Coadministration of oxaliplatin does not influence the pharmacokinetics of gemcitabine

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We investigated the possible pharmacokinetic interactions of gemcitabine and oxaliplatin in patients with advanced solid tumors. Ten patients with advanced stage solid tumors were treated with gemcitabine (1500 mg/m^2) as a 30-min intravenous infusion on days 1 and 8, followed by oxaliplatin (130 mg/m^2) as a 4-h intravenous infusion, on day 8 every 21 days. Pharmacokinetic data for 24 h after dosing were obtained for both day 1 (gemcitabine without oxaliplatin coadministration) and day 8 (gemcitabine with oxaliplatin) during the first cycle of treatment. Gemcitabine levels in plasma were quantified using a reverse-phase high-performance liquid chromatography assay with ultraviolet detection, and total and ultrafiltrated platinum levels by flameless atomic absorption spectrophotometry with deuterium correction. All pharmacokinetic parameters of gemcitabine seemed to be unchanged when coadministered with oxaliplatin (day 8) compared with pharmacokinetic data of gemcitabine given as a single agent (day 1). The mean (maximum) concentration of gemcitabine on days 1 and 8 was 13.57 (±7.42) and 10.23 (±5.21) mg/l, respectively (P=0.28), and the mean half-life was 0.32 and 0.44 h, respectively (P=0.40). Similarly, the P-values for AUC_{0-24} and the observed clearance were 0.61 and 0.30, respectively. Plasma total and free platinum levels were in agreement with other published data. Gemcitabine disposition appeared to be unaffected by oxaliplatin coadministration because no significant changes in pharmacokinetics between day 1 (gemcitabine without oxaliplatin coadministration) and day 8 (gemcitabine with oxaliplatin) were observed. *Anti-Cancer Drugs* 17:1185–1191 © 2006 Lippincott Williams & Wilkins.

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Introduction

Gemcitabine (2′,2′-difluorodeoxycytidine; Gemzar, Eli Lilly, Indianapolis, Indiana, USA) is a novel nucleoside analog of deoxycytidine with a unique mechanism of action, favorable toxicity and broad-spectrum antineoplastic activity in many solid tumors. Gemcitabine is phosphorylated intracellularly to its active forms of gemcitabine diphosphate and gemcitabine triphosphate, and thus by inhibiting ribonucleotide reductase [1] causes DNA chain termination [2]. Gemcitabine has significant activity in many tumors, including pancreatic cancer, non-small-cell lung cancer, breast cancer, ovarian cancer and bladder cancer [3]. Gemcitabine is generally very well tolerated, and causes dose-limiting myelosuppression, mild transaminase elevations, fever, rash, edema and flu-like symptoms [4]. Due to its favorable toxicity profile, high doses up to 2400 mg/m^2 have been administered on a weekly schedule for 3 consecutive weeks in cycles every 4 weeks [5].

Oxaliplatin (L-OHP, Eloxatin; Sanofi-Aventis, Bridgewater, NJ, USA) is a platinum derivative that lacks the nephrotoxicity of cisplatin and causes less myelosuppression than carboplatin, while it is active in cisplatin-resistant tumors [6]. Oxaliplatin-induced adducts inhibit DNA synthesis and resistance is due to mismatch repair and enhanced replicative bypass [6]. Oxaliplatin is active against many tumors, including colorectal cancer, ovarian cancer, non-small-cell lung cancer, breast cancer, non-Hodgkin's lymphomas and gastrointestinal tumors [7]. The recommended dose is 130 mg/m^2 administered as a 2–6 h intravenous infusion every 3 weeks. Toxicity includes dose-dependent and cumulative peripheral neuropathy that is usually reversible after discontinuation of treatment, mild hematologic toxicity, nausea, vomiting, and diarrhea.

On the basis of the different mechanisms of action of the two drugs, the in-vitro evidence of synergy when combined [8] and the broad spectrum of antineoplastic activity with nonoverlapping toxicity, phase I–II studies of the combination have already been conducted in various tumor types [9–17]. In a dose-escalation study, we have previously reported that tolerability was excellent and full doses of both drugs, e.g. gemcitabine 1200–1400 mg/m^2 on days 1 and 8 and oxaliplatin

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130 mg/m^2 on day 8, can be utilized for further phase II studies [16]. In that study, which included pharmacokinetic (PK) measurements only on day 8 of the first cycle, when both drugs were administered sequentially, we found no significant interaction between them [16]. No PK data were, however, collected from day 1 when gemcitabine was given alone, and therefore direct comparisons for the same patients between gemcitabine monotherapy and gemcitabine–oxaliplatin coadministration were not possible. Moreover, other phase I–II studies with different schedules and dosages have reported lack of any PK interaction between gemcitabine and oxaliplatin when the obtained PK measurements were indirectly compared with previous PK studies of each drug given as monotherapy [9,12,13].

To directly evaluate any possible drug–drug interaction, in the present study we obtained PK measurements on both days 1 and 8 from 10 patients with various solid tumors who received a fixed dose of gemcitabine (1500 mg/m^2) on days 1 and 8 and oxaliplatin (130 mg/m^2) on day 8. The sequence of administering gemcitabine before oxaliplatin was chosen on the basis of in-vitro data showing increased efficacy compared with the opposite sequence [8].

Patients and methods

Patients

Patients were 18–75 years of age and had histologically or cytologically confirmed, advanced or metastatic solid tumors refractory to conventional therapy. Before surgery, radiotherapy (to less than 25% of marrow-containing bones) or chemotherapy (maximum 2 prior regimens) was allowed, but a treatment-free interval of at least 4 weeks was required before study entry. Other inclusion criteria were as follows: performance status < 2 [World Health Organization (WHO)]; adequate blood counts (absolute neutrophil count > 1500/μl, Hgb > 10 g/dl, and platelets $> 100\,000$/μl); adequate renal function (serum creatinine < 2 mg/dl); adequate hepatic function (total bilirubin < 1.5 mg/dl and SGPT/SGOT < 3 times upper normal limit); pre-existing peripheral neuropathy up to National Cancer Institute grade 1; and a life expectancy of at least 3 months. All patients signed a written informed consent before entering the study. The present study was approved by the Ethics and Scientific Committees of the University Hospital of Heraklion.

Treatment

Gemcitabine was administered as a 30-min intravenous infusion on days 1 and 8 at a dose of 1500 mg/m^2. Oxaliplatin was administered on day 8, immediately following gemcitabine administration, as a 4-h intravenous infusion, without prehydration or posthydration, at a dose of 130 mg/m^2. Treatment cycles were repeated every 3 weeks. The 'standard' antiemetic regimen included ondansentron 16 mg, dexamethasone 8 mg and diazepam 5 mg given intravenously 30 min before chemotherapy administration. Days 1 and 8 treatments were administered on scheduled dates without any delay or dose reduction if the laboratory inclusion criteria were met; otherwise, even for grade 1 toxicity, which did not meet the inclusion criteria, treatment of day 1 or 8 was postponed for up to 7 days or until resolution of the prohibitive toxicity. Doses were reduced by 20% in case of febrile neutropenia or platelet transfusion. In case of grade 3–4 neurotoxicity, treatment with oxaliplatin was discontinued.

Follow-up

Hematologic toxicity was followed with at least weekly complete blood counts, differential counts and, in case of grade 3–4 toxicity, daily counts until recovery. Blood chemistry, as well as a detailed toxicity questionnaire and a physical examination were performed before each cycle. Toxicities and objective responses were graded according to WHO criteria [18]. Patients evaluable for response should have measurable disease and should have completed at least two cycles of chemotherapy.

Blood samples and pharmacokinetic assays

To study the PK profile of gemcitabine, blood sampling was performed on days 1 and 8 of the first cycle. Samples were drawn in heparinized tubes containing tetrahydrouridine (0.25 mg) to inhibit cytidine deaminase activity. Blood was collected before treatment and immediately at the end of the 30 min intravenous infusion, and then at 1, 4, 8 and 24 h after the start of the infusion. Plasma was separated by centrifugation at 1500 r.p.m. for 10 min at 4°C. After centrifugation, plasma was transferred to polypropylene tubes and frozen at −80°C until further analysis. Gemcitabine's plasma levels were quantified using reverse-phase high-performance liquid chromatography with ultraviolet detection [19]. The chromatographic system (Shimadzu LC-10A/10Avp; Shimadzu, Duisburg, Germany) consisted of an LC-10AD pump, an SCL-10Avp controller, an SIL-10 Avp autosampler and an SPD-M10Avp UV detector (monitored at 275 nm). Plasma (1 ml) was filtered through syringe filters 0.22 μm (Gelman 4612, Pall Corporation, Missouri, USA) and 20 μl of the aliquot was injected into a μ-Bondapack C18 10 μm, 300 × 3.9-mm column (Waters, Milford, Massachusetts, USA). The mobile phase consisted of ammonium acetate 0.5 mol/l at pH 6.8 (buffer A) and 50% methanol in deionized water (buffer B), and a linear gradient elution ranging from 100% buffer A to 80% buffer B over a 15-min running, at a flow rate 1 ml/min. Calculation of gemcitabine concentration was based on a standard calibration curve using standard solutions of gemcitabine (Eli Lilly) with good linearity ($r^2 = 0.9998$) over the analytical range 0.1–10 mg/l. The detection limit was determined as 0.078 mg/l of plasma.

Platinum concentration measurements were performed in all patients during the 4-h intravenous infusion of oxaliplatin (130 mg/m^2) on day 8 after gemcitabine infusion. Blood samples were drawn into heparinized tubes before starting, in the middle of and immediately at the end of the 4-h intravenous infusion, and then at 30 min, 1, 2, 4, 6 and 24 h after infusion. Plasma was separated by centrifugation at 1500 r.p.m. for 10 min at 4°C. Oxaliplatin was assayed as total platinum and ultrafiltrated platinum fraction (PUF). Therefore, plasma samples were divided into two aliquots. The first aliquot was used to determine the total platinum and was diluted by adding 25% Triton X-100; 20 µl was used without any further preparation for the measurement. The ultrafiltrated, considered as nonprotein-bound drug (free-drug), was obtained by centrifugation at 4500 r.p.m. for 30 min at −4°C using Centrex UF2 micropartition devices of 30 000-Da cut-off (Schleicher & Schuell, Dassel, Germany) and measured immediately after filtration without any preparation. Both total and ultrafiltrated platinum were determined by flameless atomic absorption spectrophotometry with deuterium correction on a Shimadzu system of an AA-6800 spectrophotometer and a GFA-EX 7 graphite furnace (Shimadzu Deutschland GmbH, Duisburg, Germany) at 265.9 nm [20]. Calculation of oxaliplatin concentration was based on a standard calibration curve (range 16–96 ng/ml) using a standard solution of platinum (Fluka, Buchs, Switzerland) with good linearity ($r^2 = 0.9998$).

The mean assay precision is expressed as the coefficient of variation of the estimated concentrations of quality control standards, averaged 2.8% for gemcitabine and 9.4% for platinum.

Pharmacokinetic analysis and statistics

The concentration–time data for both drugs were fitted to a noncompartmental model using WinNonlin software, standard version 2.1 (Pharsight, Palo Alto, California, USA). The maximum plasma concentration (C_{max}) and the time of occurrence of C_{max} (t_{max}) were the observed values. The area under the concentration versus time curve (AUC) was calculated using the linear trapezoidal method with extrapolation of the curve either to 24 h (AUC_{0-24}) or to infinity ($AUC_{0-\infty}$). AUC was extrapolated to infinity by dividing the last measured concentration by the terminal rate constant (k), defined as the slope of at least the final three points of the log-linear concentration–time plot. Terminal half-life ($t_{1/2}$) was calculated as 0.693/k and total body clearance (CL) was expressed as 'dose/AUC'. Volume at steady state (V_{ss}) was calculated by 'MRT_{inf}XCL', where MRT_{inf} is the mean residence time extrapolated to infinity. The evaluation of the potential interaction between gemcitabine and oxaliplatin was based on the significant differences on PK parameters of gemcitabine between days 1 and 8 using a paired t-test. In addition, the interpatient variability for each drug was estimated according to coefficient of variation.

Statistical analysis of PK parameters was conducted with Student's t-test (two-tailed analysis), whereas relationships between hematological toxicities and major PK parameters were assessed by means of Spearman's correlation coefficient. Both tests were performed using SPSS (Version 13.0 for Windows; SPSS 2005, Chicago, Illinois, USA). Statistical significance was accepted at the level of $P < 0.05$.

Results

Patients, response and toxicity

Ten patients with various solid tumors were enrolled in the study. The characteristics of patients are shown in Table 1. All patients were previously treated with at least one chemotherapy regimen. The median number of cycles received was 3 (range 1–6). All patients were evaluable for response and toxicity. One objective (complete response) was achieved in a patient with ovarian carcinoma who presented pulmonary and lymph node involvement; there were no partial responses. Four patients, all with breast cancer, had stable disease for a median of 5 (range 2.6–14.4) months. Five patients had progressive disease. The toxicity of the regimen is presented in Table 2. Four (40%) patients developed grade 3 neutropenia, whereas grade 3/4 thrombocytopenia occurred in three (30%) patients. Grade 3 neurosensory was observed in one (10%) patient and grade 3 asthenia in two (20%). No patient developed febrile neutropenia and there were no toxic deaths. During the first cycle, day 8 dosing was delayed in one patient because of unresolved neutropenia from day 1 gemcitabine administration. During all cycles, day 8 dosing was delayed in five out of 10 patients because of unresolved hematological toxicity.

Table 1 Patients' characteristics

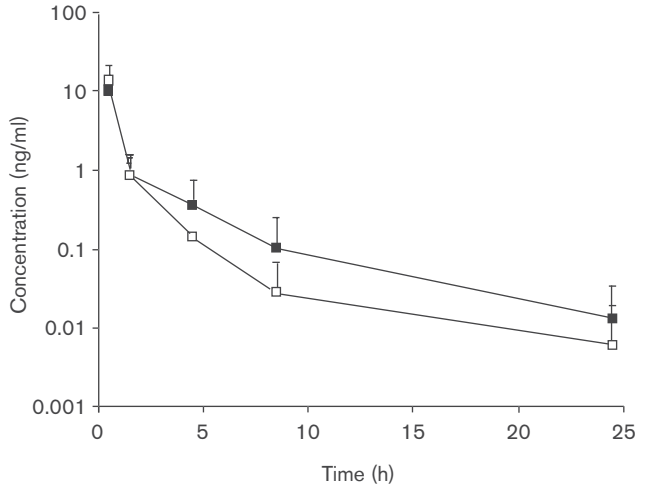
	Number of patients	%
Patients enrolled	10	
Age		
median (range)	61 (48–71)	
Gender		
male/female	2/8	20/80
Performance status (WHO)		
0	1	10
1	8	80
2	1	10
Number of previous regimens		
1	6	60
2	4	40
Type of tumor		
breast cancer	6	60
ovarian cancer	2	20
bladder carcinoma	1	10
non-small cell lung cancer	1	10

WHO, World Health Organization.

Table 2 Toxicity per [*n* (%)] patient during all cycles of treatment

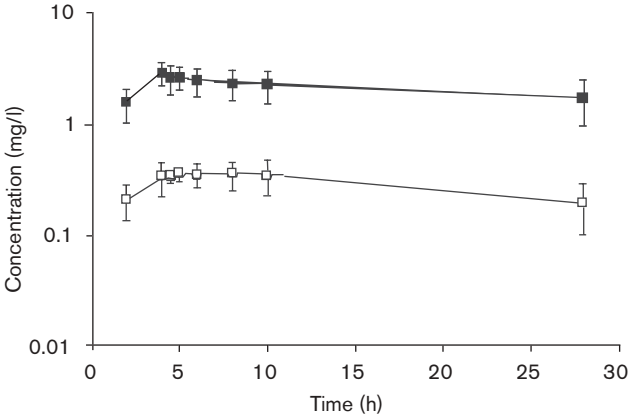
Toxicity	Grade			
	1	2	3	4
Neutropenia	1 (10)	3 (30)	4 (40)	–
Anemia	5 (50)	3 (30)	–	–
Thrombocytopenia	3 (30)	1 (10)	2 (20)	1 (10)
Nausea/vomiting	1 (10)	5 (50)	–	–
Mucositis	–	1 (10)	–	–
Diarrhea	3 (30)	1 (10)	–	–
Constipation	–	3 (30)	–	–
Neurotoxicity	6 (60)	–	1 (10)	–
Asthenia	2 (20)	3 (30)	2 (20)	–
Onycholysis	1 (10)	–	–	–
Fever with neutropenia	–	–	–	–
Non-neutropenic fever	2 (20)	–	–	–

Fig. 1



Mean observed gemcitabine concentrations (± SD) in patients ($n=10$) receiving a 30-min intravenous infusion of gemcitabine at 1500 mg/m^2 on day 1 (dashed squares) and in combination with a 4-h intravenous infusion of oxaliplatin on day 8 (opened squares).

Fig. 2



Mean observed concentrations (± SD) of total (dashed squares) and free (opened squares) platinum in plasma from patients ($n=10$) who received oxaliplatin at 130 mg/m^2 as a 4-h intravenous infusion only on day 8.

Table 3 Plasma pharmacokinetic parameters on day 1 and day 8 from patients receiving gemcitabine

	Day 1	Day 8	*P*-value[a]
C_{max} (mg/l)[b]	13.57 ± 7.42	10.23 ± 5.21	0.28
t_{max} (h)	0.5	0.5	–
$t_{1/2}$ (h)[b]	0.32 ± 0.27	0.44 ± 0.33	0.40
AUC_{0-24} (mg h/l)[b]	10.66 ± 6.92	9.14 ± 5.42	0.61
CL (l/h/m^2)[b]	275.13 ± 238.89	180.99 ± 77.92	0.30
V_{ss} (l)[b]	98.03 ± 80.54	121.74 ± 83.05	0.56

[a]*t*-test; between day 1 and day 8.
[b]Mean ± SD ($n=10$).
C_{max}, maximum concentration; AUC_{0-24}, area under the concentration–time curve with extrapolation to 24 h; t_{max}, time of occurrence of C_{max}; $t_{1/2}$, elimination half-life; CL, clearance; V_{ss}, volume of distribution.

Pharmacokinetics

PK data for gemcitabine (both for days 1 and 8) and oxaliplatin (day 8) were available in all patients. The mean concentration–time profiles of gemcitabine and platinum are shown in Figs 1 and 2. Mean and standard deviation values of the PK parameters for gemcitabine are listed in Table 3. Peak concentrations for gemcitabine were observed at the end of infusion for all patients ($t_{max} = 0.5$ h). Mean maximum concentration (C_{max}) and the mean concentration at the end of the infusion (C_{end}) of gemcitabine were the same, and they were estimated at 13.57 (± 7.42) mg/l on day 1 and 10.23 (± 5.2) mg/l on day 8, respectively. Thereafter, concentrations decreased with a mean half-life of approximately 0.32 h (or 19.2 min) for day 1 and 0.44 h (or 26.4 min) for day 8. AUC_{0-24} was not different between days 1 and 8 ranging from 10.66 to 9.14 mg h/l. The mean values for CL and V_{ss} were 275.13 l/h/m^2 and 98.03 l on day 1, and 180.99 l/h/m^2 and 121.74 l on day 8. None of the PK parameters measured were different between days 1 and 8, as the significance values ranged between 0.28 and 0.61 (Table 3).

Table 4 shows the PK parameters of free and total platinum in all patients who received oxaliplatin on day 8. Mean C_{max} was 3.09 (± 0.65) and 0.41 (± 0.07) mg/l in the total and ultrafiltrated fraction, respectively. Total platinum concentration at the end of oxaliplatin infusion (C_{end}) was 2.83 (± 0.67) and 0.36 (± 0.06) mg/l in PUF. The mean half-life was 28.13 and 22.16 h for total and free platinum, respectively. The mean areas under the concentration–time curves (AUC_{0-24} and $AUC_{0-\infty}$) were determined at 55.79 and 235.15 mg h/l for total, and 7.70 and 23.63 mg h/l for free platinum. The V_{ss} of total plasma platinum and PUF were 55.65 and 372.35 l, respectively.

Table 4 Plasma pharmacokinetic parameters of total platinum and PUF from patients receiving oxaliplatin (day 8)

	Total platinum	PUF[a]
C_{max} (mg/l)[b]	3.09 ± 0.65	0.41 ± 0.07
C_{end} (mg/l)[b]	2.83 ± 0.67	0.36 ± 0.06
$t_{1/2}$ (h)[b]	28.13 ± 8.98	22.16 ± 9.18
AUC_{0-24} (mg h/l)[b]	55.79 ± 17.11	7.70 ± 2.36
$AUC_{0-\infty}$ (mg h/l)[b]	235.15 ± 175.38	23.64 ± 16.61
CL (l/h/m^2)[b]	0.88 ± 0.57	8.93 ± 5.76
V_{ss} (l)[b]	55.66 ± 15.53	372.35 ± 106.61

[a]Platinum ultrafiltrated fraction.
[b]Mean ± SD (n = 10).
C_{max}, maximum concentration; AUC_{0-24}, area under the concentration–time curve with extrapolation to 24 h; $AUC_{0-\infty}$, area under the concentration–time curve with extrapolation to infinity; t_{max}, time of occurrence of C_{max}; $t_{1/2}$, elimination half-life; CL, clearance; V_{ss}, volume of distribution.

Table 5 Spearman correlations for hematological toxicities and C_{max}, AUC_{0-24} and CL (both drugs; day 8)

Toxicity	C_{max}		AUC_{0-24}		CL	
	Rho[a]	*P*	Rho[a]	*P*	Rho[a]	*P*
Gemcitabine						
neutropenia	−0.02	0.96	0.25	0.49	−0.17	0.66
anemia	−0.42	0.23	0.05	0.89	−0.13	0.73
thrombocytopenia	0.61	0.06	0.66[b]	0.04	0.63	0.07
Oxaliplatin (total fraction)						
neutropenia	−0.67[b]	0.03	−0.60	0.06	0.26	0.47
anemia	−0.44	0.21	0.12	0.73	−0.52	0.12
thrombocytopenia	−0.42	0.21	−0.51	0.13	0.70[b]	0.02

[a]Spearman's correlation coefficient index.
[b]The correlation is significant ($P<0.05$; two-tailed).
C_{max}, maximum concentration; AUC_{0-24}, area under the concentration–time curve with extrapolation to 24 h; CL, clearance.

CL of platinum was 0.88 l/h/m^2 in plasma and 8.93 l/h/m^2 in PUF.

Pharmacokinetics and toxicity

Further exploratory analysis was undertaken to evaluate, for both drugs, the relationship between PK parameters and toxicity. We found significant correlations (Table 5) between AUC_{0-24} and thrombocytopenia ($P < 0.05$) for gemcitabine, and CL with thrombocytopenia ($P = 0.02$) for total fraction of platinum. Anemia and neutropenia, which were common toxicities, did not show significant association with any of the PK parameters of the two drugs, except for a negative association between neutropenia and C_{max} of platinum (Table 5).

Discussion

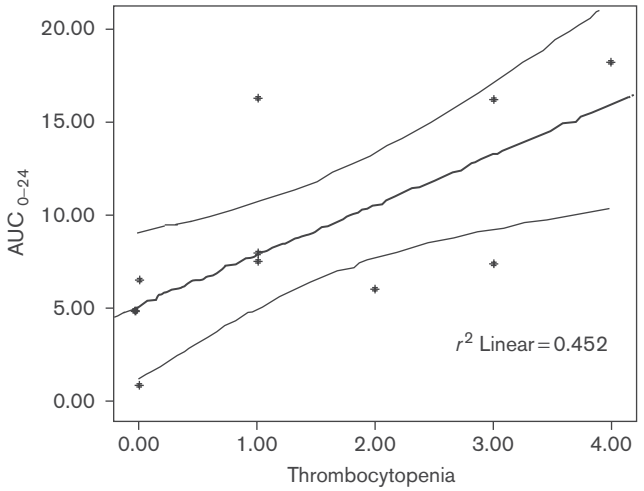
So far, all the published data on the possible PK interaction between gemcitabine and oxaliplatin were incomplete because of the absence of any internal control for the gemcitabine monotherapy in the same patients [9,12,13,16]. This study was designed to directly assess the effect of oxaliplatin on gemcitabine PKs in patients with advanced solid tumors by comparing PK parameters of gemcitabine between the combination day (day 8) and the monotherapy day (day 1). Overall, we found that the combined administration had no significant effect on the PKs of gemcitabine.

Although some of our PK data for gemcitabine or oxaliplatin showed a rather large variability, all the mean values are in accordance with other already published reports [9,12,13,21–25]. The previous dose-escalating study conducted by our group on the same drug combination showed that the PK parameters measured for both drugs were dose independent and it was concluded that, based on those data, the PK profile of both drugs was not modified as a result of the concomitant administration [16]. The present results for gemcitabine confirm our previous study, but with better coefficient variation values (43–75%). On the day of the concomitant infusion of both drugs (day 8), the maximum levels of gemcitabine concentration as well as the other PK parameters (Table 3) were similar to the data reported in other studies using the same or proportional schedule as in the present study [9,12,21–23].

Evaluation of oxaliplatin kinetics when combined with gemcitabine also has been carried out by other groups, but with different schedules and dosages [9,13,16]. The PK profile of oxaliplatin in the present study (on day 8) was also comparable to previously reported studies of oxaliplatin monotherapy administered at the same dose [24,25]. For the total drug fraction, maximum concentrations (C_{max}) were obtained at the end of 4-h infusion in most of the patients (Fig. 2), whereas the t_{max} for the – considered to be – free drug fraction was shifted to 1.0 h after infusion (Fig. 2). Taking into account the terminal half-lives of total and free fraction of oxaliplatin, the $AUC_{0-24}/AUC_{0-\infty}$ ratios for oxaliplatin were calculated to be 0.24 and 0.33, respectively. These are in accordance with the published data by Extra *et al.* [26] where the ratio was determined as 0.39 (for total drug) and 0.69 (for the free fraction). In addition, the percentage of free to total drug for AUC_{0-24} and $AUC_{0-\infty}$ reported in this study (13.8 and 10.0%, respectively) has also been reported by other groups [16,24–26]. Finally, because of the irreversible binding of platinum to proteins, DNA and other cellular macromolecules, the volume of distribution for the ultrafiltrated fraction was as high (372.35 l) as it has been previously reported [24,26,27].

Exposure to gemcitabine and oxaliplatin has been associated with hematological toxicity [16]. The correlation of PK parameters with major toxicities showed that the strongest relationship for the gemcitabine was between AUC_{0-24} and thrombocytopenia (Table 5 and Fig. 3), whereas a similar effect was observed between CL and thrombocytopenia for oxaliplatin (Table 5). The significant correlation of gemcitabine AUC_{0-24} and thrombocytopenia presented in Fig. 3 ($r^2 = 0.452$ and mean confidence intervals of 95%) is a well-known side-effect of gemcitabine treatment either as monotherapy

Fig. 3



Scatterplot of gemcitabine AUC_{0-24} and thrombocytopenia (National Cancer Institute toxicity grades 0–4), including all cycles.

[16] or in combination with agents that are similar to oxaliplatin [28]. The negative correlation between neutropenia and oxaliplatin C_{max} as well as the lack of association between anemia or neutropenia with any of the PK parameters of either drug, maybe due to the administration of growth factors (granulocyte colony-stimulating factor and/or erythropoetin) to some of the patients during the study.

To our knowledge, this is the first PK study reported for this combination comparing the PK profile of combined gemcitabine therapy with that of gemcitabine monotherapy for the same patients. Statistical analysis of all detected parameters showed no significant changes as the *P*-values for gemcitabine ranged between 0.21 and 0.51 (Table 3). A recently published study by de Lange *et al.* [29] showed that weekly administration of gemcitabine did not result in accumulation of the drug itself (gemcitabine) or its metabolites (dFdU and dFdCTP). Moreover, the concentrations of both gemcitabine and the active metabolite gemcitabine triphosphate (dFdCTP) in plasma and white blood cells, respectively, were found not to be increased when gemcitabine was combined with cisplatin in two different treatment schedules [30]. As there is no evidence of changes in gemcitabine kinetics between days 1 and 8 when given either as a single agent [29] or in combination with a platinum compound [30,31], we conclude that, based on the presented PK data, the coadministration of oxaliplatin does not influence the PKs of gemcitabine.

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