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ORIGINAL ARTICLE

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Weekly administration of topotecan and paclitaxel in pretreated advanced cancer patients: a phase I/II study

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Abstract *Purpose*: This study was a phase I/II, cohort, dose-escalation trial of topotecan and paclitaxel. Its aim was to determine the dose-limiting toxicity (DLT) of the combination and to define the maximum tolerated dose (MTD), as a recommended dose for phase II, as well as to get preliminary data on the efficacy (activity) of the drug in pretreated patients with ovarian cancer, small-cell lung cancer (SCLC) and non-small-cell lung cancer (NSCLC). *Methods*: Included in the study were 52 pretreated patients, 19 with ovarian cancer, 20 with SCLC and 13 with NSCLC. The doses of topotecan were escalated from 1.25 to 2 mg/m^2 and of paclitaxel from 60 to 80 mg/m^2. A minimum of four patients were included at each of the six levels of dose escalation. *Results*: We found that DLT due to grade 3 and 4 myelotoxicity was at levels 5 and 6 at doses of 1.75 and 80 mg/m^2 (level 5) and 2 and 80 mg/m^2 (level 6) for topotecan and paclitaxel, respectively. The MTD and recommended accepted doses are 1.75 mg/m^2 for topotecan and 70 mg/m^2 for paclitaxel. Of the 52 patients, 17 (33%) showed a response: 1 complete response (1.92%) and 16 partial responses (30.77%). *Conclusions*: Topotecan combined with paclitaxel administered once weekly for three consecutive weeks repeated for every 28 days resulted in well-tolerated toxicity at doses of 1.75 and 70 mg/m^2, respectively, and a response rate of 33% in pretreated cancer patients.

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Introduction

Several types of solid tumors have no established second-line treatment, no alternative chemotherapy and even no active treatment. Although for non-small-cell lung cancer (NSCLC), small-cell lung cancer (SCLC) and ovarian cancer, there are second-line treatments, the survival, particularly for the first two tumors, is poor [2, 12, 15, 16]. New active drugs should be further exploited and combined with other established active agents. Topotecan, a camptothecin inhibitor of topoisomerase I, is one of the promising new cytotoxic drugs which is still infrequently used in a combined chemotherapy. Preclinical data have indicated high antitumor activity in a broad range of tumors [9, 19, 20]. Five-day treatment repeated for every 3 weeks has been established in clinical trials, and the recommended dose after phase I clinical studies is 1.5 mg/m^2 daily [25]. The main adverse reaction is myelotoxicity and, in particular, grade 3 and 4 neutropenia which reached 75% of the courses in a phase II study [2] and 79% in another [6].

The first clinical trials using topotecan have shown its antitumor activity and have suggested that it is an important new cytotoxic agent for further clinical trials [22]. Dose-limiting toxicity (DLT) due to neutropenia suggested to investigators that a modification in topotecan administration was necessary. A 3-day or 4-day schedule every 3 weeks has been attempted as well as once a week [4, 8, 26], and these studies have shown that these schedules resulted in reduced myelotoxicity. Still, the optimum dose of topotecan given once weekly and particularly when combined with other cytotoxic drugs, has not yet been defined. The dosage of once-weekly topotecan administration combined with another weekly administered cytotoxic agent such as paclitaxel, was the basis for the present study. Paclitaxel is

frequently used once every 3 weeks in combination with other agents and has often been used effectively once weekly [13, 21, 27].

Topotecan has been used in a 5-day infusional mode at a dose of 1.5 mg/m^2 per day, repeated for every 3–4 weeks. Paclitaxel has been administered when combined with other agents at a dose of 175 mg/m^2 once every 3 weeks. However, there various dosages of paclitaxel have been used ranging from 135 to 250 mg/m^2 [1, 7, 23]. Paclitaxel has also been used once weekly at doses ranging from 50 to 110 mg/m^2 or higher, but when combined with other agents the suggested safe weekly dose varies from 50 to 100 mg/m^2 [3]. There are preclinical data showing that topotecan is efficacious [5]. In contrast to paclitaxel, topotecan has only infrequently been used once weekly [26] and there is no established dose for this mode of administration.

The primary objectives of the present trial were to (a) modify the administration of topotecan from 5 days every 3–4 weeks to once per week, (b) to define the DLT of topotecan as related to myelotoxicity, and (c) to determine its optimum dose when combined with paclitaxel. The secondary objective was to have a preliminary indication of the efficacy of the combination in pretreated cancers.

Patients and methods

Study design

The study was a phase I/II, cohort, dose-escalation trial of topotecan and paclitaxel. Its aims were to determine the DLT of the combination and to define the maximum tolerated dose (MTD) as a recommended dose for phase II, and to get preliminary data on the efficacy (activity) of the drug in pretreated patients with ovarian cancer, SCLC and NSCLC.

Both agents are considered to be myelotoxic and they have an established mode of administration. Our purpose here was to combine topotecan with paclitaxel, both given once weekly for three consecutive weeks repeated every 28 days, i.e., on days 1, 8 and 15. This study was designed as an uncontrolled prospective non-randomized multicenter dose-escalation study. The chemotherapy combination was defined as a 28-day cycle. The dose of topotecan started at 1.25 mg/m^2 and reached 2 mg/m^2 and the paclitaxel dose started at 60 mg/m^2 and reached 80 mg/m^2. The duration of the paclitaxel infusion was 60–90 min. Patients pretreated with paclitaxel had a treatment interval of 3–12 months (median 6 months).

Dose escalation

The plan was to test a minimum of four patients at each dose level. Dose escalation was implemented if no patient experienced DLT. If one patient experienced DLT, two more patients were accrued at that dose level. The dose increases were 0.25 and 10 mg/m^2 of topotecan and paclitaxel, respectively. When three out of four patients experienced DLT, then the MTD (i.e., one level below DLT) had been reached and three additional patients were treated at the previous dose level. All toxicities at each level were graded according to World Health Organization (WHO) criteria and also DLTs were defined on the basis of common toxicity criteria: any grade 4 hematologic toxicity, any grade 3 or 4 nonhematologic toxicity (except for nausea, vomiting and alopecia) lasting more than 3 days. The duration of hematologic toxicity was not defined, since on day 6, patients with grade 4 neutropenia were put on granulocyte colony-stimulating factor (G-CSF) for 3–5 days and treatment was postponed for 1 week. Table 1 shows the dose escalation of topotecan and paclitaxel.

Pretreatment and follow-up assessments

Eligibility. All patients were required to meet the following criteria: confirmed histologic or cytologic diagnosis of cancer, at least one bidimensionally measurable or evaluable disease, WHO performance status 0–2, a life expectancy greater than 3 months, previous treatment by standard or first-line chemotherapy, and at the time of entry to have been refractory to any prior cytotoxic treatment. Patients were eligible if they had had two or three previous courses, provided they had been off treatment for at least 3 weeks.

Assessment. Eligible patients were required to have adequate hematologic, renal and hepatic functions as defined by WBC count 3.5×10^9/l, absolute neutrophil count 1.5×10^9/l, platelet count 100×10^9/l, hemoglobin level 9 g/dl, total bilirubin level 1.5 mg/dl, ALT and AST twice the upper normal limit in the absence of liver metastases or five times the upper normal limit in case of documented liver metastasis and creatinine level 1.5 mg/dl. Informed consent was required and obtained from all patients according to local regulatory requirements. Medical history, physical examination, assessment of vital signs, electrocardiogram, chest, and

Table 1 Topotecan and paclitaxel dose escalation

Dose level	Number of patients	Topotecan dose (mg/m^2 per week)	Paclitaxel dose (mg/m^2 per wk)
I	4	1.25	60
II	4	1.50	60
III	4	1.50	70
IV	4	1.75	70
V	6	1.75	80
VI	6	2.00	80
VII	24	1.75	70
Total	52		

abdominal computed tomography (or ultrasound) were performed before treatment. During treatment (1 day before each course) blood count, blood urea and sugar, serum creatinine and uric acid tests, and ECG were done. CT scan assessments were done after three cycles (each cycle was 3 weeks, one dose per week) or earlier on disease progression.

Treatment. Topotecan (Hycamptin; Glaxo SmithKline, Brentford, UK) was supplied in vials of 4 mg lyophilized formulation and was reconstituted with 2 ml sterile water, then diluted with 5% dextrose solution and administered as a 30-min intravenous infusion. Paclitaxel (Bristol-Myers Squibb, New York, N.Y.) was infused after topotecan and after premedication with dexamethasone and both H1 and H2 receptor antagonists to prevent hypersensitivity reactions. Both treatments were given on day 1 on an outpatient basis.

Analytical method. The analysis was carried out according to a previously described HPLC method [3] with some modification. Separations were obtained using a Hewlett-Packard 1100 system with a Krosnasil-C_{18} 5 μm 4.6×150 mm column (Analysentechnik, Mainz, Germany). A 100 μl sample was injected manually onto a 10 μl loop. Analytes were isocratically eluted with a methanol/aqueous solution(41:73, v/v) mobile phase containing 75 m*M* potassium dihydrogen phosphate and 0.2% triethylamine. The aqueous mobile phase was adjusted to pH 6.5 potassium hydroxide and filtered with a 0.2 μm PALL membrane (Port Washington, N.Y.). The flow rate was 1 ml/mm during analysis. A key stone Column Hot pocket (Croco-Cil) was used to maintain the column temperature at 50°C.

Results

Patients. The patient characteristics are shown in Table 2. Entered in to the trial were 52 patients (median age 63 years, range 39–80 years; female 22, male 30), and all were evaluable for toxicity. Of these 52 patients, 19 had stage III ovarian cancer, 13 had NSCLC and 20 had SCLC, all stage IV except for one stage IIIB. All patients had undergone previous treatment and some of the patients had been heavily pretreated. The time from the end of the previous chemotherapy ranged from 3 weeks to 6 months. Of the patients with lung cancer, 16 had had radiation at the primary site or at skeletal metastases 6 months to 2 years earlier.

Treatment began in September 2002 and ended in August 2003. At the end of the study 28/52 patients (53.85%) were still alive. Median follow-up was 7 months (range 2–13+ months).

At the end of the phase I part of the study, and having established the recommended (optimum) doses (1.75 and 70 mg/m^2 of topotecan and paclitaxel, respectively), we enrolled 24 more patients and continued treatment in order to evaluate efficacy. All patients were included in the response evaluation. The total number of patients who took the recommended dose or higher was 40.

Table 2 Patient characteristics

Number of patients (*n*, %)	52	100
Gender (*n*, %)		
Male	30	57.69
Female	22	42.31
Age (years)		
Median	63	
Range	39–80	
Stage (*n*, %)		
III	20	38.46
IV	32	61.54
Histology, primary site (*n*, %)		
Small-cell lung cancer	20	38.46
Ovarian cancer	19	36.54
Non-small-cell lung cancer	13	25.00
WHO performance status (*n*, %)		
0	1	1.92
1	27	51.92
2	24	46.15
Prior chemotherapy (*n*, %)	52	100
Cisplatin compound-related	52	100
Paclitaxel-related[a]	27	51.92
Radiation	16	30.77

[a]3–12 months (median 6 months) paclitaxel-free interval

Dose intensity. The patients received 100 courses (300 weekly infusions) and the median number of courses was two (six weekly infusions). Of the 52 patients, 25 completed three courses. There was no dose reduction and the weekly dose for both drugs was as planned after having established the optimum dose; the patients received 99.5% of the planned dose intensity (range 93–100%) of each drug.

Toxicity. Hematologic toxicities based on WHO grades 1–4 per dose level is shown in Table 3 and in Table 4 nonhematologic adverse reactions are indicated. In four out of the six patients who presented with grade 3 and 4 neutropenia, treatment was postponed by 1 week, G-CSF was administered for 3–5 days and dose reduction to the previous level was applied for treatment continuation. Some of the nonhematologic adverse reactions, such as neurotoxicity and alopecia had already existed due to previous cytotoxic agent therapy. Fatigue was observed in nearly half of the patients, but only to a minor degree (grade 1). In general, treatment was well accepted, when also taking into account the fact that all patients had been pretreated and some of them not long before (ten patients had had previous chemotherapy 21–60 days before).

Response to treatment. Response and toxicity were assessed using standard WHO criteria (complete response

Table 3 Hematologic toxicities by dose level

Level	Topotecan (mg/m^2)	Paclitaxel (mg/m^2)	Patients with toxicity	Maximum toxicity grade	Toxicity type
1	1.25	60	0/4	–	–
2	1.50	60	0/4	–	–
3	1.50	70	0/4	–	–
4	1.75	70	2/4	2	Neutropenia
5	1.75	80	4/6	3/4	Neutropenia
6	2.00	80	4/6	3/4	Neutropenia
7	1.75	70	24	1–3	Leukopenia, anemia, thrombocytopenia

Table 4 Nonhematologic toxicity. The data presented are number (%) of patients

	Grade 1	Grade 2	Grade 3	Grade 4
Nausea	13 (25.0)	–	–	–
Vomiting	6 (11.54)	–	–	–
Alopecia	30 (57.69)	13 (25.0)	–	–
Fatigue	25 (48.08)	–	–	–
Diarrhea	–	1 (1.92)	–	–
Cardiotoxicity	–	–	–	–
Neurotoxicity	28 (53.85)	18 (34.62)	–	–
Nephrotoxicity	–	–	–	–

defined as complete disappearance of any sign of demonstrable disease; partial response (PR) defined as 50% reduction in measurable disease; stable disease defined as $<50\%$ decrease or $<25\%$ increase in measurable disease). The determination of measurable response on computed tomography was performed by two independent radiologists and two experienced oncologists.

One complete response (1.92%) was seen in a patient with stage III ovarian cancer. For this patient, this was second-line chemotherapy 9 months after the first treatment which was a combination of carboplatin and paclitaxel. PR was achieved in 16 patients (30.77%). The total response rate including the one complete response was 33%. Analytically, the responses per cancer type were: ovarian 1/19 (5.26%) complete response and 8/19 (42.11%) PRs, SCLC 6/20 (30%) PR, and NSCLC 1/13 (7.69%) PR. Of the 52 patients. 20 (38.46%) had stable disease for a median duration of 4 months. Disease progression was seen in 15 patients (28.35%) (Table 5). At the end of the study, 28 patients (53.85%) were still alive. Median survival was 6 months (range 2–13+ months) and median time to tumor progression was 3 months (range 2–8 months).

Discussion

The present trial was an attempt to establish to a modified mode of administration of the topoisomerase I inhibitor, topotecan. This agent has been tested in a number of prior trials and has shown adequate efficacy particularly in ovarian cancer and in SCLC. Still, topotecan remains a second-line chemotherapy agent either as monotherapy or in combination. Toxicity and especially myelotoxicity is an inhibiting factor. Given daily for 5 days, neutropenia has been reported in three out of four patients [6, 25]. Other cytotoxic drugs such as cisplatin, dacarbazine, bleomycin and even anthracyclines have been administered on consecutive days ranging from 3 to 5 days, but the final established mode of treatment has remained at 1 day. Considering the response in the present study, 1-day topotecan treatment in combination with paclitaxel did not deprive either agent of its efficacy but it did reduce the adverse reactions, particularly myelotoxicity.

Only a few attempts to change the mode of administration of topotecan have been made. Nevertheless, a schedule has not yet been defined, particularly when topotecan is combined with other cytotoxic drugs. Combination treatment of topotecan 2.25 mg/m^2 with cisplatin 40 mg/m^2 and paclitaxel 85 mg/m^2 all given weekly for 12 weeks was attempted in 37 patients with extensive SCLC. The response rate was high (81%) and toxicity was acceptable with only G-CSF support; one patient presented with neutropenia, and sepsis and anemia were also common [24]. Similar results with respect to toxicity have been reported by the same investigators using the same combination regimen, but without showing a high percentage of grade 4 neutropenia in patients with SCLC and ovarian cancer. The patients in the first study and some in the second had undergone no prior treatment and G-CSF was routinely administered [14]. However, the dose density of

Table 5 Response rate and survival. The data presented are number (%) of patients (*CR* complete response, *PR* partial response, *SD* stable disease, *PD* progressive disease)

	CR	PR	SD	PD
All patients ($n=52$)	1 (1.92)	16 (30.77)	20 (38.46)	15 (28.85)
SCLC ($n=20$)	–	6 (30.0)	–	–
Ovarian cancer ($n=19$)	1 (5.26)	8 (42.11)	–	–
NSCLC ($n=13$)	–	1 (7.69)	–	–

2.5 mg/m^2 of topotecan was only 71%. Also, the dose density of the dosages 1.50, 1.75, 2 and 2.25 mg/m^2 (the last of these was mostly used) was also low, ranging from 79% to 86% [14].

Weekly topotecan dosage also varies between other studies. The MTD of weekly topotecan combined with paclitaxel 100 mg/m^2 has been reported to be 4 mg/m^2 [18]. In this latter study, 35 patients with pretreated ovarian cancer were investigated and topotecan was given as a single agent. The authors reported that doses of topotecan lower than 4 mg/m^2 were of acceptable myelotoxicity and G-CSF was not often used. These researchers also suggested that the toxicity of weekly topotecan at 4 mg/m^2 was significantly higher than the MTD of 5-day topotecan at 1.5 mg/m^2. This high dose (4 mg/m^2) has not been used in other similar studies. A combination of cisplatin 20 mg/m^2, gemcitabine 1000 mg/m^2 and escalating doses of topotecan administered weekly (days 1, 8, 15, every 28 days) as first-line chemotherapy in patients with NSCLC, led to the conclusion that the recommended dose of topotecan is 1.75 mg/m^2 with this combination [18]. There has also been a preliminary report of weekly bolus intravenous topotecan as a single agent: the dosage reached to 2.25 mg/m^2 without major toxicity [17]. The topotecan dose of 2.5 mg/m^2 has been identified as the MTD in a study combining topotecan with gemcitabine 1000 mg/m^2 both given weekly for a variety of advanced refractory solid tumors in 38 patients. The authors indicated that granulocytopenia and thrombocytopenia were the major DLTs [10]. Gemcitabine 1250 mg/m^2 combined with topotecan in escalated doses has been administered weekly to patients with NSCLC, with topotecan doses varying from 1.00 to 2.00 mg/m^2. Severe neutropenia was seen in a minority of the patients whereas acceptable thrombocytopenia and anemia were observed in a majority [28]. Similar findings in another study have been reported [11]. Based on the above studies, the results concerning dose-related toxicity are controversial.

Our study determined that paclitaxel 80 mg/m^2 with topotecan 1.75 or 2 mg/m^2 administered weekly in combination produces a high percentage of myelotoxicity, particularly neutropenia. At level 5 (1.75 mg/m^2 topotecan and 80 mg/m^2 paclitaxel) grade 3 and 4 neutropenia was observed in four out of six patients; only one patient presented with febrile neutropenia. For this reason we tested the level 6 dosage (topotecan 2 mg/m^2 and paclitaxel 80 mg/m^2) and neutropenia was similar to that at level 5 (four out of six patients). We suggest that the recommended MTD should be 1.75 mg/m^2 topotecan and 70 mg/m^2 paclitaxel (level 4). In view of the rare need for G-CSF, coupled with the efficacy that these dosages in pretreated patients, we believe that our recommended doses could be close to the optimum schedule for future treatments. Efficacy was high at 33% and median survival was 6 months (range 2–13+ months).

The combination of topotecan with paclitaxel on a weekly schedule could be suggested as a second-line treatment in ovarian and SCLC. Whether this combination shows more efficacy and results in less toxicity than single-agent treatment is debatable. Comparison in randomized trials might be needed. But, if one looks at the toxicity of the 5-day schedule of topotecan where myelotoxicity is more or less intolerable, our reported combination may be preferable to the topotecan single treatment 5-day schedule. The neurotoxicity of paclitaxel is reduced by weekly administration so that patients pretreated with this agent may tolerate it.

In conclusion, modified once-weekly topotecan administration combined with paclitaxel also once weekly at doses of 175 and 70 mg/m^2, respectively, results in acceptable toxicity as well as a reasonably high response rate in pretreated SCLC and ovarian cancer.

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