Chromatogr B 963:437–441
17. Ma J, Verweij J, Planting AST et al (1995) Current sample handling methods for measurement of platinum–DNA adducts in leucocytes in man lead to discrepant results in DNA adduct levels and DNA repair. Br J Cancer 71:512–517
18. Loos WJ, de Bruijn P, van Zuylen L et al (1999) Determination of 5-fluorouracil in microvolumes of human plasma by solvent extraction and high-performance liquid chromatography. J Chromatogr B Biomed Sci Appl 735:293–297
19. Launay-Iliadis MC, Bruno R, Cosson V et al (1995) Population pharmacokinetics of docetaxel during phase I studies using nonlinear mixed-effect modelling and nonparametric maximum-likelihood estimation. Cancer Chemother Pharmacol 37:47–54
20. Casale F, Canapro R, Serpe L et al (2004): Plasma concentrations of 5-fluorouracil and its metabolites in colon cancer patients. Pharmacol Res 50:173–179
21. Minami H, Ohe Y, Niho S et al (2004) Comparison of pharmacokinetics and pharmacodynamics of docetaxel and cisplatin in elderly and non-elderly patients: why is toxicity increased in elderly patients? J Clin Oncol 22:2901–2908
22. Bruno R, Vivier N, Vergniol JC et al (1996) A population pharmacokinetic model for docetaxel (Taxotere): model building and validation. J Pharmacokinet Biopharm 24:153–172
23. Bruno R, Vivier N, Veyrat-Follet C, Montay G, Rhodes G (2001) Population pharmacokinetics and pharmacokinetic–pharmacodynamic relationships for docetaxel. Invest New Drugs 19:163–169
24. Bissery M, Vrignaud P, Lavelle F (1995) Preclinical profile of docetaxel (Taxotere): efficacy as single agent and in combination. Semin Oncol 22(Suppl 13):3–16
25. Ajani JA, Fodor M, Van Cutsem E et al (2005) Multinational randomized phase II trial of docetaxel (T) and cisplatin (C) with or without 5-fluorouracil (FU) in patients (Pts) with advanced gastric or GE junction adenocarcinoma (AGC-AGE-JC). J Clin Oncol 23:5660–5667
26. Ajani JA, Van Cutsem E, Moiseyenko V et al (2003) Docetaxel (D), cisplatin, 5-fluorouracil compared with cisplatin (C) and 5-fluorouracil (F) for chemotherapy-naïve patients with metastatic or locally recurrent, unresectable gastric carcinoma (MGC): interim results of a randomized phase III trials (V325). Proc Am Soc Clin Oncol A #999
27. Roth AD, Maibach R, Falk S et al (2004) Docetaxel–cisplatin–5FU (TCF) versus docetaxel–cisplatin (TC) versus epirubicin–cisplatin–5FU (ECF) as systemic treatment for advanced gastric carcinoma (AGC): a randomized phase II trial of the Swiss Group for Clinical Research (SAKK). Proc Am Soc Clin Oncol 22(14S):4020
28. Yuki S, Komatsu Y, Machida N et al (2005) Phase I study of docetaxel, cisplatin and 5-fluorouracil (TPF) as first-line chemotherapy in patients with advanced esophageal cancer. Hokkaido Gastrointestinal Cancer Study Group (HGCSG) study. Proc Am Soc Clin Oncol 23:4181
29. Scanlon KJ, Newman EM, Lu Y et al (1986) Biochemical basis for cisplatin and 5-fluorouracil synergism in human ovarian carcinoma cells. Proc Natl Acad Sci 83:8923–8925
30. Scanlon KJ, Lu Y, Kashani-Sabet M et al (1988) Mechanisms for cisplatin-Fura synergism and cisplatin resistance in human ovarian carcinoma cells in vitro and in vivo. Adv Exp Med Biol 244:127–135
31. Crul M, van Waardenburg RCAM, Beijnen JH, Schellens JHM (2002) DNA-based drug interactions of cisplatin. Cancer Treat Rev 28:291–303
32. Ma J, Verweij J, Planting AST et al (1996) Docetaxel and paclitaxel inhibit DNA-adduct formation and intracellular accumulation of cisplatin in human leukocytes. Cancer Chemother Pharmacol 37:382–384
33. McLeod HL (1998) Clinically relevant drug–drug interaction in oncology. Br J Clin Pharmacol 45:539–544