

Drug-Administration Sequence Does Not Change Pharmacodynamics and Kinetics of Irinotecan and Cisplatin

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ABSTRACT

In this study, 11 patients with solid tumors were randomized to receive irinotecan (CPT-11; 200 mg/m²) as a 90-min i.v. infusion, immediately followed by cisplatin (CDDP; 80 mg/m²) as a 3-h i.v. infusion in the first course and the reversed sequence in the second course or *vice versa*. No significant differences in any toxicity were observed between the treatment schedules (decrease in absolute neutrophil count, 74.7 ± 18.3 versus 80.3 ± 18.0%; *P* = 0.41). CPT-11 lactone clearance was similar to single agent data and not significantly different between study courses (60.4 ± 17.1 versus 65.5 ± 16.3 liter/h/m²; *P* = 0.66). The kinetic profiles of the major CPT-11 metabolites SN-38, SN-38 glucuronide, 7-ethyl-10-[4-*N*-(5-aminopentanoic acid)-1-piperidino]carbonyloxycamptothecin (APC), and 7-ethyl-10-[4-*N*-(1-piperidino)-1-amino]carbonyloxycamptothecin (NPC) were also sequence independent (*P* ≥ 0.20). In addition, CPT-11 had no influence on the clearance of nonprotein-bound CDDP (40.8 ± 16.7 versus 50.3 ± 18.6 liter/h/m²; *P* = 0.08) and the platinum DNA-adduct formation in peripheral leukocytes in either sequence (1.94 ± 2.20 versus 2.42 ± 1.62 pg Pt/μg DNA; *P* = 0.41). These data indicate that the toxicity of the combination CPT-11 and CDDP is schedule independent and that there is no mutual pharmacokinetic interaction.

INTRODUCTION

Topoisomerase I inhibitors have demonstrated important antitumor activity as single agents in various tumor types. Their mechanism of action suggests that they might interfere in processes involved in DNA repair and might enhance cytotoxicity when combined with DNA-damaging agents. Interactions of topoisomerase I inhibitors with platinum-derivatives have been studied *in vitro* and *in vivo*, and the interaction observed for the combination of CPT-11² and CDDP varied with the cell line studied (1–4). Preclinical data also seemed to suggest the potential of a sequence-dependent effect, with synergy increasing when CDDP preceded CPT-11 incubation as compared with concomitant exposure to both drugs in various cell lines (2). However, the sequence-dependent cytotoxicity of the combination of topoisomerase I inhibitors and platinum-derivatives also seemed to vary with the cell line studied and the schedule used (1, 2).

In general, the design of effective combination chemotherapy regimens requires adequate attention to possible drug interactions at the pharmacokinetic and/or pharmacodynamic level. Until now, the importance of drug sequencing for the combination of topoisomerase I inhibitors and platinum-derivatives has clinically only been investigated for the combination of topotecan and CDDP (5, 6). When CDDP was administered before a 5-day schedule of topotecan, significantly more and severe hematological toxicity was encountered than with the alternate sequence. Pharmacokinetic studies suggested that the differences in toxicity were due, in part, to a slower topotecan clearance when CDDP preceded topotecan (5).

In all Phase I studies on the combination of CPT-11 and CDDP, CPT-11 administration preceded that of CDDP (1, 7–13), and pharmacokinetic data were only scarcely obtained (8). Against this background, we initiated a study in which patients were treated in a randomized cross-over design to determine whether the sequence of CPT-11 and CDDP administration has any influence on the observed toxicity or is related to any pharmacokinetic interaction between the drugs.

MATERIALS AND METHODS

Eligibility Criteria. Patients with a histologically or cytologically confirmed diagnosis of a malignant solid tumor

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² The abbreviations used are: CPT-11, irinotecan (7-ethyl-10-[4-(1-piperidino)-1-piperidino]-carbonyloxycamptothecin); CDDP, cisplatin; *V*_{ss}, volume of distribution at steady state; AUC, area under the plasma concentration-time curve; SN-38, 7-ethyl-10-hydroxycamptothecin; SN-38G, SN-38 glucuronide; APC, 7-ethyl-10-[4-*N*-(5-aminopentanoic acid)-1-piperidino]carbonyloxycamptothecin; NPC, 7-ethyl-10-[4-*N*-(1-piperidino)-1-amino]carbonyloxycamptothecin; UNL, upper normal limit; CYP450, cytochrome P-450.

Table 1 Summary of hematological pharmacodynamics

Data were obtained from patients after treatment with a 90-min i.v. infusion of CPT-11 at a dose level of 200 mg/m² given either before (CPT-11→CDDP; first course) or after CDDP at a dose level of 80 mg/m² (CDDP→CPT-11; second course) or *vice versa*. The relative hematological toxicity (*i.e.*, the percentage decrease in blood cell count) was defined as: %decrease = [(pretherapy value-nadir value)/(pretherapy value)] × 100%. Data represent mean values ± SD.

Parameter	CPT-11→CDDP	CDDP→CPT-11	CL (θ) ^a	P ^b
Leukocytes				
Nadir (×10 ⁻⁹ /liter)	2.54 ± 1.15	2.23 ± 1.29	-1.70 and 1.08	0.50
%decrease WBC	65.7 ± 20.9	69.6 ± 18.1	-19.6 and 27.5	0.61
Neutrophils				
Nadir (×10 ⁻⁹ /liter)	0.93 ± 0.85	0.89 ± 0.67	-0.83 and 0.75	0.87
%decrease ANC	74.7 ± 18.3	80.3 ± 18.0	-15.1 and 26.5	0.41
Platelets				
Nadir (×10 ⁻⁹ /liter)	219 ± 57.6	198 ± 61.2	-47.8 and 7.0	0.09
%decrease PLC	34.3 ± 18.8	38.8 ± 25.4	-18.5 and 27.5	0.55

^a CL (θ), 95% confidence limits for the mean difference; ANC, absolute neutrophil count; PLC, platelet count.

^b Paired Student's *t* test.

refractory to standard forms of therapy were eligible. All patients had adequate hematopoietic [absolute neutrophil count ($\geq 2.0 \times 10^9$ /liter) and platelet count ($\geq 100 \times 10^9$ /liter)], renal [serum creatinine concentration ($\leq 135 \mu\text{mol/liter}$) or creatinine clearance ($\geq 60 \text{ ml/min}$)], and hepatic function [total serum bilirubin ($\leq 1.25 \times \text{UNL}$) and serum aspartate aminotransferase and alanine aminotransferase ($\leq 3.0 \times \text{UNL}$); in case of liver metastasis: total serum bilirubin ($\leq 1.5 \times \text{UNL}$) and serum aspartate aminotransferase and alanine aminotransferase ($\leq 5.0 \times \text{UNL}$)]. All patients gave written informed consent before study entry.

Treatment Plan and Drug Administration. Patients were randomized to one of two treatment groups. In group A, patients received CPT-11 as a 90-min i.v. infusion at a dose of 200 mg/m² on day 1, immediately followed by the infusion of CDDP at a dose of 80 mg/m² as a 3-h i.v. infusion diluted in 250 ml of sodium chloride 3% (w/v) on day 1. Doses were selected based on experience obtained in a preceding Phase I study.³ In the second course, the sequence of administration of CPT-11 and CDDP was reversed, administering CDDP before CPT-11 at the same doses. In case a patient encountered neutropenic fever or grade 3 or 4 nonhematological toxicity (except nausea and vomiting), the dose of CPT-11 was reduced to 175 mg/m² and CDDP was reduced to 60 mg/m² in the second course. Group B patients received the two treatment cycles in reverse order.

In all patients, premedication consisted of ondansetron (8 mg i.v.) combined with dexamethasone (10 mg i.v.) administered 30 min before the start of the chemotherapy. The administration of chemotherapy was followed by infusion of 2000 ml of dextrose/saline applied over 8 h and another 1000 ml of the same solution infused over the following 8 h to avoid CDDP-induced renal damage.

Pharmacokinetic Sampling and Analysis. Blood samples for pharmacokinetic analysis were obtained during the first

and second treatment cycle (total blood volume, 283 ml). Blood was drawn from a vein in the arm opposite to that used for drug infusion and collected in 10-ml heparinized tubes. For analysis of CPT-11 kinetics, samples were obtained at the following time points: before infusion; 0.5, 1, and 1.5 h during infusion; and 0.17, 0.33, 0.5, 1, 1.5, 2, 4, 5, 8.5, 11, 24, 32, 48, and 56 h after infusion. Samples for measurement of CDDP concentrations were obtained immediately before infusion; 1, 2, and 3 h during infusion; and 0.5, 1, 2, 3, 4, and 24 h after infusion.

Plasma samples were assayed for total drug forms of CPT-11 and metabolites and the lactone forms of CPT-11 and SN-38, according to validated reversed-phase high performance liquid chromatography methods reported previously (14, 15). Nonprotein-bound and total CDDP concentrations in plasma and platinum DNA-adduct levels in leukocytes were determined by flameless atomic absorption spectrometry (16).

Individual plasma concentrations of CPT-11 and its metabolites were fitted to a three-compartment model using Siphar v4.0 (SIMED, Creteil, France), as described (17). Metabolic ratios for the various CPT-11 metabolites were calculated as defined by Rivory *et al.* (18) and included the relative extent of conversion of CPT-11 to SN-38 (*i.e.*, $\text{AUC}_{\text{SN-38}}/\text{AUC}_{\text{CPT-11}}$), the relative extent of glucuronidation of SN-38 (*i.e.*, $\text{AUC}_{\text{SN-38G}}/\text{AUC}_{\text{SN-38}}$), and the relative extent of metabolism (*i.e.*, $\text{AUC}_{\text{APC or NPC}}/\text{AUC}_{\text{CPT-11}}$). Kinetic profiles of CDDP were obtained similarly using a one- or two-compartment model with extended least-squares regression analysis, as reported earlier (16). The platinum DNA-adduct levels in leukocytes were expressed as pg platinum/ μg DNA (pg Pt/ μg DNA).

Statistical Considerations. Pharmacokinetic parameters for all compounds are reported as mean values ± SD. Differences in pharmacodynamic and pharmacokinetic parameters between sequences were evaluated statistically using a paired Student's *t* test and the 95% confidence limits for the mean difference using Number Cruncher Statistical System version 5.X (Dr. Jerry Hintze, Kaysville, UT) and STATGRAPHICS Plus version 2.0 (Manugistics Inc., Rockville, MA). The power to discern potentially clinically relevant differences in the test parameters >30% (π) was determined at $\alpha = 0.05$ and previous

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pharmacological data (17).⁴ Probability values (two-sided) of <0.05 were regarded as statistically significant.

RESULTS

Toxicity and Pharmacodynamics. A total of 11 patients, 6 males and 5 females with a median age of 59 years (range, 41–66) and a median performance score of 1 (range, 0–1), was accrued to the study. However, one patient was taken off study after receiving one course of chemotherapy because of deterioration of his condition due to disease progression. The predominant tumor type was colorectal cancer ($n = 7$), and the main toxicity consisted of neutropenia (grade 3 or 4 in both sequences was observed in 6 of 10 cycles). Four patients encountered neutropenic fever (first course, $n = 2$; second course, $n = 2$) in the sequence CDDP→CPT-11, and one patient (first course only) in the sequence CPT-11→CDDP, which required dose reductions for the second course in three cases (CDDP→CPT-11, $n = 2$; CPT-11→CDDP, $n = 1$). Hence, only eight patients received the planned dose in the sequence CPT-11→CDDP, compared to nine patients in the reversed sequence. Paired analysis of hematological pharmacodynamic parameters indicated, however, that drug-sequencing had no significant influence on the observed myelotoxicity (Table 1), including the percent decrease in absolute neutrophil count ($\pi = 0.93$). The severity and incidence of nonhematological toxicities, including nausea [grade 2 or 3, $n = 4$ (CPT-11→CDDP) versus $n = 4$ (CDDP→CPT-11)], vomiting (grade 3 or 4, $n = 1$ versus $n = 2$), and diarrhea (grade 3 or 4, $n = 0$ versus $n = 1$), were also sequence independent.

Pharmacokinetics. The pharmacokinetics of CPT-11 and its metabolites SN-38, SN-38G, APC, and NPC could best be described by a three-compartmental model (Fig. 1A), in line with previous findings (17). Elimination of CPT-11 was characterized by a decay in an apparent tri-exponential manner and indicated no significant difference between sequences (Table 2). Analysis of the 10 paired, dose-normalized AUCs of CPT-11 lactone in both sequences demonstrated also no significant differences, indicating that treatment with CDDP immediately before CPT-11 did not alter the clearance of CPT-11 lactone ($\pi = 0.99$). The AUC ratios of CPT-11 lactone to total drug were 0.37 ± 0.07 and 0.35 ± 0.14 , whereas for SN-38 these were 0.67 ± 0.15 and 0.62 ± 0.27 , in the sequences CPT-11→CDDP and CDDP→CPT-11, respectively (Table 3).

The mean values for the apparent terminal half-lives of SN-38 and SN-38G, APC and NPC were similar in both sequences of drug administration (Table 3). In addition, the relative extent of conversion of CPT-11 to SN-38 was not influenced by the administration sequence (0.047 ± 0.018 versus 0.046 ± 0.027 , $P = 0.92$), and neither was the relative extent of glucuronidation of SN-38 (9.12 ± 5.22 versus 9.01 ± 6.99 , $P = 0.87$). No sequence dependence was observed in the metabolism

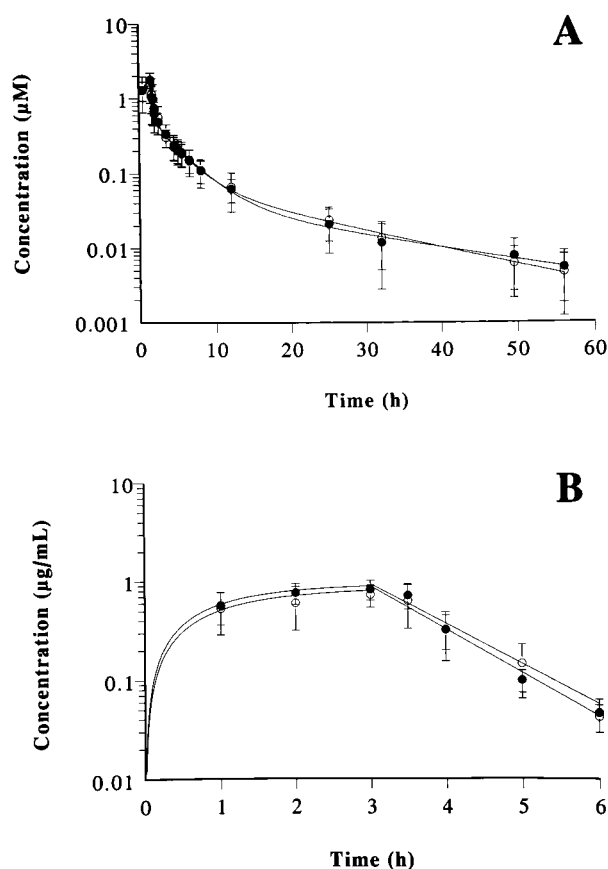


Fig. 1 Plasma concentration-time curves of CPT-11 lactone (A) and unbound CDDP (B) in 10 patients given CPT-11 before (●) or after CDDP (○). Data represent mean values (symbols) \pm SD (bars).

of CPT-11 to APC and NPC, as estimated from the relative extent of oxidative metabolism [APC: 0.23 ± 0.10 versus 0.23 ± 0.08 ($P = 0.77$); NPC: 0.012 ± 0.011 versus 0.011 ± 0.009 ($P = 0.14$)].

CDDP pharmacokinetics could best be described with a two-compartment model (Fig. 1B), as described (16). The total body clearance and the V_{ss} of unbound CDDP were the same in both sequences ($\pi = 0.64$), indicating no influence of the drug sequence on the protein binding of CDDP (Table 4). The platinum-DNA adduct levels in leukocytes peaked consistently at 1 h after the end of infusion, and showed wide interpatient variability (Table 4). Administration of CPT-11 before CDDP resulted in a mean value of 1.94 ± 2.20 pg Pt/ μ g DNA that was comparable with 2.42 ± 1.62 pg Pt/ μ g DNA observed in the reverse sequence ($P = 0.41$).

DISCUSSION

This study was performed to explore the influence of alternate sequences of CPT-11 and CDDP on the observed side effects and pharmacokinetic behavior of both drugs. Using a randomized cross-over design for the administration sequence, no substantial differences in any toxicity were observed between the two treatment schedules. The pharmacokinetics of the lac-

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Table 2 Summary of dose-normalized pharmacokinetic parameters of CPT-11 lactone

Data were obtained from 10 cancer patients after treatment with a 90-min i.v. infusion of CPT-11 at a dose level of 200 mg/m² given either before (CPT-11→CDDP; first course) or after CDDP at a dose level of 80 mg/m² (CDDP→CPT-11; second course) or *vice versa*. In three second courses, the CPT-11 and CDDP doses were reduced to 175 mg/m² and 60 mg/m², respectively, due to severe toxicity encountered in the first course (CPT-11→CDDP, *n* = 1; CDDP→CPT-11, *n* = 2). All parameters were calculated by compartmental analysis, and data represent dose-normalized (to 200 mg/m²) mean values ± SD.

Parameter	CPT-11→CDDP	CDDP→CPT-11	CL (δ) ^a	<i>P</i>
C _{max} (μM)	1.89 ± 0.393	1.74 ± 0.449	-0.55 and 0.34	0.60
t _{1/2} (α) (h)	0.180 ± 0.146	0.167 ± 0.097	-0.17 and 0.13	0.79
t _{1/2} (β) (h)	1.70 ± 0.81	1.98 ± 0.85	-0.46 and 1.03	0.87
t _{1/2} (γ) (h)	12.2 ± 2.85	12.3 ± 2.63	-2.08 and 2.48	0.85
AUC (μM·h)	6.13 ± 2.07	5.58 ± 1.86	-1.01 and 0.87	0.89
CL (liter/h/m ²)	60.4 ± 17.1	65.5 ± 16.3	-9.31 and 13.9	0.66
MRT (h)	7.98 ± 2.07	7.46 ± 1.53	-1.43 and 1.05	0.74
V _{ss} (liter/m ²)	477 ± 131	483 ± 166	-279 and 121	0.39

^a CL (δ), 95% confidence limits for the mean difference; C_{max}, maximum concentration; t_{1/2}(*i*), half-life of the *i*-th disposition phase; CL, total body clearance; MRT, mean residence time.

^b Paired Student's *t* test.

Table 3 Summary of dose-normalized pharmacokinetic parameters of total CPT-11 and metabolites (lactone plus carboxylate forms)

Data were obtained from 10 cancer patients after treatment with a 90-min i.v. infusion of CPT-11 at a dose level of 200 mg/m² given either before (CPT-11→CDDP; first course) or after CDDP at a dose level of 80 mg/m² (CDDP→CPT-11; second course) or *vice versa*. In three second courses, the CPT-11 and CDDP doses were reduced to 175 mg/m² and 60 mg/m², respectively, due to severe toxicity encountered in the first course (CPT-11→CDDP, *n* = 1; CDDP→CPT-11, *n* = 2). All parameters were calculated by compartmental analysis, and data represent dose-normalized (to 200 mg/m²) mean values ± SD.

Parameter	CPT-11→CDDP	CDDP→CPT-11	CL (δ) ^a	<i>P</i> ^b
<i>CPT-11</i>				
t _{1/2} (h)	12.9 ± 3.52	11.4 ± 2.27	-4.22 and 1.03	0.25
AUC (μM·h)	16.6 ± 6.52	17.3 ± 8.66	-1.36 and 2.16	0.20
AUC _L /AUC _T	0.37 ± 0.07	0.35 ± 0.14	-0.094 and 0.076	0.62
<i>SN-38</i>				
t _{1/2} (h)	25.5 ± 7.6	21.9 ± 3.9	-4.09 and 0.95	0.81
AUC (μM·h)	0.30 ± 0.17	0.29 ± 0.14	-0.23 and 0.19	0.19
AUC _L /AUC _T	0.67 ± 0.15	0.62 ± 0.27	-0.017 and 0.019	0.84
<i>SN-38G</i>				
t _{1/2} (h)	21.4 ± 6.19	22.7 ± 3.71	-3.20 and 5.78	0.88
AUC (μM·h)	5.39 ± 3.60	5.50 ± 3.50	-2.32 and 2.56	0.53
<i>APC</i>				
t _{1/2} (h)	10.1 ± 4.17	9.05 ± 2.60	-3.35 and 1.29	0.23
AUC (μM·h)	3.91 ± 2.73	4.04 ± 2.48	-0.81 and 1.06	0.34
<i>NPC</i>				
t _{1/2} (h)	5.32 ± 2.86	6.05 ± 3.64	-1.52 and 3.65	0.75
AUC (μM·h)	0.32 ± 0.37	0.22 ± 0.23	-0.24 and 0.043	0.35

^a CL (δ), 95% confidence limits for the mean difference; t_{1/2}, half-life of the terminal disposition phase; AUC_L, AUC of the lactone form; AUC_T, AUC of total drug.

^b Paired Student's *t* test.

tone form of CPT-11 revealed a substantial degree of interpatient variability, in line with previous observations (17). In addition, the observed kinetic parameters of CPT-11 were similar to single agent data (18), indicating no apparent interaction between CDDP and CPT-11. The sequence of drug administration had also no influence on the pharmacokinetics of CPT-11 and its metabolites SN-38 and SN-38G and the CYP450 3A4-mediated metabolites APC and NPC at the dose levels administered. This contrasts the reduction of topotecan clearance observed previously in patients after CDDP administration (5). Our findings, however, are consistent with previous *in vitro* studies, indicating that CDDP had no statistically significant effect on the carboxylesterase-mediated bioactivation of CPT-11 to SN-38 using human hepatic microsomes (19). In that

study, there was also a lack of protein-binding site displacement of CPT-11 by CDDP in a clinically relevant concentration range (19).

The total body clearance and V_{ss} of unbound CDDP, as well as the plasma AUC of total CDDP, indicated no significant influence of CPT-11 (or its metabolites) on the protein binding and plasma disposition of CDDP. The values of the maximal platinum DNA-adduct formation in peripheral leukocytes and the area under the DNA-adduct *versus* time curve were consistent with single-agent data (16) and were independent of the drug sequence. In preclinical studies, however, topoisomerase I inhibitors delayed the repair of platinum-induced DNA interstrand cross-links without modifying their formation (1). Although there is no formal proof that this preclinical observation also

Table 4 Summary of dose-normalized pharmacokinetic parameters of CDDP

Data were obtained from 10 cancer patients after treatment with a 3-h i.v. infusion of CDDP at a dose level of 80 mg/m² given either after (CPT-11→CDDP; first course) or before CPT-11 at a dose level of 200 mg/m² (CDDP→CPT-11; second course) or *vice versa*. In three second courses, the CDDP and CPT-11 doses were reduced to 60 mg/m² and 175 mg/m², respectively, due to severe toxicity encountered in the first course (CPT-11→CDDP, *n* = 1; CDDP→CPT-11, *n* = 2). All parameters were calculated by compartmental analysis, and data represent dose-normalized (to 80 mg/m²) mean values ± SD.

Parameter	CPT-11→CDDP	CDDP→CPT-11	CL (δ) ^a	P ^b
C _{max} (μg/ml)	0.84 ± 0.30	0.77 ± 0.25	-1.03 and 1.17	0.36
t _{1/2} (h)	0.73 ± 0.23	0.49 ± 0.15	-0.62 and 1.10	0.074
AUC _{fu} (μg·h/ml)	2.35 ± 0.83	2.01 ± 0.66	-0.25 and 0.95	0.10
AUC _{tot} (μg·h/ml)	39.8 ± 12.9	35.8 ± 6.4	-1.84 and 9.96	0.58
CL (liter/h/m ²)	40.8 ± 16.7	50.3 ± 18.6	-20.2 and 1.05	0.081
V _{ss} (liter/m ²)	35.5 ± 14.3	30.0 ± 11.6	-0.47 and 11.5	0.083
A _{max} (pg Pt/μg DNA)	1.94 ± 2.20	2.42 ± 1.62	-1.55 and 0.59	0.41

^a CL (δ), 95% confidence limits for the mean difference; C_{max}, maximum concentration; t_{1/2}(el), half-life of the terminal disposition phase; AUC_{fu}, AUC of unbound CDDP; AUC_{tot}, AUC of total CDDP; CL, total body clearance; A_{max}, maximum CDDP DNA-adduct level in leukocytes.

^b Paired Student's *t* test.

applies to the clinical situation, it is possible that the small patient population studied, in combination with the extreme variability in platinum DNA-adduct values, would not allow any alteration to be observed even if it were present.

In our study, CDDP was immediately administered at the end of the CPT-11 infusion, or *vice versa* in the alternate sequence. The lack of sequence dependence in the kinetic profiles of both drugs in this schedule does not necessarily indicate that any reciprocal pharmacokinetic interference will be absent when the administration interval is increased. In this respect, it is noteworthy that CDDP can modulate specific CYP450 mRNA levels and may alter hepatic drug metabolism *in vivo* (20), a mechanism that has recently been proposed to account for drug interactions between CDDP and paclitaxel (21) or CDDP and etoposide (22). In view of the major role of CYP450 isozymes in CPT-11 metabolism and disposition (17), drug interactions with CDDP cannot be excluded *a priori* in case of alternative schedules of administration.

In conclusion, no sequence-dependent side effects between CPT-11 and CDDP could be demonstrated in this study, nor an indication of a mutual pharmacokinetic interaction. On the basis of these findings and the conflicting data on the mechanism of drug interaction between topoisomerase I inhibitors and platinum derivatives in preclinical models, no clear preference in administration sequence can yet be formulated.

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