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Influence of the cisplatin hydration schedule on topotecan pharmacokinetics

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Abstract

The study described here was designed to investigate the influence of the hydration schedule of cisplatin on the pharmacokinetics of topotecan. To test this hypothesis, 13 adult cancer patients were treated with intravenous (i.v.) cisplatin followed by i.v. topotecan for 5 days every 3 weeks using a short hydration schedule (SHS) for cisplatin in the first course and a hyper-hydration schedule (HHS) in the second course or *vice versa*. Topotecan pharmacokinetic analysis was performed in plasma, whole blood and red blood cells in both courses on days 1, 2 and 5. 11 patients received both courses and were pharmacokinetically evaluable. No significant differences between the two studied schedules were noted in the clearances of topotecan on day 1 in the different matrices. However, in both hydration schedules, on average, slightly lower topotecan clearances were observed on both days 2 and 5 compared with day 1 in all of the matrices, while no differences were noted between days 2 and 5. This alteration was independent of the schedule used and was less pronounced than that which has been initially reported for SHS and, overall, will not have clinical consequences.

Keywords: Accumulation; Cisplatin; Combination; Interaction; Pharmacokinetics; Renal; Topotecan; Toxicity

1. Introduction

Cisplatin and topotecan (Hycamtin) combination therapy is promising given their *in vitro* synergism, non-overlapping dose-limiting toxicity and broad antitumour activity [1]. Significantly more haematological toxicity occurs in the sequence cisplatin followed by topotecan, compared with the reversed sequence [2,3]. In a phase I and pharmacological study [2] combining a dose of 50 mg/m^2 of cisplatin (on day 1), diluted in approximately 85 ml NaCl 3%, using a short hydration schedule (SHS) of 2 l, followed by 0.75 mg/m^2 intravenous (i.v.) topotecan on days 1–5, a substantially slower topotecan clearance (CL) was observed on day 2, compared with days 1 and 5. The authors suggested that cisplatin induces acute, subclinical renal tubular damage on day 2 and thereby impairs the systemic clearance of topotecan, which is cleared significantly (approximately 50%) by the kidneys [4]. In contrast, in another study [3], administration of a fixed dose of 75 mg/m^2 of cisplatin on day 1, followed by escalating doses of oral topotecan on days 1–5, using a 4-l hyper-hydration schedule (HHS) with cisplatin administration in 250 ml NaCl 3%, no pharmacokinetic (PK) interaction was observed.

We hypothesised that the difference between the observations might be due to the use of the SHS in the first mentioned study [2], which might cause, as suggested, subclinical renal toxicity affecting the topotecan PK, as has been described for patients with impaired renal function [5–7]. The assumption that the SHS produces more renal toxicity than the HHS is based on animal studies showing that extensive hydration and administration of cisplatin in a sufficient amount of hypertonic saline induces chloruresis, protecting the kidneys by decreasing the formation of toxic metabolites of cisplatin [8,9]. To test this hypothesis, we treated

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patients with i.v. cisplatin on day 1 in combination with i.v. topotecan on days 1–5 using HHS and SHS in the first and second 3-weekly cycle, respectively, or *vice versa*. Pharmacokinetic analysis of topotecan was performed in plasma, red blood cells (RBC) and whole blood to fully explore the influence of the cisplatin administration and hydration schedules on the overall topotecan disposition.

2. Patients and methods

2.1. Eligibility

Patients with a histologically- or cytologically-confirmed diagnosis of a malignant solid tumour, refractory to standard therapy or for which no recognised therapy was available, were eligible for this study. Additional eligibility criteria included: age between 18 and 75 years; Eastern Cooperative Oncology Group (ECOG) performance status (PS) $\leqslant 1$; adequate haematopoietic (white blood cell count (WBC) $\geqslant 4.0\times10^9$/l, absolute neutrophil count $\geqslant 1.5\times10^9$/l and platelet count $\geqslant 100\times10^9$/l), hepatic (bilirubin within normal limits, aspartate aminotransferase and alanine aminotransferase $\leqslant 2$ times the upper limit of institutional normal) and renal function (creatinine clearance $\geqslant 60$ ml/min). All patients should have an estimated life expectancy $\geqslant 12$ weeks, and no previous chemotherapy was allowed for at least 4 weeks prior to enrolment. The study protocol was approved by the Erasmus MC Ethics Board, and written informed consent before study entry was obtained from all of the patients.

2.2. Treatment and drug administration

Glaxo SmithKline (Harlow, UK) supplied the lyophilised vial preparations containing 5 mg of topotecan lactone. The drug was administered once daily for 5 consecutive days every 3 weeks in 50 ml of 0.9% saline as a 30-min i.v. infusion at a dose level of 0.75 mg/m^2, or 0.50 mg/m^2 in the case of severe haematological toxicities being observed in the previous course. On the first treatment day, topotecan administration was preceded by a single 3-h i.v. infusion of cisplatin (Pharmachemie, Haarlem, The Netherlands) at a dose of 50 mg/m^2 using a SHS or HHS (Table 1). A restricted randomisation was performed to avoid bias in the cycle sequence and to keep the number of patients evenly distributed between the arms. This was achieved by choosing a randomised block using a table of random numbers to create the allocation sequence [10].

2.3. Sample collection and processing

Blood samples for topotecan pharmacokinetic analysis were collected in 4.5-ml glass tubes containing lithium heparin as an anticoagulant. Sample collection was performed prior to dosing, at 15 min after the start of infusion, immediately before the end of infusion, and at 15 and 30 min and 1, 2, 3, 4, 6, 8 and 10 h after the end of infusion. All samples were immediately placed on ice and processed as recently described in Ref. [11] within 10 min after collection for the separation of the plasma and RBC fractions.

2.4. Drug measurement and pharmacological analysis

Simultaneous determination of the lactone and carboxylate forms of topotecan in plasma was performed by high-performance liquid chromatography with fluorescence detection [12] with minor modifications [3], while concentrations of topotecan in whole blood and RBC were determined by a recently described method [11]. The topotecan pharmacokinetic profiles in the different matrices were analysed using the software package Siphar version 4.0 (InnaPhase, Philadelphia, PA) by two- or three-compartment models, based on the best fitted curve through individual plasma, whole blood or red blood cell concentration time curves, after zero-order input. The area under the concentration-time curve (AUC) values were extrapolated to infinity as calculated from the model based on the best fitted curves. The CL values were calculated by dividing the dose in mg/m^2 by the observed AUC, while CL ratios were calculated for day 2 to day 1 and day 5 to day 1 by dividing the respective CL values.

2.5. Statistical considerations

All parameters are reported as mean values $\pm$standard deviation (S.D.) Two-tailed paired Student's *t*-tests were performed to evaluate statistically significant differences between groups, using the Number Cruncher Statistical System (NCSS) package (Version 5.X; J.L. Hintze, East Kaysville, UT, USA). Probability values of less than 0.05 were regarded as significantly different in all tests applied.

3. Results

3.1. Patients' characteristics

11 of 13 patients entered in the study received both courses of the HHS and SHS combination treatment and were evaluable for topotecan PK in all matrices. No significant differences ($P\geqslant 0.47$) were observed in any of the studied patient characteristics between the courses (Table 2). In 5 of the administered courses, the topotecan dose had to be reduced from 0.75 to 0.50 mg/m^2 due to severe (grade 4) haematological toxicity in the previous course.

Table 1
Cisplatin and topotecan administration schedules (all i.v.)

	Hyper-Hydration Schedule (HHS)	Short Hydration Schedule (SHS)
Day 1		
$T=-3.5$ h	1 l 2.5% dextrose/0.45% NaCl	1.5 l 2.5% dextrose/0.45% NaCl
$T=-0.5$ h	500 ml 0.9% NaCl	500 ml 0.9% NaCl
	8 mg ondansetron/10 mg dexamethasone	8 mg ondansetron/10 mg dexamethasone
$T=0$h	50 mg/m^2 cisplatin diluted in 250 ml 3% NaCl	50 mg/m^2 cisplatin diluted in 85 ml 3% NaCl
$T=3$h	0.50 or 0.75 mg/m^2 topotecan diluted in 48 ml 0.9% NaCl	0.50 or 0.75 mg/m^2 topotecan diluted in 48 ml 0.9% NaCl
$T=3.5$h	3 l 2.5% dextrose/0.45% NaCl over 13 h	0.5 l 2.5% dextrose/0.45% NaCl over 1 h
Days 2–5		
$T=0$ h	0.50 or 0.75 mg/m^2 topotecan diluted in 48 ml 0.9%NaCl	0.50 or 0.75 mg/m^2 topotecan diluted in 48 ml 0.9%NaCl

i.v., intravenous; T, time; h, hours.

Table 2
Patients' characteristics

	All	HSS	SHS
No. of patients entered	13		
No. of patients receiving two courses	11		
Gender			
Female	6		
Male	5		
Age (years)			
Median (range)	54 (36–68)		
Topotecan dose			
0.50 mg/m^2		1	4
0.75 mg/m^2		10	7
Serum creatinine (μmol/l)		68±14	67±11
Total protein (g/l)		75±5.6	76±4.4
Albumin (g/l)		39±3.1	39±2.3
Total bilirubin (μmol/l)		5±3	5±3
Alkaline phosphatase (U/l)		104±24.7	106±23.0
γ-GT (U/l)		47±28	49±29
AST (U/l)		25±6.8	25±9.6
ALT (U/l)		20±9.9	19±11

HSS, hyper-hydration schedule; SHS, short hydration schedule; γ-GT, γ-glutamyl transferase; AST, aspartate aminotransferase; ALT, alanine aminotransferase.

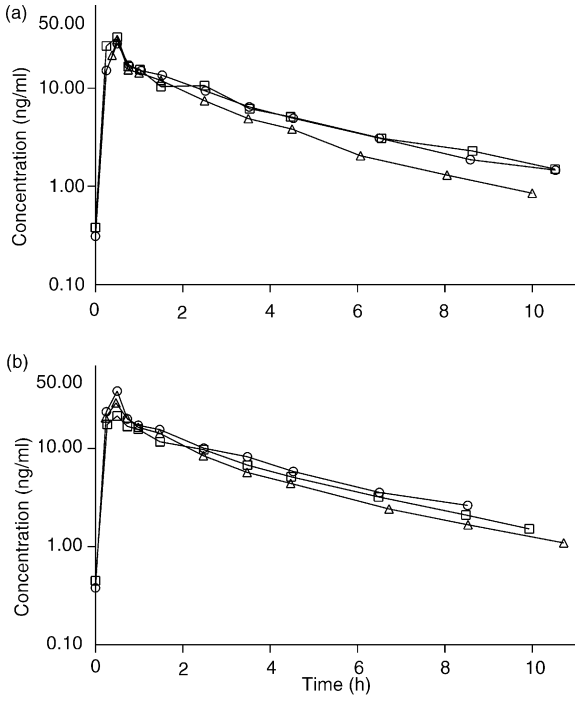

Fig. 1. Typical kinetic curves, in a single patient, of total topotecan in the plasma compartment after the administration of 0.75 mg/m^2 topotecan. The triangles, circles and squares represent the exposure of total topotecan at days 1, 2 and 5, respectively. (a) represents the curves with cisplatin administered in the combination with the hyper-hydration schedule (HHS), while (b) represents the curves in the combination with the short hydration schedule (SHS).

3.2. Topotecan pharmacokinetics

Typical kinetic curves of total topotecan in the plasma compartment at days 1, 2 and 5 after the administration of 0.75 mg/m^2 are shown in Fig. 1. Fig. 1(a) represents the curves with cisplatin administered in the combination with HHS, while Fig. 1(b) represents the curves in the combination with SHS. The topotecan CL in the plasma compartment (total and lactone), whole blood (total) and RBC (total) on day 1 of both courses is listed in Table 3, as are the CL ratios for day 2 versus day 1 and day 5 versus day 1. No significant differences were observed between the 2 studied schedules in the topotecan CL on day 1 in the plasma lactone ($P=0.71$), plasma total ($P=0.37$), whole blood total ($P=0.91$) and RBC total values ($P=0.98$). The topotecan CL on day 1 were significantly different compared with day 2 ($P\leqslant 0.015$) and day 5 ($P\leqslant 0.036$) in all studied matrices and both schedules, while the CL on days 2 and 5 were not significantly different ($P\geqslant 0.22$) in both schedules and all matrices. Paired total topotecan plasma CL of the patients on days 1, 2 and 5 after the administration of cisplatin on day 1 in the HHS and SHS are shown in Figs. 2(a) and (b), respectively.

4. Discussion

In the United States, low-dose cisplatin is frequently administered in an outpatient setting using a SHS [2],

Table 3
Topotecan clearances (CL) in different matrices in 11 evaluable patients

Matrix and form	Hyper-Hydration Schedule (HHS)			Short Hydration Schedule (SHS)		
	CL Day 1 (l/h/m^2)	CL ratio day 2/day 1	CL ratio day 5/day 1	CL Day 1 (l/h/m^2)	CL ratio day 2/day 1	CL ratio day 5/day 1
Plasma lactone	37.7±8.06	0.87±0.10	0.89±0.14	37.0±7.16	0.89±0.091	0.85±0.11
Plasma total	14.4±2.20	0.83±0.10	0.86±0.10	13.8±2.87	0.86±0.12	0.86±0.13
Blood total	14.3±3.05	0.82±0.11	0.86±0.11	14.4±2.43	0.85±0.096	0.82±0.094
Red blood cells total	16.9±3.02	0.86±0.11	0.89±0.11	16.9±3.37	0.85±0.13	0.84±0.12

Data are presented as mean±standard deviation (S.D.)

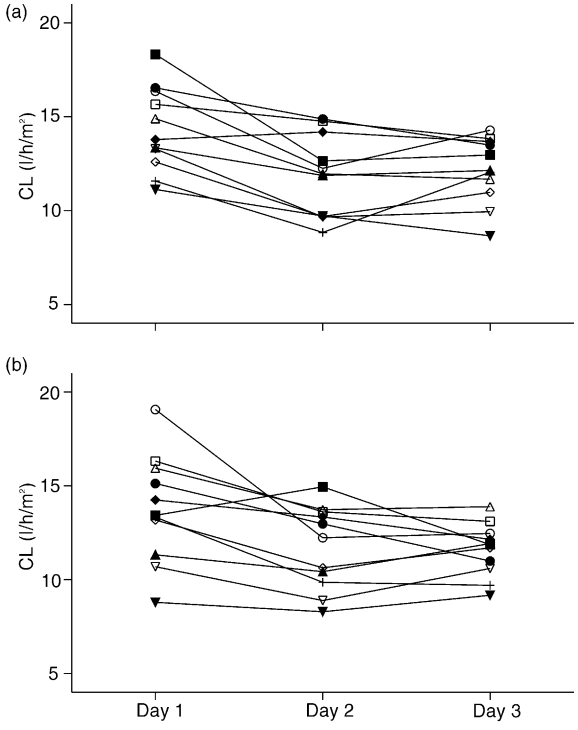

Fig. 2. Paired total topotecan plasma CL of the 11 evaluable patients on days 1, 2 and 5 after the administration of cisplatin on day 1 in the hyper-hydration schedule (HHS) (a) and the short hydration schedule (SHS) (b).

whereas in Europe, most patients receiving cisplatin are hospitalised for 1 or 2 nights for pre- and/or post-hydration [3]. In a study using the SHS [2], a substantially slower topotecan clearance (CL) was observed on day 2, compared with days 1 and 5, which might have important clinical implications since the systemic exposure of topotecan is related to haematological toxicities [13,14], while in a study using the HSS, no PK interaction was observed. The differences in the administration and hydration during cisplatin administration may well be the reason for the different observations in the 2 studies.

However, this study shows that the observed small decrease in topotecan CL in all matrices on day 2 was maintained on day 5 and was not different between the two applied cisplatin administrations and hydration schedules. However, the reduction of topotecan CL was less pronounced than described earlier [2] and is not caused by major subclinical renal damage, while a clinically insignificant minor renal damage by cisplatin can not be excluded. In addition, the reduction in topotecan CL on both days 2 and 5 in all of the studied matrices might also partly be related to topotecan accumulation as shown in Fig. 1, by the presence of systemic topotecan prior to the administration on days 2 and 5. The observed dramatically altered topotecan CL in the 2 patients in the study of Rowinsky and colleagues [2], might be due to a day-to-day variation in topotecan PK, as also has been described earlier in Ref. [14]. In that study [14], the AUC ratios of day 4 or day 5 to day 1 varied from 0.52 to 2.57 after the administration of single-agent topotecan as a 30-min infusion on days 1–5, every 3 weeks, at dose levels of 0.50–1.5 mg/m^2. In addition, the study presented here suggests that the reduction of the topotecan lactone and total plasma CL is not a result of an altered blood distribution of topotecan, since equal changes in total topotecan CL were seen in whole blood and RBC.

In conclusion, we have shown, contrary to an earlier report [2], no profound pharmacokinetic interaction of cisplatin, administered on day 1, on i.v. topotecan, administered on days 1–5, and therefore these drugs can be safely combined in this sequence. The observations presented here might not only be relevant for the combination of cisplatin with topotecan, but also for other anticancer agents that are mainly excreted by the kidneys.

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