Myelotoxicity of oral topotecan in relation to treatment duration and dosage: a phase I study

George P. Stathopoulos[a], Alexandros Ardavanis[b], Pavlos Papakotoulas[g], Dimitrios Pectasides[c], George Papadopoulos[a], Dimosthenis Antoniou[d], Athanasios Athanasiadis[f], Dimitrios Trafalis[a], Athanasios Anagnostopoulos[a], John Koutantos[a] and Michael Vaslamatzis[e]

Oral topotecan has been recently brought into clinical practice at a dose of 2.3 mg/m^2 for 5 days, every 3 weeks. Published data show quite high myelotoxicity. The aim of this trial was to define the daily dose and treatment duration, which permits safe toxicity. The study was designed to begin at a low daily dosage of 1.5 mg/m^2 and was escalated by increasing the topotecan dose and the day-treatment duration. The plan was to end up with 2.3 mg/m^2 daily for 5 days. In cases of tolerability with the last dosage given, we would then continue testing a higher daily dosage. Treatment repetition was planned to be every 21 days. Dosage levels were 1.5, 2.0 and 2.3 mg/m^2 for 3 days, 2.0 and 2.3 mg/m^2 for 4 days, and 2.3 mg/m^2 for 5 days. Toxicity was scored according to the Common Toxicity Criteria. Thirty-two patients (27 male, five female, median age 60 years, range 46–77 years) with small-cell lung cancer were included. The patients on 1.5 and 2 mg/m^2 for 3 days showed no myelotoxicity. Four (25%) patients on 2.3 mg/m^2 3-day treatment developed grade 3–4 neutropenia. Three of five patients (60%) treated for 4 days at a dose of 2.3 mg/m^2 developed grade 3–4 neutropenia and less than half (two of five, 40%) of these patients had thrombocytopenia. Eight patients (66.7%) on the 5-day treatment presented with serious grade 3–4 myelotoxicity. Two treatment-related deaths were observed in the 5-day group and one in the 4-day group. Granulocyte growth factor was applied in over 60% of the patients. In conclusion, a dose of 2.3 mg/m^2 for 5 days was intolerable. Dose-limiting toxicity was 2.3 mg/m^2 for 4 days without prophylactic granulocyte colony-stimulating factor administration. The safe duration of oral topotecan treatment and the maximum tolerated dose seem to be not longer than 3 days at a dose of 2.3 mg/m^2. *Anti-Cancer Drugs* 21:202–205 © 2010 Wolters Kluwer Health | Lippincott Williams & Wilkins.

Anti-Cancer Drugs 2010, **21:**202–205

Keywords: myelotoxicity, oral, topotecan

[a]Department of First Oncology, Errikos Dunant Hospital, [b]Department of Oncology, Saint Savas Hospital, [c]Department of Oncology, Attikon Hospital, [d]Department of Oncology, First Clinic, Hospital of Thoracic Diseases, [e]Department of Oncology, Evangelismos Hospital, Athens, [f]Oncology Clinic, General Hospital, Larissa and [g]Theagenion Hospital, Thessaloniki, Greece

Correspondence to Dr George P. Stathopoulos, MD, Department of First Oncology, Errikos Dunant Hospital, Semitelou 2A, Athens 115 28, Greece
Tel: +30 210 7752600; fax: +30 210 7251736;
e-mail: dr-gps@ath.forthnet.gr

Received 29 September 2009 **Revised form accepted** 5 November 2009

Introduction

Topotecan is one of the two camptothecin agents that have been used in clinical practice for a limited number of malignancies. It is a topoisomerase I inhibitor and one of the promising new cytotoxic agents. Preclinical data have indicated high antitumor activity in a broad range of malignant tumors [1–3]. The main use of topotecan in clinical practice is as second-line chemotherapy in small-cell lung cancer (SCLC) [4] and in ovarian cancer [5]. When given intravenously, topotecan is commonly administered for 5 consecutive days on a 3-week schedule. However, this schedule leads to a high incidence of grade 3 and 4 neutropenia with a reported incidence of 75 [4] and 79% [6] across different studies. This unacceptable toxicity led to trials administering topotecan on a 3-day schedule [7–8]. Alternatively, topotecan has been tested once in a weekly administration for 3 consecutive weeks, resulting in a reduction of myelotoxicity, without a decrease in effectiveness [9–11].

During the last few years, oral topotecan for clinical use has been tested for toxicity and effectiveness. It was reported that oral topotecan has similar efficacy to the intravenous formulation in patients with relapsed SCLC [12,13]. Some years ago, a phase I study was conducted to test the dose-limiting toxicity (DLT) and the maximum tolerated dosage (MTD) of topotecan. Twenty-nine patients, 22 of whom were evaluable, were included. The patients, seven of whom had not been pretreated had various malignancies [14]. The DLT was determined to be 2.7 mg/m^2 on 5-day treatment. The 2.3 mg/m^2 5-day treatment has been found to be feasible with uncomplicated common toxicity (grade 2–3 neutropenia) [15]. On the basis of a pharmacokinetic study no schedule preference could be expressed, but based on patient convenience, administration once daily for 5 days could be favored [16]. At that time, 10 years ago, questions concerning the optimal topotecan dose were raised, following its approval for clinical use. In clinical practice

0959-4973 © 2010 Wolters Kluwer Health | Lippincott Williams & Wilkins DOI: 10.1097/CAD.0b013e3283350092

the hematological toxicity associated with the recommended phase II dose has been an area of concern, particularly in patients with renal impairment or those who have received extensive earlier alkylating therapy [17]. In one study, in patients with relapsed SCLC, the response rate was 18.3% for oral administration and 21.9% for intravenous administration [18]. Another phase III study comparing oral topotecan with best supportive care versus supportive care alone, showed that the addition of topotecan to best supportive care prolonged survival and the difference was statistically significant [19]. A problem was raised by the results of this latter study: the investigators used the same mode of treatment as with intravenous, administering oral topotecan for 5 consecutive days. Toxicity was 61% neutropenia, 38% thrombocytopenia, and 25% anemia. This toxicity may be considered unacceptable as the median treatment-free interval was 84 days.

We conducted a trial in patients with SCLC, administering oral topotecan as second-line or third-line chemotherapy. The aim of the study was to define the MTD and DLT.

Patients and methods

Study design

The study was a phase I cohort, dose and day escalation trial of topotecan, designed as a prospective nonrandomized multicenter trial. Drug administration was defined to start at a low dose for 3-day treatment, repeated every 3 weeks, then escalation was implemented according to the toxicity results (mainly myelotoxicity) to define the dose and the day duration of each course of treatment.

This study was conducted with the approval of the appropriate ethics committees of the participating hospitals and all patients gave informed written consent.

Dose escalation

Before planning the escalation, eight patients were initially treated simultaneously at six different clinics. The myelotoxicity that was detected led us to start the escalation of the drug dosage and the duration, so as to define the DLT and MTD as follows: at the beginning the defined dosage was 1.5 mg/m^2 for a duration of 3 days; three patients were included. If there was no myelotoxicity, treatment repetition was done 3 weeks later, from the first day of the earlier treatment. Dosage escalation is shown in Table 1. To arrive at the dosage according to treatment guidelines, four patients were tested without receiving prophylactic granulocyte colony-stimulating growth factor; the daily dosage was 2.3 mg/m^2 for 5 consecutive days. For toxicity evaluation we included the eight patients who had been treated before the dose escalation was implemented.

Table 1 **Topotecan dose escalation**

No. of patients	Topotecan dose (mg/m^2 per day)	Duration of treatment (days)
3	1.5	3
4	2.0	3
4	2.3	3
4	2	4
5	2.3	4
4 + 8	2.3	5
Total 32		

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 bi-dimensionally measurable or evaluable disease, WHO performance status 0–2, a life expectancy of greater than 3 months, earlier treatment by standard or first-line or second-line chemotherapy, and at the time of entry, to have been refractory to any earlier cytotoxic treatment. Patients were eligible if they had had two or three earlier courses, provided they had been off treatment for at least 3 weeks. 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/l, total bilirubin level 1.5 mg/dl, alanine transferase, and aspartic transferase twice the upper normal limit in the absence of liver metastases or five times the upper normal limit in case of documented liver metastases and creatinine level 1.5 mg/dl.

Assessment

Medical history, physical examination, assessment of vital signs, electrocardiogram, chest, and abdominal computed tomography (or ultrasound) were performed before treatment. During treatment (1 day before each course) blood count, blood urea and glucose, serum creatinine and uric acid tests, and ECG were done. CT scan assessments were done after three cycles (3-day treatment) or earlier on disease progression.

Treatment

Topotecan hydrochloride (Hycamptin; Glaxo Smith Kline, Middlesex, UK) was supplied in capsules of 1 mg or 0.25 mg for oral use on an empty stomach [20] for 5 consecutive days, repeated every 21 days, bone marrow recovery permitting. Topotecan was administered for 3, 4, or 5 days in 21-day treatment cycles. If the toxicity was unacceptable the patient continued on a lower dose or shorter treatment duration. No prophylactic growth factor was administered.

Results

The patients' characteristics are shown in Table 2. Thirty-two patients entered the trial (median age 60 years, range 46–77 years; 27 males and five females). In all patients the diagnosis was SCLC treated before by one

Table 2 Patients' characteristics at baseline

	n (%)
No. of patients	32 (100)
Sex (*n* %)	
Male	27 (84.4)
Female	5 (15.6)
Age (years)	
Median	60
Range	46–77
Stage	
Limited	12 (37.5)
Advanced	20 (62.5)
Histology	
Small-cell lung cancer	32 (100)
WHO performance status	
0	2 (6.3)
1	18 (56.3)
2	12 (37.5)
Prior chemotherapy	
First-line	
Cisplatin–etoposide	22 (68.8)
Carboplatin–etoposide	8 (25.0)
Paclitaxel–cisplatin	4 (12.5)
Radiation	12 (37.5)
Second-line	
Carboplatin	5 (15.6)
Paclitaxel	4 (12.5)

Table 3 Myelotoxicity of topotecan

			Grade		
			3–4	2–4	2–3
No. of patients	Duration[a] of treatment (days)	Dosage (mg/m^2, daily)	Neutropenia (%)	Thrombo-cytopenia (%)	Anemia (%)
3	3	1.5	–	–	–
4	3	2	–	–	–
4	3	2.3	25.0	25.0	20.0
4	4	2	57.1	25.0	25.0
5	4	2.3	60.0	40.0	20.0
4 + 8	5	2.3	66.7	58.3	50.0

[a]5-day duration: two events due to febrile leukopenia; 4-day duration: one event due to febrile leukopenia.

Table 4 Nonhematologic toxicity

	Grade 1–3, *n* (%)
Nausea/vomiting	7 (21.9)
Diarrhea	4 (12.5)
Asthenia	5 (15.6)

or two lines of chemotherapy (plus or minus radiation therapy). The time from the end of the earlier treatment ranged from 3 weeks to 4 months. Treatment began (patient recruitment) in June 2008 and ended in March 2009. At the end of the study 12 of 32 patients were still alive. The total number of cycles was 53 (median 2, range 1–3).

Toxicity

Serious hematologic toxicity based on Common Toxicity Criteria [15], is shown in Table 3. Non-hematologic toxicities such as nausea, vomiting, and diarrhea were observed in a small number of patients (Table 4), but were not serious and did not lead to stopping of treatment. Asthenia was detected but not to a serious degree, in a few patients. Patients with serious toxicity either refrained from treatment or were placed at a lower scale of treatment duration, that is, from 5 days to 4 days of treatment, or from 4 days to 3 days and the dosage was also reduced from 2.3 to 2.00 mg/m^2. Treatment was postponed by 1 or 2 weeks in all patients who had the 5-day treatment and in 4 days for those who had 4-day treatment. The most serious observed toxicities involved a high percentage (66.7%) of grade 3–4 hematologic toxicity in patients on the 5-day treatment and in two patients, treatment-related events occurred. A lower percentage (60%) of hematologic toxicity was seen on the 4-day treatment and in one patient, a treatment-related event occurred. On 3-day treatment the toxicity was well tolerated. DLT was considered to be the 4-day treatment at a dose of 2.3 mg/m^2 and the MTD was 2.3 mg/m^2 for 3 days without granulocyte colony-stimulating factor being applied prophylactically.

Response

Partial responses were not observed but nearly half of the patients had disease control (15 patients, 46.9%) for 2–4 months (stable disease). The median survival was 7 months (range 2 weeks to 10 + months).

Discussion

Some years ago, questions regarding the optimal dose of intravenous or oral topotecan administration were raised following its approval for clinical use [21]. It has been noted that hematologic toxicity associated with the recommended dose has been an area of concern, particularly in patients with renal impairment or those having undergone extensive pretreatment [22,23]. Hematologic toxicity has also been an issue with the development of the combination regimen, incorporating topotecan with alkylating agents or taxanes, and fatal sepsis has been reported [22,23]. Oral topotecan has been shown to be of similar effectiveness as the intravenous formulation [12,13]. In the past, four schedules were evaluated: topotecan administered once daily for 5 days, for 10 days every 21 days, twice daily for 10 days and, BID for 21 days [14]. DLT was defined on the basis of myelosuppression and diarrhea. The evaluation of the efficacy and safety of topotecan in combination with other agents such as cisplatin or paclitaxel as first-line treatment were found to be similar [22,23].

This trial has attempted to define a dosage of oral topotecan administration that is not intolerably toxic. It has been shown that this agent produces hematologic toxicity both when administered intravenously and orally. When insisting on giving topotecan in either mode for

5 consecutive days, the hematologic adverse reactions dominate and the efficacy of this agent cannot be determined. Traditionally, it is known that a 2-cytotoxic or 3-cytotoxic agent combination is more active chemotherapy versus single agent treatment. No patient would tolerate a combination of topotecan with a second cytotoxic drug when toxicity is the main inhibiting factor. This trial has come to the conclusion that 3-day administration of 2.3 mg/m^2 topotecan is the MTD without providing a granulocyte colony-stimulating growth factor. If there is a need to combine topotecan with another oral agent, such as etoposide, further phase I studies should be conducted.

The 5-day treatment at 2.3 mg/m^2 daily may be tolerated by some patients but they are in the minority. Of course, second-line treatment has the disadvantage that patients may have an exhausted bone marrow resulting from heavy first-line treatment. SCLC often recurs soon, that is, a few months after the end of first-line chemotherapy plus radiotherapy, in patients with limited disease.

We believe that this trial has determined that in the oral administration of topotecan, the MTD is 2.3 mg/m^2 administered for 3 consecutive days and that more than a 3-day administration renders the treatment seriously toxic.

References

1 Burris HA III, Hanauske AR, Johnson RK, Marschal MH, Kuhn JG, Hilsenbeck SC, *et al*. Activity of topotecan, a new topoisomerase I inhibitor, against human tumor colony-forming units in vitro. *J Natl Cancer Inst* 1992; **84**:1816–1820.

2 Houghton PJ, Cheshire PJ, Myers L, Stewart CF, Synold TW, Houghton JA. Evaluation of 9-dimethylaminomethyl-10 hydroxycamptothecin against xenografts derived from adult and childhood solid tumors. *Cancer Chemother Pharmacol* 1992; **31**:229–233.

3 Kingsbury WD, Boehm JC, Jakas DR, Halden KG, Hecht SM. Synthesis of water-soluble (aminoalkyl) camptothecin analogues: inhibition of topoisomerase I and antitumor activity. *J Med Chem* 1991; **34**:98–107.

4 Ardizzoni A, Hansen H, Dombernowsky P, Gamucci T, Kaplan S, Postmus P. Topotecan, a new active drug in the second-line treatment of small-cell lung cancer: a phase II study in patients with refractory and sensitive disease. *J Clin Oncol* 1997; **15**:2090–2096.

5 Markman M. Topotecan: an important new drug in the management of ovarian cancer. *Semin Oncol* 1997; **4** (**Suppl 5**):55–58.

6 Bokkel Huinick WT, Gore M, Carmichael J, Gorden A, Malfetano J, Hudson I, *et al*. Topotecan vs paclitaxel for the treatment of recurrent epithelial ovarian cancer. *J Clin Oncol* 1997; **15**:2183–2193.

7 Belinson J, Kennedy A, Webster K, Kulp B, Peterson G, Markman M. Preliminary results of a Cleveland Clinic Cancer Center Gynecologic Oncology Program phase 2 trial of topotecan administered on a 3-day schedule as salvage therapy of platinum and paclitaxel refractory ovarian cancer. [abstract] *Proc Am Soc Clin Oncol* 1999; **18**:369a.

8 Sun W, Stevenson JP, Gallagher M, Giantonio B, Algazy K, Haller D, *et al*. A phase I trial of topotecan and gemcitabine administered weekly for 3 consecutive weeks to patients with advanced tumors. *Cancer* 2001; **92**:414–419.

9 Rowinsky EK. Weekly topotecan: an alternative to topotecan's standard daily $\times$ 5 day schedule? *Oncologist* 2002; **7**:324–328.

10 Stathopoulos GP, Rigatos SK, Christodoulou Ch, Malamos NA, Deliyiannis F, Stathopoulos JG, *et al*. Weekly administration of topotecan and paclitaxel in pretreated advanced cancer patients: a phase I/II study. *Cancer Chemother Pharmacol* 2004; **54**:259–264.

11 Stathopoulos GP, Katis C, Tsavdaridis D, Dimitroulis J, Karaindros D, Stathopoulos J, *et al*. Front-line paclitaxel and topotecan chemotherapy in advanced or metastatic non-small-cell lung cancer: a phase II trial. *Cancer Chemother Pharmacol* 2006; **58**:555–560.

12 Von Pawel J, Gatzemeier U, Pujol JL, Moreau L, Bildat S, Ranson M, *et al*. A phase II comparator study of oral versus intravenous topotecan in patients with chemosensitive small cell lung cancer. *J Clin Oncol* 2001; **19**:1743–1749.

13 Eckardt JR, Von Pawel J, Hainsworth JD, Corso S, Rimaldi D, Preston A, *et al*. Single agent oral topotecan (PO) versus intravenous topotecan (IV) in patients (pts) with chemosensitive small cell lung cancer (SCLC): an international phase III study. [abstract 2488]. *Proc Am Soc Clin Oncol* 2003; **22**:619.

14 Gerrits CJH, Burris H, Schellens JMH, Eckardt JR, Planting AST, van der Berg MEL, *et al*. 5 days of once daily oral topotecan a phase I and pharmacologic study in adults. *Ann Oncol* 1996; **7** (**Suppl 5**):5970.

15 National Cancer Institute, Cancer therapy evaluation programs Common Toxicity Criteria Version 2.0, 1999.

16 Gerrits CJH, Schellens JHM, Burris H, Eckhardt JR, Planting AST, van der Berg MEL, *et al*. A comparison of clinical pharmacodynamics of different administration schedules of oral topotecan (Hycamptin). *Clin Cancer Res* 1999; **5**:69–75.

17 O'Reilly S. Topotecan: what dose, what schedule, what route? *Clin Cancer Res* 1999; **5**:3–5.

18 Gralla RJ, Eckardt J, Grotzinger KM. Quality of life with single agent oral topotecan vs intravenous topotecan in patients with chemosensitive small cell lung cancer [SCLC (**Suppl 2**; abstract P-578)]. *Lung Cancer* 2003; **41**:S237.

19 Nicum SJ, O'Brien MER. Topotecan for the treatment of small-cell lung cancer. *Expert Rev Anticancer Ther* 2007; **7**:795–801.

20 O'Reilly S, Armstrong DK, Grochow LB. Life threatening myelosuppression in patients with occult renal failure receiving topotecan. *Gynecol Oncol* 1997; **15**:329–330.

21 Armstrong DK, O'Reilly S. Clinical guidelines for managing topotecan related hematologic toxicity. *Oncologist* 1998; **3**:4–10.

22 Miller AA, Libenbaum RC, Lynch TJ, Rosner GL, Ratain MJ, Green MR, *et al*. Treatment related fatal sepsis from topotecan/cisplatin and topotecan/paclitaxel. *J Clin Oncol* 1996; **14**:1964–1965.

23 Libenbaum RC, Ratain MJ, Miller AA, Hargis JB, Hollis DR, Rosner GL, *et al*. Phase I study of paclitaxel and topotecan in patients with advanced tumors: a cancer and leukemia group B study. *J Clin Oncol* 1995; **13**:2230–2237.