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A phase I study of intraperitoneal topotecan in combination with intravenous carboplatin and paclitaxel in advanced ovarian cancer

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Abstract

The aim of this study was to determine the maximum tolerated dose (MTD) of intraperitoneal (i.p.) topotecan combined with standard doses of intravenous (i.v.) carboplatin and paclitaxel and to investigate its pharmacokinetics. Women with primary ovarian cancer stage IIb – IV received six cycles of i.v. carboplatin and paclitaxel with escalating topotecan doses i.p. of 10, 15, 20 and 25 mg/m^2. Twenty-one patients entered this trial. Febrile neutropenia, thrombocytopenia requiring platelet transfusion and fatigue grade 3 were dose-limiting toxicities (DLT) at 25 mg/m^2 i.p. and 20 mg/m^2 i.p. of topotecan was considered to be the MTD. The mean plasma $t_{1/2}$ was 3.8 ± 2.3 h for total topotecan and 4.4 ± 3.9 h for active lactone. The area under the curve (AUC) was proportional with dose, $R = 0.54$, $p < 0.05$ for total topotecan and the peritoneal / plasma AUC ratio was 46 ± 30. Fifteen patients who completed treatment had a median progression-free survival (PFS) of 27 months. In this setting the MTD of topotecan is 20 mg/m^2 i.p. The efficacy of this regimen should be explored further in a formal phase III study.

Keywords: Pharmacokinetics; Topo-isomerase inhibitors; Chemotherapy; Taxol; Paraplatin; Hycamtin; Paclitaxel

1. Introduction

Carboplatin in combination with paclitaxel constitutes the standard chemotherapeutic approach of advanced primary ovarian cancer [1]. The survival of patients diagnosed with advanced disease is still poor [2]. A possible way to improve outcome is to add another active drug. Several drugs have shown activity against platinum-pre-treated ovarian cancer, suggesting the possibility of using them in combination with platinum-paclitaxel as part of first-line schedules. Epirubicin, liposomal doxorubicin, topotecan, etoposide, gemcitabine and vinorelbine have been tested as a third agent in these regimes [3,4]. Most triplet regimens have exhibited dose-limiting bone marrow toxicity, and individual drug doses utilised were much lower than comparable single agents or doublets, raising questions about efficacy. The addition of topotecan to standard treatment in ovarian cancer is of interest. Objective response rates ranging from 13% to 33% have been reported for topotecan administered intravenously (i.v.) in patients with recurrent ovarian cancer [5–7]. In a phase III study of 226 patients who relapsed after initial treatment with a platinum-based regimen, topotecan had an efficacy equivalent to paclitaxel [8]. A study with a triple i.v. schedule with cisplatin, paclitaxel and 5 days of i.v. topotecan

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has shown that the administration of full doses of this agent is limited by myelotoxicity [9]. A combination of carboplatin, paclitaxel and topotecan divided over 3 days was limited by thrombocytopenia [10]. This might be circumvented by the intraperitoneal (i.p.) administration of cytotoxic agents, which exposes the tumour to high concentrations for longer time periods with less systemic exposure and side-effects [11,12]. Three randomised studies have evaluated the role of i.p. therapy as first-line treatment of ovarian cancer [13–15]. Two multicentre phase III studies employing i.p. cisplatin as initial treatment of small-volume advanced ovarian cancer have demonstrated that regional therapy results in a modest improvement in both progression-free (PFS) and overall survival (OS) compared with i.v. cisplatin, but more myelotoxicity [13,15]. A recently presented third study comparing cisplatin i.p. and paclitaxel i.v. day 1 and paclitaxel i.p. on day 8 with a standard schedule with 24 h paclitaxel infusion followed by cisplatin [16], supported these data, demonstrating an improvement in PFS with i.p. therapy in small-volume ovarian cancer is possible, but more toxicity in the i.p. arm was reported [14]. These three studies indicate that i.p. therapy in ovarian cancer deserves further investigation.

Intraperitoneal administration of topotecan is feasible in ovarian cancer [17,18]. It can be delivered safely to the peritoneal cavity with a pharmacokinetic advantage for local exposure. The study of Hofstra and colleagues [17] with i.p. topotecan has shown that cytotoxic plasma levels can be achieved with minor myelotoxicity. The recommended dose for further i.p. studies was 20 mg/m^2.

The aim of this current study was to evaluate the optimal i.p. dose of topotecan and the pharmacokinetics of topotecan in combination with standard doses of carboplatin and paclitaxel in first-line treatment of ovarian cancer.

2. Patients and methods

In this phase I, dose-escalating study standard i.v. doses of carboplatin and paclitaxel were administered with increasing doses of topotecan i.p. to women with advanced ovarian cancer.

2.1. Eligibility criteria

Women with histologically proven International Federation of Gynecology and Obstetrics (FIGO) stage IIB-IV epithelial ovarian carcinoma were eligible. Other inclusion criteria were: no prior chemotherapy, no concurrent other anti-tumour or investigational therapy; Eastern Cooperative Oncology Group (ECOG) performance status less than 3; age over 18 years; life-expectancy more than 6 months; adequate bone marrow function with an absolute neutrophil count (ANC) $> 1.5 \times 10^9$/l or leukocyte count $> 3.0 \times 10^9$/l and platelet count $> 100 \times 10^9$/l; serum bilirubin $< 1.5 \times$ upper normal limit (UNL); alkaline phosphatase and alanine aminotransferase (ALAT) $< 2 \times$ UNL; serum creatinine $< 1.5 \times$ UNL and a creatinine clearance > 1 ml/s. Patients were excluded with previous or concomitant malignancies, bowel obstruction or massive ascites. Patients with peritoneal adhesions, which prevented homogeneous distribution of i.p. fluid, were excluded. The study was approved by the local Ethical Committee. All patients gave their written informed consent.

2.2. Drug administration

All patients had a surgically subcutaneously/totally implanted peritoneal-access-port (PAP) catheter. Before administration of i.p. topotecan, adequate fluid distribution was checked by an abdominal scan after instillation of ^{99m}Tc-colloid.

On day 1, i.p. topotecan (Hycamtin, GlaxoSmithKline, New Jersey, USA), dissolved in 1 l normal saline (pH = 4) was infused over 1 h into the abdominal cavity, followed by an i.p. infusion of 1 l normal saline, both at 37 °C. Thereafter, paclitaxel (Taxol, Bristol Myers Squibb, Princeton, USA) 175 mg/m^2 was administered i.v. in 1 l normal saline over 3 h. Finally, carboplatin (Paraplatin, Bristol Myers Squibb, Princeton, USA) dissolved in 250 ml normal saline was administered i.v. over 30 min after completion of the paclitaxel infusion. The carboplatin dose was calculated with the Calvert formula [19] and targeted on an area under the curve (AUC) of 6 (mg/ml min). The glomerular filtration rate in the Calvert formula was calculated using the creatinine clearance as measured or calculated according to Cockcroft and Gault with the serum creatinine level [20]. Dexamethasone 20 mg i.v., clemastine 2 mg i.v. and cimetidine 300 mg i.v. were administered in 1 l normal saline over 1 h to all patients as pre-medication prior to initiation of paclitaxel infusion, to avoid hypersensitivity reactions associated with paclitaxel and to prevent nausea and vomiting.

2.3. Study design

Topotecan dose levels were 10, 15, 20, 25 mg/m^2 with three patients on each dose level. At each dose level at least 2 weeks should pass between the entry of the first and the next two patients. A cycle was defined as 21 days and a cohort was defined as a minimum of three evaluable patients at a particular dose. Every patient who completed one full cycle was considered evaluable for toxicity.

Dose escalation was based on the safety assessments of all patients in each cohort. There was no dose escalation within a cohort. Before the dose could be escalated, at least three patients having received one full treatment

cycle should be evaluable at a given dose level. An additional three patients (total of six) were treated if one or two of the first three patients exhibited a dose-limiting toxicity (DLT). If two patients exhibited a DLT, the previous dose level was extended to six patients and this was considered to be the maximum tolerated dose (MTD). Escalations continued until the MTD was reached. MTD is defined as the dose level in which DLT in no more than two patients occurred. DLTs were defined according to the common toxicity criteria (CTC) criteria version 2.0: absolute neutrophil count (ANC) $< 0.5 \times 10^9$/l associated with grade 3 fever/infection (e.g. temperature $\geqslant$ 38.5 °C, need for IV antibiotics and/or hospitalisation), platelets $< 20 \times 10^9$/l requiring platelets transfusion or grade 4 thrombocytopenia for more than 5 days. Grade 3 nausea (no fluid intake), diarrhoea ($\geqslant$7 times per day) or vomiting ($\geqslant$6 times per day) were not considered to be DLTs if they were short-lasting and did not require i.v. fluids. Grade 3 fatigue (bed-ridden) was a DLT, but grade 3 fatigue after intervention surgery was not scored as being chemotherapy-related. No dose reductions were indicated for nadir counts, unless clinical symptoms were present. For DLT, topotecan dose reduction to the previous dose level was allowed. Reduction of carboplatin by 10% of the total dose was allowed for grade 4 haematological toxicity. Paclitaxel could be reduced accordingly, if toxicity occurred.

Cycles were repeated every 3 weeks, for a maximum of six cycles. In case of inadequate bone marrow recovery on day 21 (ANC $< 1.5 \times 10^9$/l or platelets $< 100 \times 10^9$/l), the treatment cycle was postponed for one week. If no recovery had occurred by day 35, the patient was withdrawn from the study. Intervention surgery or second-look laparotomy was considered after three treatment cycles in case of macroscopic tumour following primary surgery and absence of progressive disease. Patients went off the study in cases of tumour progression, impaired distribution of i.p. topotecan, unacceptable toxicity or refusal of treatment.

2.4. Toxicity

Study visits were planned at screening, day 1 and 15 of each cycle. At baseline and before each cycle of therapy, assessment included vital signs, weight, physical examination, ECOG score and laboratory profile, including serum CA-125 (IMX CA-125, Abbott Diagnostics, Chicago, IL). On day 15 of each cycle, a complete blood count was performed. A screening visit was held less than 15 days prior to first cycle. Toxicity was recorded according to the CTC grading system.

2.5. Tumour responses

In all patients, response was assessed after completion of treatment. Computerised tomographic (CT)-scans were performed if residual lesions after primary surgery were $\geqslant$2 cm in diameter. All patients were followed until tumour progression or death. A complete response (CR) was defined as no clinical evidence of disease including a normalised CA-125 level. A partial response (PR) was defined by $a > 50\%$ decrease of repeated CA-125 levels or $a > 50\%$ decrease in the diameter of lesions on CT scan or at vaginal examination. Stable disease was defined as $\leqslant$50% decrease or <25% increase in total tumour size. Tumour progression was defined as two consecutive increases of CA-125 over 2× UNL, $\geqslant$25% increase in diameter of existing or newly found lesions on CT scan or at vaginal examination.

2.6. Pharmacokinetics

Pharmacokinetic (PK) sampling for the determination of topotecan as the total of the lactone and hydroxy-carboxylate forms (total levels) and the lactone form was performed on day 1 of the first treatment cycle. Plasma and peritoneal fluid samples were collected at 0, 1, 2, 4, 6, 10 and 24 h after the start of i.p. topotecan. Plasma and i.p.-fluid were collected in heparinised tubes on ice. Before the collection of each i.p. sample, 2 ml of peritoneal fluid was discarded for potential topotecan-residue in the catheter (internal volume approximately 0.5 ml). All samples were centrifuged immediately after sampling at 3000*g* for 5 min at 4 °C. To stabilise the pH-dependent, reversible hydrolytic dissociation of topotecan (i.e. to prevent the conversion of the lactone form into the open-ring form), 0.5 ml of matrix was added to 1 ml of methanol (−20 °C). Samples were then centrifuged at 3000*g* for 5 min at 4 °C and the supernatant was transferred to a clean tube and all samples were stored at −80 °C until analysis.

Total and lactone levels of topotecan in plasma and peritoneal fluid were determined using a validated high-performance liquid chromatography (HPLC) method as previously reported in [21]. The concentration versus time curves were fitted by using the Kinfit computer program, based on a one compartmental model for the peritoneal and plasma kinetics [22]. The total area under the concentration–time curve (AUC) was calculated by the linear trapezoidal method. PK parameters were calculated using standard equations [23]. To investigate whether the PK of i.p. topotecan was changed in this combination study, we compared the data with results obtained in an earlier study, when i.p. topotecan monotherapy was given [17].

Parameters of all pharmacological analyses are reported as mean values ± standard deviations (SD), unless stated otherwise. The relationships between peak plasma concentrations of topotecan and the administered level or corresponding AUC values were analysed by means of a Spearman's correlation coefficient [24].

3. Results

Between January 2000 and February 2002, 21 women with primary, previously untreated ovarian epithelial cancer were entered into this study. Patient characteristics are summarised in Table 1. One patient was not eligible due to abdominal fluid escape/leakage into the pleural cavity and was treated with standard chemotherapy. She is not considered in this report, but is described separately in [25].

3.1. Toxicity

Three patients were entered at the lowest topotecan dose level (10 mg/m^2) and completed 6 cycles without dose reduction. Three out of 18 cycles were delayed, two cycles due to myelosuppression by one week and one due to intervention surgery. Diarrhoea grade 3 was seen in one patient together with a skin rash, as a reaction to paclitaxel or topotecan, in the sixth treatment cycle, but was short-lasting and did not require admission.

One of the first three patients at 15 mg/m^2 i.p. topotecan developed an episode of febrile neutropenia during her first cycle and three additional patients were entered at this dose level. One of these three additional patients developed a wound infection without neutropenia (CTC grade 2) at the insertion site of the PAP-catheter with fatigue grade 3 after the first cycle. The infected catheter had to be removed so the patient went off the study and continued i.v. treatment with just carboplatin and paclitaxel. Therefore, a seventh patient was entered. No other DLT occurred and no dose reduction was necessary in the remaining six patients. Four patients completed six treatment cycles, but in one patient topotecan was withheld after four cycles due to impaired distribution and pain during administration of i.p. fluid. Another patient requested to stop after four cycles. Nine out of 33 cycles were delayed by one week because of myelosuppression.

At the 20 mg/m^2 dose level, three additional patients were entered, as the third patient needed a platelet transfusion after the fifth cycle. A 35-year old nulliparous patient developed abdominal pain grade 3 and nausea/vomiting grade 2 on day 1 of the first cycle. This was considered to be due to chemical peritonitis, which was followed by a short-lived grade 4 neutropenia, nadir on day 12. This patient was known to have a latex allergy. Although skin tests showed no signs of allergy for topotecan or paclitaxel, further administration of topotecan was discontinued in this patient and she received five additional cycles of carboplatin and paclitaxel without complications. Another patient discontinued i.p. treatment due to impaired fluid distribution following intervention debulking surgery after three cycles. Three of the other four patients completed six cycles, but one discontinued study treatment at her request after completing four cycles. There was one 10% dose reduction of carboplatin for the sixth cycle because of thrombocytopenia grade 4 and the need for a single platelet transfusion as mentioned above. Six cycles were delayed, three by one week for myelosuppression, two at the request of the patient and one for intervention surgery.

At the 25 mg/m^2 dose level, two additional patients were treated, as one of the first three patients experienced febrile neutropenia. Febrile neutropenia occurred in one patient, aged 71 years with World Health Organisation (WHO) performance status of 2, during the first cycle and in another patient, aged 38 years, after 5 cycles. Both received a single platelet transfusion for thrombocytopenia grade 4 and discontinued i.p. topotecan treatment after this episode. Both patients and another patient experienced grade 3 fatigue, scoring a total of seven treatment-related DLT events. Diarrhoea grade 3 and a skin rash were seen in another patient. No dose reduction or delay was necessary. Two patients completed six cycles and one discontinued at their request after four cycles.

An overview of the haematological toxicities is presented in Tables 2A and 2B. Thrombocytopenia and

Table 1
Patients' characteristics

	Number of patients
Total	21[a]
Age, median (range), in years	51 (24–76)
Performance score (ECOG)	
0	2
1	18
2	1
Tumour histology	
Serous cystadenocarcinoma	13
Endometroid carcinoma	2
Mucinous cystadenocarcinoma	1
Clear-cell carcinoma	1
Mixed (endometroid + clear-cell)	2
Unknown	2
Tumour differentiation grade	
1	2
2	8
3	11
Tumour stage	
IIb	1
IIc	6
III	12
IV	2
Residual tumour after primary debulking surgery (cm)	
Microscopic	9
<2	8
>2	4

ECOG, Eastern Cooperative Oncology Group.
[a] One patient with intrathoracic spread of intraperitoneal (i.p.) fluid is not considered here [25].

febrile neutropenia were dose-related. Frequent non-haematological toxicities were nausea, vomiting, pain, fatigue, diarrhoea, alopecia and neuropathy (Tables 3A and 3B). Although minor toxicity was frequent, grade 3 nausea occurred in only 13/99 (13%) of all cycles, grade 3 vomiting in 2%, diarrhoea in 2%, grade 3 abdominal pain in 2% and fatigue in 4% of 99 treatment cycles. Despite grade 3 nausea/vomiting and/or diarrhoea in some patients, this was short-lived and no patient required admission for i.v. fluids or parenteral feeding. No evident hypersensitivity reaction to topotecan, paclitaxel or carboplatin was observed and the skin rash combined with grade 3 diarrhoea in two patients were considered to represent cytotoxicity.

A total of 99 topotecan i.p. cycles were administered with a median of 6 cycles (range 1–6 cycles). Topotecan was withheld in six patients (29%), due to impaired distribution of i.p. fluid in two (one patient in the third and one in the fourth cycle), an infected implanted i.p. catheter (one patient after the first cycle), chemical peritonitis (one patient after the first cycle) and neutropenic fever (2 patients at the first and fifth cycles, respectively). They all continued with i.v. carboplatin and paclitaxel. Treatment was postponed in a total of 18 cycles (18%): in 14 cycles for myelosuppression, in two cycles on request of the patient and in two cycles for intervention surgery. Reduction of carboplatin dose by 10% occurred in one patient after 5 cycles for grade 4 thrombocytopenia.

The DLTs are listed in Table 4. The MTD is topotecan i.p. 20 mg/m^2 in combination with carboplatin (AUC = 6) and paclitaxel (175 mg/m^2 in 3 h).

Table 2A
Haematological toxicity: maximal CTC grade per patient

Topotecan dose (mg/m^2)	Number of patients	Number of patients with CTC grade 3–4 toxicity						Platelet transfusion	Febrile neutropenia
		Anaemia		Leucopenia		Thrombocytopenia			
	CTC Grade:	3	4	3	4	3	4		
10	3	0	0	3	0	1	0	0	0
15	7	0	0	3	1	2	0	0	1[a]
20	6	1	0	3	2	4	1	1[a]	0
25	5	1	0	4	2	2	2	2[a]	2[a]

CTC, common toxicity criteria.
[a] Dose-limiting toxicity (DLT).

Table 2B
Haematological toxicity: maximal CTC grade per cycle

Topotecan dose (mg/m^2)	Number of cycles	Number of cycles with CTC grade 2–4 toxicity					
		Anaemia		Leucopenia		Thrombocytopenia	
	CTC Grade:	2	3	3	4	2	3
10	18	12	0	9	0	8	1
15	33	26	0	11	1	27	2
20	26	17	0	11	2	6	7
25	22	14	1	11	1	5	2
Total	99		1		4		12

Table 3A
Non-haematological toxicity: maximal CTC grade per patient

Topotecan dose (mg/m^2)	Number of patients	Number of patients with CTC grade 1–3 toxicity											
		Nausea		Vomiting		Diarrhoea		Abdominal pain		Fatigue		Peripheral neuropathy	
	CTC Grade:	2	3	2	3	2	3	2	3	2	3	1	2
10	3	2	1	2	0	0	1	0	0	2	0	2	0
15	7	4	1	2	0	0	0	1	1	5	1[a]	5	1
20	6	1	1	1	0	0	0	1	0	2	0	3	0
25	5	3	0	2	2	0	1	0	0	2	3[a]	4	1

[a] DLT.

Table 3B
Non-haematological toxicity: maximal CTC grade per cycle

Topotecan dose (mg/m^2)	Number of cycles	Number of cycles with CTC grade 2–3 toxicity									
		Nausea		Vomiting		Diarrhoea		Abdominal pain		Fatigue	
	CTC Grade:	2	3	2	3	2	3	2	3	2	3
10	18	3	2	4	0	0	1	0	0	2	0
15	33	5	10	3	0	0	0	1	2	6	1[a]
20	26	4	1	1	0	0	0	1	0	2	0
25	22	5	0	6	2	1	1	0	0	7	3[a]
Total	99		13		2		2		2		4

[a] DLT.

Table 4
DLTs per topotecan dose level

Topotecan dose (mg/m^2)	Total number of patients	Total number of patients with DLT	Type of DLT			Total number of DLT[a]
			Neutropenic fever	Platelet transfusion	Fatigue grade 3	
10	3	0	0	0	0	0
15	7	1	1	0	1	2
20	6	1	0	1	0	1
25	5	3	2	2	3	7

[a] There can be more than one DLT per patient.

3.2. Anti-tumour activity

Of the 21 patients, 15 patients (71%) completed the full i.p. treatment, six patients were not evaluable for an assessment of anti-tumour activity. Only four patients with residual disease could be assessed for tumour response; one patient had a CR and three had a PR after six treatment cycles. All 15 evaluable patients had a median PFS of 27 months in a Kaplan–Meier log-rank analysis at a median follow-up of 18 months (data not shown).

3.3. Intraperitonial pharmacokinetics

Peritoneal samples for PK analyses were available from eight patients Table 5. In the other patients, collection of peritoneal fluid from the PAP-catheter was impossible due to pericatheter fibrosis, leading to backflow obstruction. The elimination phase of total topotecan (lactone plus carboxy forms) from the peritoneal cavity was best described by a mono-exponential model. The mean half-life ($t_{1/2}$) for the peritoneal compartment

Table 5
Pharmacokinetics of intraperitoneal total topotecan and lactone

	Patient no.	Dose (mg/m^2)	AUC $0 \rightarrow \infty$ (h μg/l)	CL (l/h m^2)	V_{ss} (l/m^2)	$t_{1/2}$ (h)	MRT (h)	k_{el} (h^{-1})
Topotecan	5	15	48940	0.3	1.3	2.7	3.9	0.25
	6	15	68050	0.0	0.0	2.1	3.0	0.33
	7	15	31400	0.6	1.7	1.9	2.8	0.36
	8	15	25480	0.0	0.0	2.6	3.8	0.26
	9	15	95290	0.2	0.8	3.2	4.7	0.21
	12	15	48560	1.1	1.8	1.2	1.7	0.60
	10	20	58120	0.3	1.0	2.3	3.3	0.30
	15	20	138700	0.2	1.7	6.6	9.6	0.10
	Mean			0.3	1.0	2.8	4.1	0.30
	SD			0.4	0.7	1.6	2.4	0.14
Lactone	5	15	36230	0.7	4.3	4.5	6.4	0.16
	6	15	54160	0.0	0.0	2.1	3.1	0.33
	7	15	18440	1.66	4.0	1.7	2.4	0.41
	8	15	3674	0.0	0.0	2.4	3.5	0.29
	9	15	74370	0.21	0.9	1.7	2.5	0.40
	15	20	66900	0.38	2.9	5.4	7.7	0.13
	Mean			0.5	2.0	3.0	4.3	0.29
	SD			0.6	2.0	1.6	2.2	0.12

C_{max}, peak plasma concentration; $AUC_{0\rightarrow\infty}$, area under the curve; CL, i.p. clearance; V_{ss}, volume of distribution at steady-state; $t_{1/2}$ elimination half life; MRT, mean residence time; k_{el} elimination rate constant; SD, standard deviation.

was 2.8 ± 1.6 h for total topotecan and 3.0 ± 1.6 h for lactone. The peritoneal to plasma AUC ratio for total topotecan was 46 ± 30. The peritoneal lactone/total topotecan AUC ratio was 0.14–0.80, median 0.67.

3.4. Plasma pharmacokinetics

The plasma kinetics of topotecan in 17 patients were best described by a one compartmental model developed for intramuscular injections. The plasma PK parameters of total topotecan and lactone are presented in Table 6. The plasma peak levels (C_{max}) of total topotecan were reached at 2.8 ± 1.3 h (T_{max}, mean ± standard deviation) and of plasma lactone 2.1 ± 1.0 h after the start of i.p. administration and were both dose-dependent ($R = 0.79$ and $R = 0.49$, respectively, $P < 0.05$ for both) (data not shown). The apparent $t_{1/2}$ was 3.8 ± 2.3 h for total topotecan and 4.4 ± 3.9 h for lactone. The AUC, which represents the total plasma exposure time, was proportional with dose, $R = 0.54$, $P < 0.05$ for total topotecan in contrast to $R = 0.35$ for lactone, which was not dose-proportional (data not shown). The mean apparent plasma clearance of total topotecan was 14.0 ± 3.5 l/h/m^2 with a mean volume of distribution (V_{ss}) of 74 ± 49 l/m^2. The mean plasma clearance of lactone was 58.3 ± 24.6 l/h/m^2 with a mean volume of distribution (V_{ss}) of 380 ± 354 l/m^2. It is appropriate to speak of "apparent" plasma clearance (Cl/F) and volume of distribution (V_{ss}/F), as the exact fraction of the total amount of active lactone administered i.p., which reaches the plasma compartment over time is unknown. The plasma AUC ratio of lactone versus total topotecan (lactone + carboxy-forms) ranged from 0.16 to 0.77

Table 6
Pharmacokinetics of total plasma topotecan and plasma lactone

	Patient no.	Dose (mg/m^2)	AUC $0 \rightarrow \infty$ (h μg/l)	CL (l/h m^2)	V_{ss} (l/m^2)	$t_{1/2}$ (h)	MRT (h)	k_{el} (h^{-1})	T_{max} (h)	C_{max} (μg/l)
Topotecan	1	10	1132	13.5	64	3.3	5.1	0.21	0.7	145
	5	15	1723	9.4	35	2.6	7.7	0.27	4.2	163
	6	15	1491	5.4	44	5.7	8.2	0.12	2.7	138
	7	15	1369	15.1	58	2.6	5.7	0.26	2.7	144
	8	15	1958	13.8	77	3.9	7.3	0.18	2.9	126
	9	15	1052	14.8	246	11.5	16.6	0.06	5.7	44
	12	15	927	18.8	68	2.5	5.5	0.27	2.7	137
	10	20	2028	10.4	50	3.3	6.7	0.21	2.9	243
	11	20	1504	15.0	65	3.0	6.1	0.23	2.7	192
	13	20	1276	15.7	20	0.9	1.3	0.79	3.2	278
	14	20	1529	14.5	67	3.2	4.7	0.22	2.7	189
	15	20	1551	13.3	124	6.5	9.3	0.11	5.6	100
	16	25	1655	17.1	62	2.5	4.7	0.27	1.3	377
	17	25	1965	13.8	59	3.0	4.3	0.24	2.4	289
	18	25	2119	13.1	68	3.6	5.1	0.19	2.2	282
	19	25	1372	20.6	86	2.9	4.2	0.24	1.3	265
	20	25	1919	14.3	68	3.3	4.7	0.21	2.3	265
	Mean			14.0	74	3.8	6.3	0.24	2.8	
	SD			3.5	49	2.3	3.2	0.15	1.3	
Lactone	1	10	209	58.6	343	4.1	6.5	0.17	1.5	23
	5	15	1329	30.1	101	2.3	7.3	0.30	4.0	53
	6	15	539	0.0	0.1	2.7	4.0	0.25	0.5	132
	7	15	243	80.3	388	3.4	6.3	0.21	2.5	26
	8	15	340	54.1	270	3.5	6.6	0.20	2.7	35
	9	15	254	59.4	1525	17.8	26.4	0.04	2.5	9
	12	15	161	103.4	408	2.7	5.4	0.25	2.2	27
	10	20	787	34.7	176	3.5	6.3	0.20	2.1	84
	11	20	240	87.9	424	3.3	6.6	0.21	2.8	26
	13	20	436	45.9	42	1.1	0.9	0.63	3.3	98
	14	20	276	71.7	394	3.8	5.5	0.18	1.9	37
	15	20	355	59.4	855	9.9	14.4	0.07	3.2	21
	16	25	396	59.4	257	3.0	4.5	0.23	0.3	94
	17	25	383	64.4	321	3.5	4.9	0.20	1.3	72
	18	25	352	73.4	440	4.2	6.0	0.17	1.3	49
	19	25	331	75.1	348	3.2	4.6	0.22	0.9	59
	20	25	747	33.4	164	3.4	4.9	0.20	2.2	107
	Mean			58.3	380	4.4	7.1	0.22	2.1	
	SD			24.6	354	3.9	5.6	0.12	1.0	

C_{max}, peak plasma concentration; $AUC_{0\rightarrow\infty}$, area under the curve; CL, total body clearance; V_{ss}, volume of distribution at steady-state; $t_{1/2}$ elimination half life; T_{max}, time to reach C_{max}; MRT, mean residence time; k_{el} elimination rate constant.

(median 0.23) and was not proportional with the dose of topotecan (Fig. 1).

Fig. 2 shows the peritoneal and plasma concentration versus time curve of total topotecan and lactone for one representative patient at 20 mg/m^2, indicating that peritoneal concentrations are approximately 50 times higher than plasma levels and that plasma topotecan levels were sustained for several hours above a threshold concentration of 100 μg/l, which is reported to be an active concentration *in vitro* [26].

4. Discussion

The results of the present phase I trial demonstrate that full doses of i.p. topotecan can be combined with full standard doses of i.v. carboplatin and paclitaxel. Febrile neutropenia and thrombocytopenia, requiring platelet transfusion, were dose-limiting together with grade 3 fatigue at the 25 mg/m^2 level of i.p. topotecan, while other toxicity was acceptable. In most studies with i.v. topotecan given as monotherapy, the DLTs are neutropenia and in some more prolonged schedules thrombocytopenia as well [27–29]. The DLT for the topotecan monotherapy schedule with escalating doses daily i.v. for five consecutive days has been defined as neutropenia at a cumulative dose of 7.5 mg/m^2 [30]. In the present combination study, topotecan 20 mg/m^2 i.p. was the MTD. This MTD of i.p. topotecan without growth factor support and combined with standard dose carboplatin/paclitaxel is therefore almost three-fold its cumulative i.v. dose. This may be related to the pharmacokinetics of i.p. administration, resulting in less systemic exposure and less myelotoxicity. This combination regimen was generally well tolerated. Cycles could be given to most patients with minimal dose adaptations. However, this route of topotecan administration led to complications in four patients: impaired distribution of i.p. fluid (in two patients), an infected i.p. catheter (one) and chemical peritonitis (one), while a fifth patient was not eligible because of intrathoracic fluid leakage. The PK data of topotecan do not differ from the previous phase I study with i.p. topotecan monotherapy [17]. This indicates that adding carboplatin and paclitaxel does not interfere with topotecan pharmacokinetics.

Fig. 1. Ratio plasma lactone/total topotecan AUC at various dose steps. $R = 0.12$, non-significant (NS).

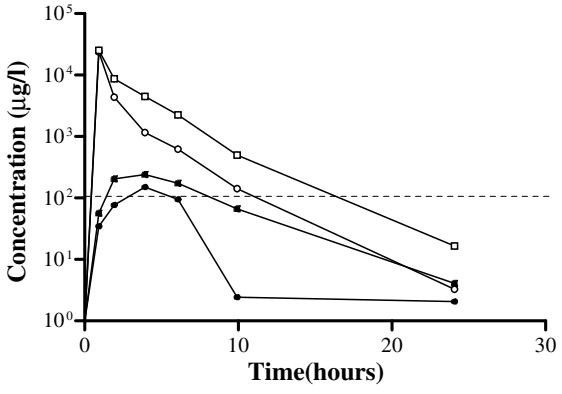

Fig. 2. Plasma and intraperitoneal (i.p.) concentration of lactone and total topotecan in a representative patient after 20 mg/m^2 topotecan i.p. Squares: total topotecan; circles; lactone; open symbols: peritoneal samples, closed symbols: plasma samples. The interrupted line represents the minimal inhibitory topotecan concentration *in vitro* 100 μg/l. Note the log scale.

In humans, the plasma pharmacokinetics of i.v. topotecan is linear and dose-proportional. Myelosuppression in topotecan i.v. studies is related to the magnitude (AUC) of plasma topotecan exposure [31]. *In vitro* studies have demonstrated, that topotecan concentrations of 45–100 μg/l are needed to induce inhibition of DNA repair and cytotoxic effects [26]. In the present study, we have demonstrated that peritoneal concentrations of total topotecan are approximately 50 times higher than the plasma levels and that at the MTD, peak plasma total topotecan levels range between 100 and 278 μg/l and therefore are lying above the *in vitro* cytotoxic range. At the MTD, peak plasma lactone levels range between 21 and 98 μg/l.

The pharmacokinetics can not be simply compared with published data on oral or i.v. administration, because the i.p. route is best compared with i.m. injections, for which no data are available. In an acid or low pH environment, active lactone is stable. At pH 7.4, the closed-ring lactone is hydrolysed into the less active, open-ring hydroxy form. The half-life of i.p. lactone indicates the rate of this process, as the pH of the solution will be swiftly neutralised within the abdominal cavity. The mean i.p. $t_{1/2}$ proved to be 3.0 ± 1.6 h, comparable to the $t_{1/2}$ 2.8 h for total topotecan, which is the result of production by hydrolysed lactone and loss from the abdominal cavity. For plasma, the lactone and total topotecan apparent half-lives were 4.4 ± 3.9 and 3.8 ± 2.3, respectively, somewhat higher because of the inflow from the abdomen. In the study by Rowin-

sky and co-workers, the half-lives after i.v. bolus administration were 3.0 ± 0.5 h for active, closed-ring lactone, data were not given for total topotecan. These authors report an *ex vivo* half-life for lactone in a typical 5% dextrose solution of 30 min at pH 4.5, and this was even faster at physiological pH. In the study of Herben and colleagues [9] using a much lower dose of 0.3–0.4 mg/m^2 topotecan i.v., a similar $t_{1/2}$ for lactone (2.1 ± 0.5) and for total topotecan (2.2 ± 0.3) were reported.

In a study with continuous infusion of topotecan in children with acute leukaemia, steady-state plasma concentrations >1 ng/ml (>1 μg/l) were found to induce responses, while C_{ss} > 5 μg/l induced mucositis [32]. In this study, these concentrations were exceeded by far, but were not sustained for more than 24 h as they were in the paediatric study, in which a continuous infusion of 120 h was used.

A study with i.p. topotecan by Plaxe and co-workers [18] found a MTD of only 4.0 mg/m^2 (recommended dose 3.0 mg/m^2) when given as continuous i.p. infusion. The kinetics of total topotecan in that study reached a plasma steady-state concentration of 6–10 μg/ml persisting for 36 h, indicating that the duration of exposure is a significant factor in the determination of toxicity, as reported by others [33]. In view of these points, the AUC may be a better parameter for predicting the effect and toxicity than the steady-state concentration [34].

Three multicentre phase III studies have demonstrated that patients with optimally debulked disease are the prime candidates for i.p. chemotherapy [13–15]. In this study, escalating doses were used, which hampers an evaluation of the activity of the regimen used. The PFS of the group with optimal debulking was 19$^+$ months, compared with 9.5 months in the group with suboptimal surgery. In the group of optimally debulked patients, most are still disease-free. However, the follow-up is too short to make a reliable assessment of response duration and survival. In conclusion, febrile neutropenia, thrombocytopenia requiring transfusion and grade 3 fatigue were dose-limiting at the 25 mg/m^2 level of i.p. topotecan in combination with i.v. carboplatin and paclitaxel, while other toxicity was acceptable, apart from catheter-related complications. In this combination, the drugs could be administered at standard dosages, contrary to i.v. topotecan. The efficacy of topotecan i.p. in combination with carboplatin and paclitaxel i.v. should be explored further in a formal phase III study.

Conflict of interest statement

There are no financial and personal relationships with other people or organisations that could inappropriately influence or bias our work.

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