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Topotecan preceded by oxaliplatin using a 3 week schedule: a phase I study in advanced cancer patients

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Abstract

Combinations of topoisomerase I (topo I) poisons and platinum derivatives have synergistic antitumoral effects. However, their clinical development is limited by supra-additive haematological toxicity. The aim of this study was to determine whether sustained doses of topotecan and oxaliplatin could be achieved using a synergistic sequence. 34 advanced cancer patients and 186 cycles were evaluable for toxicity over five dosing levels. Oxaliplatin at 85–110 mg/m^2 was given on day 1, followed by topotecan 0.5–1.25 mg/m^2/day×5 from day 1 to 5, every 3 weeks. Plasma pharmacokinetics (PK) of total and ultrafiltrable platinum, total and lactone forms of topotecan were determined in the first cycle. The dose-limiting toxicity (DT) was identified as grade 4 thrombocytopenia. The occurrence of grade 4 thrombocytopenia did not correlate with topotecan PK, but it did with the patient's characteristics. Severe thrombocytopenia was seen in 1/8 of patients without clinical or biological evidence of malnutrition, with a creatinine clearance higher than 1 ml/s, and no more than two previous chemotherapy regimens, while it was seen in 8/10 patients with one of these characteristics ($P < 0.004$). In conclusion, the recommended doses of oxaliplatin 110 mg/m^2 and topotecan 1 mg/m^2/day, every 3 weeks can be administered to patients with a favourable general status and pretreatment characteristics and a phase II study is worthwhile in ovarian cancer patients.

Keywords: Malnutrition; Ovarian cancer; Oxaliplatin; Performance status; Thrombocytopenia; Topotecan

1. Introduction

Interest in combining platinum derivatives and topoisomerase I poisons has been invoked based on data from preclinical studies [1,2] and on their potential applications in the clinic. However, the combination of topotecan with cisplatin appeared to be limited by severe haematotoxicity, especially thrombocytopenia [3–5]. When cisplatin, or carboplatin, was given prior to topotecan, following the determination of a schedule-dependent synergy in preclinical studies, a greater than 50% dose reduction was required of the recommended dose of topotecan monotherapy, limiting the dose to 0.5 mg/m^2/day. This sequence effect could be explained in part *in vitro* by the slower reversion of platinum-induced DNA crosslinks in the presence of a camptothecin derivative [2]. Similar supra-additive toxicity was observed when another camptothecin derivative, CPT-11, was combined with cisplatin [6]. Effective dosing of topotecan could be achieved using the non-synergic sequence, with carboplatin given after topotecan [7]. Oxaliplatin, a diaminocyclohexane platinum derivative, was firstly shown to be active in metastatic colorectal cancer patients [8,9]. Both oxaliplatin and topotecan, when given alone, appeared at least as active as paclitaxel when given as second-line therapy to advanced ovarian cancer patients [10,11]. Thus, this

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suggested that ovarian cancer patients might benefit from the combination of topotecan with a platinum derivative. Additionally, loss of mismatch repair affects the ability of cisplatin to generate tumour cell variants that are resistant to other drugs, including topotecan, but not oxaliplatin [12]. We previously reported our experience of the combination of another camptothecin derivative, CPT-11, with oxaliplatin, and showed that the haematological tolerability was better than with cisplatin [13,14]. In particular, thrombocytopenia was sporadic and mild. Hence, the combination of these two agents appeared an attractive therapeutic option. We initiated this phase I study to evaluate the toxicity of this schedule in patients with advanced malignancies. The objectives were to determine the maximum tolerated dose (MTD) and to define the dose-limiting toxicities (DLTs) of topotecan and oxaliplatin in combination. A secondary objective was to describe antitumour activity, focusing on platinum- and paclitaxel-pretreated ovarian cancer patients.

2. Patients and methods

2.1. Patient eligibility

Patients were selected based on eligibility criteria commonly used for phase I trials in oncology [13,14]. Briefly, all patients had histologically-proven advanced cancer, were more than 18 years old. They had a performance status World Health Organization (WHO) $\leqslant 2$ and hepatic, renal and haematological biological parameters within pre-determined baseline limits (total bilirubin level $\leqslant 1.25\times$Upper Limit Normal (ULN); aspartate aminotransferase (AST), alanine aminotransferase (ALT), alkaline phosphatase $<2.5\times$ULN or $<5\times$ULN if hepatic metastases were present; serum creatinine $\leqslant 1.5\times$ULN; white blood cell (WBC) count $\geqslant 4\times10^9$ cells/l; absolute neutrophil count $\geqslant 1.5\times10^9$ cells/l; platelet count $\geqslant 100\times10^9$ cells/l; haemoglobin $\geqslant 100$ g/l). Exclusion criteria were: chemotherapy or radiotherapy given within 4 weeks before study entry (6 weeks for nitrosourea and mitomycin C), prior chemotherapy with oxaliplatin or a camptothecin derivative, previous malignancy (with the exception of excised cervical carcinoma-*in-situ* or basal/squamous cell skin carcinoma), peripheral neuropathy of any grade, pregnant women or women with childbearing potential, concomitant and uncontrolled non-malignant disease, including active infection. The ethics committee of Bicêtre University Hospital (Val de Marne, France) approved the protocol, and signed informed consent was obtained from all of the patients prior to inclusion. Complete blood cell counts and differential, blood chemistries, and disease-specific serum tumour markers were determined at baseline and before each cycle. Complete blood cell counts were repeated twice weekly. Patients were evaluated weekly for toxicity while on the study.

2.2. Evaluation of toxicity: definitions of DLT and MTD

All toxicities, except peripheral sensory neuropathy, were graded using version 1 of the National Cancer Institute Common Toxicity Criteria (NCI CTC). Oxaliplatin neurosensory toxicity was described according to the specific grading previously described in Refs. [9,13]. Grade 1: paresthesias/dysesthesias of short duration with complete recovery before the next cycle; grade 2: paresthesias/dysesthesias that persist between two cycles without functional impairment; grade 3: permanent functional impairment. The DLTs were defined as grade 4 neutropenia lasting for more than 7 days, any febrile grade 3 or 4 neutropenia, grade 4 thrombocytopenia or grade 3 with haemorrhage, grade 3 peripheral sensitive neuropathy, grade 4 vomiting, and grade 3 or 4 other non-haematological toxicity (excluding alopecia). In case of DLT, the treatment was to be discontinued until recovery to grade $\leqslant 1$, and, if clinically indicated, resumed for the subsequent cycle at the dose level immediately below that which resulted in the DLT. A minimum of 3 patients were entered at each dose level, with a minimum 1 week interval between the entry of the first patient and the next 2 patients at a given dose level. Dose escalation to the next dose level was conditioned by the evaluation of at least one treatment cycle of each of the 3 patients included at the same dose level. If 1 of the 3 patients at a given dose level experienced a DLT in the first two cycles, at least 3 additional patients were included at the same dose level. To reduce the risk of premature interruption of the study for DLTs that would not be related to excessive exposure to the drugs, the maximum tolerated dose (MTD) was defined as the dose resulting in at least 2 patients developing the same DLT at the first administration, as we previously described for the combination of CPT-11 and oxaliplatin [13,14]. The recommended dose, defined as the dose immediately below the MTD, was further administered to additional patients to confirm its toxicity and safety profile.

2.3. Treatment plan

Oxaliplatin was diluted in 250 ml 5% dextrose and administered as a 120-min infusion every 21 days. Topotecan was diluted in 100 ml 5% dextrose and administered as a 30-min daily infusion for 5 days. Topotecan was started immediately at the end of oxaliplatin infusion on the first day of each cycle. The starting doses of topotecan and oxaliplatin were 0.5 and 85 mg/m^2, respectively; the doses of each agent were esca-

Table 1
Dose escalation scheme and treatment

Dose level	Oxaliplatin (mg/m^2)	Topotecan (mg/m^2)	Patients (*n*)	Cycles (*n*)	Median cycles/patient (range)
I	85	0.5	11	60	4 (1–12)
II	85	0.75	6	40	7 (2–12)
III	85	1.0	4	27	7 (2–10)
IV	110	1.0	9	36	4 (1–9)
V	110	1.25	4	23	6 (2–9)
Total			34	186	4 (1–12)

lated according to the five dosing levels indicated in Table 1. No intrapatient dose escalation was allowed.

Treatments were done on an outpatient basis. Antiemetic therapy always contained at least an intravenous (i.v.) injection of 3 mg of granisetron before the oxaliplatin infusion, eventually associated with 40 mg of methylprednisolone. Topotecan infusions were preceded by the i.v. administration of 100 mg of Alizapride. Topotecan was continued as a single agent in cases where oxaliplatin was discontinued due to cumulative neurotoxicity.

2.4. Pharmacokinetic study

For both drugs, blood samples were collected using an indwelling i.v. cannula placed in the opposite arm to that of infusions. Blood samples for topotecan were taken immediately before, and at 15 min, 0.5, 1, 2, 2.25, 2.5, 2.75, 3, 3,5, 4.5, 5, 7, 9 and 24 h after the start of the infusion. The levels of the total and lactone forms of topotecan were determined using the high-performance liquid chromatographic (HPLC) method as previously described in Ref. [15], with a lower limit of detection of 0.25 ng/ml. The topotecan pharmacokinetic (PK) analyses were performed on days 1 and 5 of cycles 1 and 3 of the treatment.

For oxaliplatin, heparinised blood samples were collected at the following times: Before infusion, 15 min, 1, 2, 2.25, 2.5, 2.75, 3, 3.5, 4.5, 5, 7, 9, 24, 48, 72, 120 and 192 h after the start of the infusion. The oxaliplatin PK analysis were performed in cycles 1 and 3 of the treatment. Oxaliplatin, was assayed as total and ultrafiltrable platinum, using flameless atomic absorption spectrometric analysis, with the lower limit of detection for platinum being 5 ng/ml.

Both drug concentration–time data were fitted using the MicroPham program (S. Urien, Inserm, Centre René Huguenin, Saint-Cloud, France). Urine was collected up to 48 h and analysed for total topotecan and platinum.

2.5. Assessment of response

Objective responses were recorded according to standard WHO/International Union Against Cancer (UICC) response criteria [16]. An imaging assessment of tumoral target lesions was repeated every three cycles, whenever measurable disease was evidenced during the baseline work-up.

3. Results

3.1. Patient population

Table 2 lists the characteristics of the 34 patients entered in the study. 47% of the accrued patients had hepatocarcinoma or ovarian cancer. Most patients (88%) had a performance status of 0 or 1. All patients, but 3 (one radiation-refractory brain tumour, 2 unresectable hepatocellular carcinomas), had metastatic disease. All the 34 patients included were eligible and evaluable for both toxicity and response.

3.2. Study treatment

A total of 186 cycles of treatment were administered for the five dose levels of the combination. Most patients were treated as outpatients. Fig. 1 describes the revisions in patient eligibility requirements during the course of the study. Sixty cycles were given at the first dose level with a median number of cycles per patient of 4 (range 1–12). Grade 4 thrombocytopenia was observed in the first cycle in 2 of the initial 6 patients included at this dose level. This acute DLT contrasted with the lack of haematological toxicity of more than grade 2 in the other 4 patients, who received up to 12 cycles. This noticeable interindividual heterogeneity in treatment toxicity was not associated with any detectable PK interaction between topotecan and oxaliplatin, with similar topotecan area under the curve (AUC) measurements in patients experiencing or not the DLT episodes. These results in this subset of patients led us to consider the toxic effects as patient-related rather than dose-related. Indeed, the 2 patients who experienced DLT (1 with metastatic breast cancer and 1 with soft-tissue sarcoma) had an altered clinical performance status (PS-2) and were heavily pretreated. Therefore, a dose escalation to dose level II was allowed after a protocol amendment, which restricted inclusion criteria to PS 0–1 patients and no more than two previous chemo-

therapy regimens. Toward the end of the study, 5 additional patients were also included at dose level I to determine whether this dose level could be recommended in patients with an altered clinical or biological status, or those that had been heavily pretreated.

6 patients received a median of seven cycles (range 2–12) at the second dose level. Despite the restriction in the inclusion criteria, the same toxicity pattern was observed as was seen at the first dose level. 2 patients experienced grade 4 thrombocytopenia in the first cycle, again suggesting again that the MTD had been achieved. However, similar to the observation described for the patients included at dose level I, none of the 4 other patients included at this dose level experienced a DLT following 24 cycles of treatment. This observation led us to search for other clinical or biological parameters, which could account for this difference in patient tolerability. One of the 2 patients who experienced DLT had a borderline creatinine clearance albeit with serum creatinine within the range of normal values. The 4 patients who experienced DLT in the first cycle (at either of the first two dose levels) had biological evidence of malnutrition (decreased albumin and prealbumin serum levels) and/or of acute inflammation (increased C-reactive protein and orosomucoid plasma levels). This led us to consider that severe haematological toxic effects were still more likely to be due to the patient's general status rather than to the drug concentrations in the plasma. A dose escalation to the third dose level was initiated after a new protocol amendment added as an inclusion criteria a creatinine clearance higher than 1 ml/s and a (C-reactive protein×orosomucoid)/(albumin×prealbumin) ratio of less than 1. This formula, initially described by Ingelbleeck and colleagues in Ref. [17] is routinely used to assess nutritional status, and has proven valuable in assessing morbidity and mortality risks in many clinical entities [18,19].

Table 2
Patient characteristics

Characteristics	No. of patients (%)
Sex	
Male	18 (53%)
Female	16 (47%)
Age (years)	
Median (range)	54 (32–75)
ECOG performance status	
0	11 (32%)
1	19 (56%)
2	4 (12%)
Previous treatment	
Prior radiotherapy	7 (21%)
Prior surgery	23 (68%)
Prior chemotherapy regimens	24 (71%)
1–2	18 (53%)
>2	6 (18%)
Primary tumour	
Liver (HCC)	9 (26%)
Ovary	7 (21%)
Kidney	4 (12%)
Unknown primary	5 (14%)
Lung (SCLC)	2 (6%)
Other[a]	7 (21%)
Metastatic site	
Liver	18 (53%)
Lymph nodes	16 (47%)
Lung	15 (44%)
Number of involved organs	
1 site	14 (41%)
⩾2 sites	20 (59%)

HCC, hepatocellular carcinoma; SCLC, small-cell lung carcinoma; ECOG, Eastern Cooperative Oncology Group.

[a] Other: astrocytoma, peritoneal carcinomatosis, stomach, breast, leiomyosarcoma of the duodenum, pancreas, non-small cell lung carcinoma.

At the third dose level, no DLT was observed in 4 patients who received a median of seven cycles (range 2–10). As a consequence, a dose escalation to the fourth dose level was allowed. One patient among the 6 initial patients included experienced a DLT (grade 4 neutropenia for more than 7 days). At the fifth dose level, 2 patients, among the 4 included, experienced at least one haematological DLT in the first cycle. This dose level appeared not to be tolerable and was considered as the MTD. 3 additional patients were added to dose level IV at the end of the study to ensure the safety of this dose level in the subset of patients cautiously selected as described above.

3.3. Reasons for study withdrawal

21 (62%) patients were withdrawn from the study because of evidence of progressive disease. 2 patients discontinued after 11 and 12 cycles, at the investigator's decision, while the disease was stabilised. 3 patients discontinued treatment to undergo surgical resection of their metastases, following three, eight and nine cycles, respectively of the combination regimen. 2 patients left the study for personal reasons. 6 (18%) patients discontinued treatment due to toxicity. Three of them experienced acute limiting haematological toxicity, including one septic shock during neutropenia for a patient at dose level I. Another patient developed a rash and discontinued treatment with an initial diagnosis of allergy to either topotecan or oxaliplatin, but she experienced the same symptoms when she started another chemotherapy regimen, thus the allergy was probably related to the antiemetic agents. The other 2 patients were advanced ovarian cancer patients responding to therapy who developed a cumulative neurosensory toxicity after cumulative doses of 855 and 990 mg/m^2, given over nine cycles. They continued treatment with topotecan alone.

3.4. Toxicity

Acute haematological and non-haematological toxicities per patient, per dose level, and per cycle are presented in Tables 3 and 4, respectively. The DLT was thrombocytopenia. The main non-haematological toxicity was diarrhoea (see Table 4). Other toxicities with cumulative characteristics were neurosensory, anaemia and alopecia. One patient entered at the first dose level had a septic shock

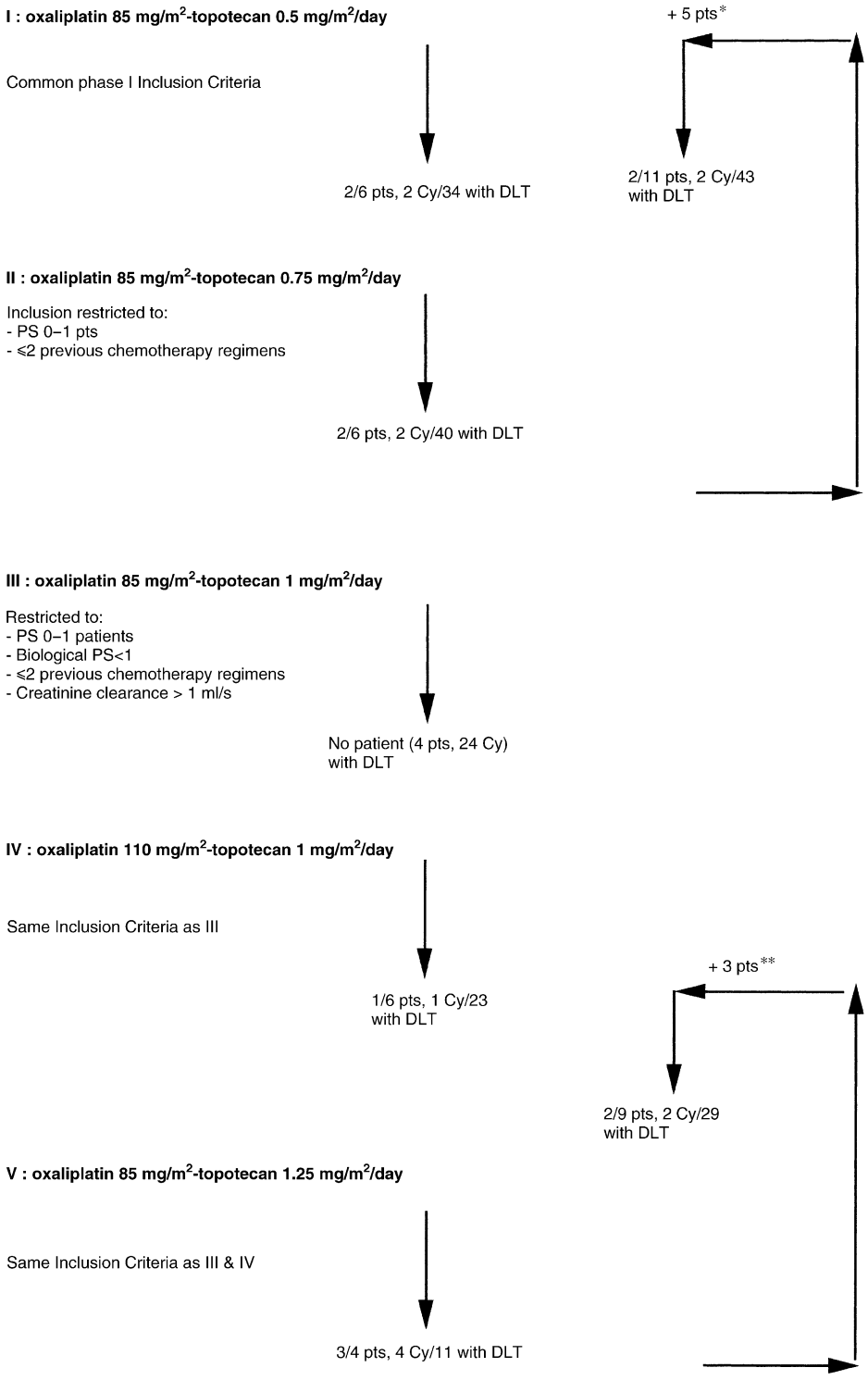

Fig. 1. Revisions in patient eligibility criteria during the course of the study. Cy, cycle; pts, patients; PS, performance status; DLT, dose-limiting toxicity.
* Patients responding to common phase I inclusion criteria.
**Patients responding to restricted inclusion criteria (as described at dose level IV).

Table 3
Summary of acute haematological toxicity

Dose level	No. of patients (%)/cycles (%)			
	Grade 3–4 neutropenia without fever	Grade 3–4 febrile neutropenia	Grade 3–4 thrombocytopenia	Grade 3–4 anaemia
I	7 (64%)/17 (28%)	1 (9%)/1 (2%)	6 (55%)/13(22%)	7 (64%)/18(30%)
II	5 (83%)/21 (53%)	–	2 (33%)/12 (30%)	3 (50%)/5 (13%)
III	4 (100%)/8 (30%)	–	1 (25%)/1 (4%)	2 (50%)/3 (11%)
IV	9 (100%)/25 (69%)	1 (11%)/2 (6%)	4 (44%)/9 (25%)	6 (67%)/12 (33%)
V	4 (100%)/20 (87%)	2 (50%)/2 (9%)	3 (75%)/13 (57%)	3 (75%)/13 (57%)
Total	29 (85%)/91 (49%)	4 (12%)/5 (3%)	16 (47%)/48 (26%)	21 (62%)/51 (27%)

following the first administration. No lethal toxicity was observed.

3.5. Haematological toxicity

The frequency of haematological adverse events for the 34 patients is listed in Tables 3 and 5. Toxicity was summarised as the worst CTC grade experienced by each patient and as the worst CTC grade experienced within each course for each patient. Grade 3–4 neutropenia was topotecan dose-dependent, occurred in a majority (64%) of patients from dose level I and was observed in all patients at dose level III. The median onset of grade 4 neutropenia occurred on day 8, with a median duration of 5 days. Two grade 4 neutropenia lasting longer than 7 days were recorded at dose levels IV and V. No patient received prophylactic granulocyte-colony stimulating factor (G-CSF), with 1 patient receiving therapeutic G-CSF. Anaemia was seen with a cumulative dosing pattern. 22 (65%) patients required at least one transfusion of red blood cells. Platelets were routinely transfused when the platelets were less than 20×10^9 cells/l, this occurred in 4 (12%) patients and after five (2.7%) cycles. Thrombocytopenia was the main limiting toxicity at the two initial dose levels, but after eligibility modifications its incidence decreased allowing dose escalation to dose level III. As a consequence, despite a 2-fold increase in the topotecan dose from dose level I to III, thrombocytopenia was 2-fold less frequent at dose level III (see Table 3) and none of the patients treated at dose level III experienced grade 4 thrombocytopenia (see Table 5).

Table 4
Summary of acute non-haematological toxicities

Dose level	No. of patients (%)/cycles (%) with grade 3–4		
	Nausea/vomiting	Diarrhoea	Asthenia
I	1 (9%)/1 (2%)	4 (36%)/5 (8%)	2 (18%)/2 (3%)
II	–	1 (17%)/1 (3%)	2 (33%)/5 (13%)
III	1 (25%)/3 (11%)	–	–
IV	–	2 (22%)/3 (8%)	–
V	–	1 (25%)/4 (17%)	–
Total	2 (6%)/4 (2%)	8 (24%)/13 (7%)	4 (12%)/7 (4%)

3.6. Infectious complications

Febrile neutropenia complicated five (3%) of the 186 cycles. Its sporadic nature was probably due, in part, to the short duration of the nadir and the lack of concomitant mucositis on one hand, and to the good general condition of most of the patients entered in the study (see Table 2) on the other. One episode was a septic shock in the first cycle in a patient with PS 2 who developed a bacterial pneumonia during neutropenia, associated with concomitant severe diarrhoea. Two episodes of febrile neutropenia occurred at dose level IV and the other two at the MTD, but without septic episodes.

Table 5
DLTs at first cycle

Dose level	Thrombocytopenia	Grade 3–4 febrile neutropenia	Grade 4 neutropenia >7 days	Asthenia	Diarrhoea
I	2 (18%)[a]	1 (9%)[a]	–	1 (9%)	3 (27%)
II	2 (33%)	–	–	1 (17%)	–
III	–	–	–	–	–
IV	1 (11%)[a]	1 (11%)	1 (11%)	–	2 (22%)
V	1 (25%)[b]	1 (25%)	1 (25%)	–	–
Total	6 (18%)	3 (9%)	2 (6%)	2 (6%)	5 (15%)

[a] One patient experienced both febrile neutropenia and grade 4 thrombocytopenia.
[b] One patient experienced both grade 4 Neutropenia >7 days and grade 4 thrombocytopenia.

3.7. Neuropathy

Neurosensory toxicity was prevalent as cumulative toxicity. Its severity was characteristically preceded by progressively persistent paresthesias between cycles. The severity of symptoms was usually maximal 1–2 months after treatment interruption, followed by a gradual reversibility of symptoms, as previously described in Refs. [13,14]. Severe cumulative neurosensory toxicity was never seen below the 500-mg/m^2 oxaliplatin cumulative dose, and was generally prevalent above 800 mg/m^2. Of note, one ovarian cancer patient with grade 1 neuropathy had exacerbation of her symptoms immediately following the second-look surgery, after 990 mg/m^2 of oxaliplatin treatment.

3.8. Other non-haematological toxicities

Non-haematological toxicity was generally mild. No alopecia was noticeable at dose level I. Using daily doses of topotecan equal to or higher than 1 mg/m^2, hair loss was common, but could be efficiently prevented by scalp cooling during the topotecan administration. Nausea and vomiting were common during the initial 48 h following the oxaliplatin infusion and was generally mild. Interestingly, two side-effects were unexpectedly frequent following the combination treatment, but were previously well identified with another camptothecin derivative, CPT-11 [13,14]. First, the incidence of diarrhoea appeared to be higher than reported with either agent alone (see Table 4). Diarrhoea usually occurred between days 8 and 15, being severe in 8 (24%) patients and following 13 (7%) of cycles. Second, a transient increase in unconjugated bilirubin could be detected in patients. This bilirubin elevation was measured on day 5 (the last day of the topotecan infusion) and bilirubin levels returned to basal values prior to the next treatment administration, suggesting a possible competition between bilirubin and topotecan for the UGT1A1 isoenzyme, as previously described for CPT-11 treatment [13,14,20]. Few patients complained of constipation during the 5 days of each cycle treatment, possibly because of the additive effects of topotecan and granisetron on intestinal motricity.

3.9. Relationship between toxicity and pharmacological parameters

25 patients were evaluable for PK analysis. The results obtained during the first cycle are presented in Table 6a and b. We failed to detect any PK interaction between topotecan and oxaliplatin and the main PK parameters of each agent were those expected when given alone (see Tables 6a and b). The PK parameters for oxaliplatin did not differ significantly from those observed as a single agent administration [21] or in combination with CPT-11 [13]. Similarly, topotecan PK parameters were in the same range as those previously reported in a phase I clinical trial of topotecan alone [22–25]. At all dose levels, a large interpatient variability was observed in the topotecan AUC. No relationship was found between the topotecan AUC and the occurrence of the main DLT, grade 4 thrombocytopenia (Fig. 2). At each dose level, the patient with the highest AUC did not experience DLT. The mean AUC achieved by the patients enrolled at dose level III and who did not experience severe thrombocytopenia was higher than the mean AUC of patients experiencing DLT. For a given dose level, except for dose level I, the mean AUC was similar or higher in patients who did not experience severe thrombocytopenia (see Fig. 2). No grade 4 thrombocytopenia was observed in all of the patients who achieved the highest quartile of topotecan AUC (>69 ng/ml/h). In contrast, 3 patients experiencing

Table 6
Plasmatic pharmacokinetic parameters of (a) oxaliplatin and (b) topotecan

(a)	Total oxaliplatin			Ultrafilterable oxaliplatin		
	85 mg/m^2	110 mg/m^2	CV (%)	85 mg/m^2	110 mg/m^2	CV (%)
Cmax (ng/ml)	2225±415	3222±364	15	900±275	1077±168	24
AUC (ng/ml×h)	151±48	206±66	32	7.8±3.7	8.1±3.1	40
Clt (l/h/m^2)	0.61±0.17	0.57±0.13	25	12.7±4.8	15.5±6.0	35
$T_{1/2}$ (h)	104±23	86±23	25	23±9	22±10	41
(b)	Total topotecan			Lactone form		
	0.5 mg/m^2	1 mg/m^2	CV (%)	0.5 mg/m^2	1 mg/m^2	CV (%)
Cmax (nmol/l)	4.37±1.07	9.04 26±2.33	26	2.52±0.61	6.39±1.96	30
AUC (nmol/l×min)	696.4±372.5	1235.5±510.6	50	ND	388±215	35
Clt (l/h/m^2)	26±18	25±13	47	ND	81±35	42
$T_{1/2}$ (h)	2.4±0.6	3.0±1.9	56	ND	0.9±0.6	50

Cmax, maximal plasma concentration; AUC, area under the curve; Clt, clearance; $T_{1/2}$, plasmatic half-life; CV, coefficient of variation; ND, not determined.

Table 7
Grade 3–4 haematological toxicity at topotecan 0.5 or 0.75 mg/m^2/day (patients (%)/cycles (%))

	Patients (*n*)	Cycles (*n*)	Grade 3–4 neutropenia	Febrile neutropenia	Anaemia	Thrombocytopenia
High risk	10	43	6 (60%)/14 (33%)	2 (20%)/2 (5%)	7 (70%)/13 (30%)	8* (80%)/23 (53%)
Low risk	8	55	5 (63%)/18 (33%)	–	2 (25%)/2 (4%)	1* (13%)/2 (4%)

*$P < 0.004$.

grade 4 thrombocytopenia had a topotecan AUC of less than 40 ng/ml/h and less than that of 50% of the patients treated in this study. Altogether, these results indicated the lack of correlation between the topotecan AUC and the occurrence of the acute DLT, thrombocytopenia.

3.10. Relationship between toxicity and patients' characteristics

As mentioned above, the 2 patients who experienced acute DLT at dose level I were heavily pretreated. Based on this observation, the following patients included in the study were not allowed to have more than two previous chemotherapy regimens. Patients with a PS of 2 also appeared more susceptible to developing severe treatment toxicity. All 4 patients with PS-2 entered in the study experienced at least one DLT episode in the first cycle. This was in agreement with our previous study of the combination of another camptothecin derivative, CPT-11, with oxaliplatin [13,14]. However, one patient with a clinical PS of 1, entered at dose level II, experienced a DLT at the first cycle. Since the analysis of the PK of topotecan and oxaliplatin did not suggest that these DLTs were related to excessive exposure to topotecan or oxaliplatin, we attempted to better define patients who might tolerate this combination treatment. We measured the plasma concentrations of proteins reflecting inflammatory and nutritional biological status and added as a new inclusion criteria the normality of the biological PS (BPS) defined as described earlier.

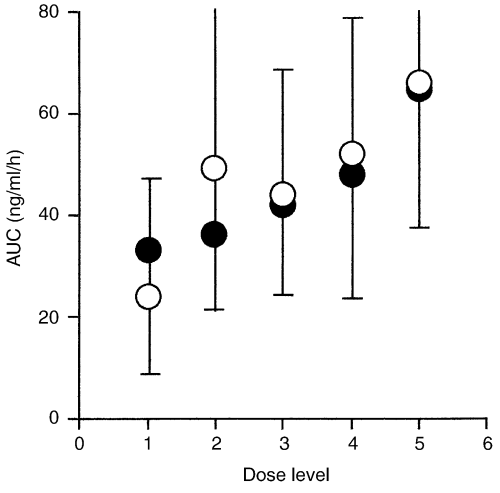

Fig. 2. Lack of correlation between topotecan AUC and thrombocytopenia. The topotecan area under the curve (AUC) of patients experiencing grade 4 thrombocytopenia (black circles) and the mean and range of topotecan AUC in the other patients (white circles) are shown. At each of the five dose levels, the highest topotecan AUC was observed in a patient who did not experience grade 4 thrombocytopenia.

'Low-risk' patients were defined with all of the following characteristics, as having received no more than two previous chemotherapy regimens, and having a creatinine clearance higher than 1 ml/s, and a clinical PS of less than 2, and a biological PS of less than 1. Table 7 compares treatment tolerability for the two initial topotecan doses depending on the patient's characteristics. The prevalence of severe neutropenia was similar in the two patient populations but the neutropenic episodes remained asymptomatic in the 'low-risk' patients. Anaemia was more severe and required more red blood cells transfusions in the 'high-risk' patients, defined as failing one or more criteria of the 'low-risk' definition. Notably, severe thrombocytopenia concerned 6-fold more patients and occurred 13-fold more often in the 'high-risk' patients. Based on these results, the phase I dose escalation was continued, but restricted to the 'low-risk' patients. Table 8 summarises the treatment tolerability in this subset of patients and shows that dose escalation was possible up to the fifth dose level (110 mg/m^2 oxaliplatin and 1.25 mg/m^2/day topotecan, each agent given at 80% of the single-agent dosing). This dose level appeared to be the MTD in this patient population.

3.11. Antitumoral activity

Among the 34 patients, 33 were evaluable for response. Objective tumour responses were observed in 5 (15%) patients. 4 of these patients had advanced ovarian cancer. The fifth patient had primary peritoneal carcinomatosis. In addition, a total of 19 (56%) patients

Table 8
Grade 3–4 treatment and haematological DLT in low-risk patients

Dose level	Patients (*n*)	Cycles (*n*)	DLT at first cycle
I	4	31	–
II	4	24	–
III	4	27	–
IV	8	30	2
V	4	23	3
Total	24	135	5 (21%)

had stable disease as the best response to treatment. Progressive disease at the first evaluation was observed in 9 patients (27%). It was reported that in 1 patient with a soft-tissue sarcoma (dose level I), one with heavily pretreated metastatic breast cancer (dose level I), one with hepatocellular carcinoma (dose level IV) and one with liver metastases of an unknown primary tumour (dose level I), representing a low 12% outright disease progression rate on therapy. The median time to progression for the entire population was 4.7 months (95% Confidence Interval (C.I.): 3.0–6.4) and the median overall survival was 17 months.

The 7 ovarian cancer patients included were all pretreated with cisplatin or carboplatin, plus paclitaxel. 2 of them had relapsed within 6 months after the end of the first-line treatment and could be considered as resistant to cisplatin. One patient was considered as refractory based on a surgical evaluation following first-line treatment, which revealed new peritoneal lesions. The 2 cisplatin-resistant patients and the cisplatin-refractory patients had a documented partial response to topotecan–oxaliplatin, 1 of these having peritoneal carcinomatosis, liver metastases and pleural effusion. As assessed in June 2001, the median time to disease progression in the 4 responders was 11 months and in the 7 ovarian cancer patients was 5.5 months (range 1.5–20). Their median survival was 16 months from inclusion in the study.

Additionally, a man with a primary peritoneal carcinomatosis achieved an objective response after treatment with two chemotherapy regimens and is alive and well more than 18 months after the end of the treatment.

The antitumour activity was also noteworthy in the 9 patients with hepatocellular carcinoma. None of them experienced an objective tumour response, but the median duration of disease stability was 4 months, with 2 of them having a sustained decrease in alpha-fetoprotein (AFP) levels, and 1 patient was able to undergo a liver transplantation. One patient with fibrolamellar carcinoma with rapidly progressing lung metastases had prolonged disease stabilisation and remained in complete remission more than 12 months after a new surgical resection of their lung metastases.

2 patients with pretreated metastatic small-cell lung carcinoma (SCLC) received 10 and six cycles of the study treatment after a first-line therapy combining etoposide and cisplatin. Both patients had prolonged stable disease for 7 and 6 months, respectively, associated with a decrease in Neuron Specific Enolase (NSE) serum levels and minor response at the computed tomography (CT)-scan evaluation.

4. Discussion

The development of topotecan in combination with platinum derivatives is attractive for a variety of solid tumours, but is a difficult issue. To date, it has never been possible to combine full doses of topotecan with full doses of a platinum derivative using the sequence of administration (platinum prior to topotecan), the most active *in vitro*. The recommended dose of cisplatin was commonly a 2-fold decrease leading to 50 mg/m^2 [4,5,26–28], a dose which has been proven to be suboptimal [29]. Conversely, the dose of topotecan may be decreased to a dose range (usually 0.75 mg/m^2/day [4,28], sometimes less [26,27] for which its antitumoral effect has not been studied. Alternatively, it has been proposed to give topotecan prior to cisplatin [30]. The aim of this clinical and pharmacological study was to determine whether combining topotecan with oxaliplatin was feasible and whether it would allow the administration of sustained doses of topotecan, as well as of oxaliplatin. The DLTs of topotecan are haematological represented by a grade 3–4 neutropenia (in 90% of patients) with the nadir on days 8–10 and, more rarely, (in 15% of cases), thrombocytopenia, which is maximal on days 14–15.

Several studies have shown PK–pharmacodynamic relationships for topotecan [31]. Considering the present and most used schedule of administration of topotecan, (i.e. the 30-min i.v. infusion on 5 subsequent days every 3 weeks), a correlation has been shown between the total plasma AUC observed on day 1 and the percentage decrease in white blood cells [21–23]. There is a well known large interindividual variability in topotecan clearance [24,32]. Significant correlations have been found between creatinine clearance based on the Cockcroft–Gault formula and topotecan clearance [23,32]. The use of the estimated creatinine clearance may allow the interindividual variability to be halved [32]. To target a given AUC, an estimation of topotecan clearance in a patient from a single-point sampling 4- or 8-h after the end of topotecan infusion has been proposed to monitor topotecan levels [32]. Nevertheless, in this study, we failed to identify a relationship between estimated creatinine clearance and the occurrence of DLTs, except in 1 patient. The PK of oxaliplatin were as expected when given as a single agent [20]. As previously observed with CPT-11 [12], the combination of topotecan with oxaliplatin did not result in PK interactions of either agent. Moreover, topotecan AUC did not differ significantly between patients having grade 4 thrombocytopenia or not. Since neither creatinine clearance nor the PK of topotecan in combination could be used as guidelines for dose-escalation, we searched for other patient-dependent parameters, which might alter the pharmacodynamics of the combination in the absence of detectable PK abnormalities. The role of the cellular response to topotecan-induced DNA damage in normal tissues might be the main discriminator between patients having very different toxicities for the same drug exposure. The topoisomerase I- and oxaliplatin-mediated

DNA damages are well characterised and induce supra-additive cytotoxicity in cells [33,34]. Interestingly, the clinical reality of this cellular supra-additive toxicity could be well evidenced when we compared the toxicity observed at dose level III versus dose level IV. While there was no change in the dose of topotecan, there was a sharp increase in the severity of the acute haematological toxicity and rates in the first cycle following a moderate increase in the oxaliplatin dose. Oxaliplatin is well known to be devoid of haematological toxicity at or below recommended levels (85 mg/m^2 every 2 weeks or 130 mg/m^2 every 3 weeks) [10]. However, to date, there is no possibility to detect potential differences in the cellular response to DNA damage in normal tissues. We hypothesised that the general medical condition of the patient, and especially their nutritional status, could be a determinant of the cellular events occurring downstream from the DNA damage. We previously reported that the clinical PS was a critical parameter to define the recommended doses of the combination of oxaliplatin with CPT-11 [13]. Here, we also found a clear difference in treatment tolerability between patients with a clinical PS of 2 versus those with a PS of 0–1. However, using PS, the number of prior chemotherapy regimens and creatinine clearance was still not able to discriminate enough in order to detect all of the patients who were susceptible to experiencing severe haematological toxicity. We therefore used a malnutrition index to detect patients with an increased risk of toxicity. Patients with a high-risk profile could experience life-threatening toxicity at first cycle, even when treated at the lowest dose level (one septic shock). It is noteworthy that the first cycle was the most toxic and the following cycles at the same dose level were much better tolerated, as we previously described following topotecan treatment in Ref. [35]. This subset of patients is not routinely suitable for this combination therapy and, more generally, for receiving chemotherapy. This 'nutritional status-based' selection of patients allowed a 2-fold increase in the topotecan dose with a resultant acceptable toxicity. However, our biological criteria evaluating nutritional and inflammatory status needs further prospective evaluation and a multivariate analysis for full validation prior to be proposed for routine use.

In conclusion, we observed with the topotecan–oxaliplatin combination similar pharmacodynamic interactions to those previously reported with cisplatin. However, it appears 1 mg/m^2/day of topotecan can be recommended using the optimal administration sequence defined in preclinical studies, and with almost full doses of the platinum derivative. For this purpose, we restricted the dose escalation to patients with no evidence of renal dysfunction, no evidence of malnutrition and those who were not heavily pretreated. The antitumour activity elicited in the ovarian cancer patients, and the ancillary signs of antitumour activity in SCLC and hepatocellular carcinoma hint at its potential for clinical usefulness. In particular, heavily pretreated advanced ovarian cancer patients appeared to benefit from this combination treatment which should be further evaluated in a phase II study as second-line treatment in such ovarian cancer patients.

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