Cancer Chemother Pharmacol (2007) 60:123–128
DOI 10.1007/s00280-006-0383-6

ORIGINAL ARTICLE

Weekly administration of topotecan–paclitaxel as second-line treatment in ovarian cancer

G. P. Stathopoulos · N. A. Malamos · G. Aravantinos · S. Rigatos · Ch. Christodoulou · J. Stathopoulos · D. Skarlos

Received: 12 June 2006 / Accepted: 31 October 2006 / Published online: 17 November 2006

Abstract
Purpose To investigate the weekly administration of topotecan combined with paclitaxel in pretreated advanced ovarian cancer patients; our objectives were to determine efficacy, toxicity and survival
Methods The chemotherapy agents, topotecan and paclitaxel were administered on a weekly basis for 3 consecutive weeks, every 28 days. The plan was to give three courses (each course included three once-weekly infusions). The dose of topotecan was 1.75 mg/m^2 and of paclitaxel 70 mg/m^2.
Results From January 2004 until January 2006, 45 patients were enrolled in this multicenter trial; 44 patients were evaluable for response and toxicity. The median age was 60 years old (range 39–82 years) and performance status was 0–2. Thirty-nine patients were in stage III and 5 in stage IV. All patients had been pretreated with carboplatin or cisplatin in combination with paclitaxel**.** Complete and partial responses were seen in 39% of the patients, stable disease in 43% and progressive disease in 18%; median survival time was 9 months, range 2–24+ months, (95% CI: 7.9–10.2). There was a notable absence of grade 3 toxicity except for neutropenia in 11% of the patients.
Conclusion The combination of topotecan and paclitaxel administered on a weekly basis is a well-tolerated chemotherapy schedule. The response rate of 39% is quite high for patients with pretreated ovarian cancer.

Keywords Topotecan · Paclitaxel · Weekly administration · Pretreated ovarian cancer

G. P. Stathopoulos (✉) · J. Stathopoulos
First Department of Oncology, Errikos Dunant Hospital, Semitelou 2A, 115 28 Athens, Greece
e-mail: dr-gps@ath.forthnet.gr

N. A. Malamos
Oncology Unit, Helena Hospital, Athens, Greece

G. Aravantinos · S. Rigatos
Ag. Anargyri Hospital, Athens, Greece

Ch. Christodoulou · D. Skarlos
Second Department of Oncology, Errikos Dunant Hospital, Athens, Greece

Introduction

Advanced ovarian cancer is treated with chemotherapy or chemotherapy in combination with surgery. Cytotoxic drugs have shown moderate to high effectiveness [1, 2]. A cure rate after chemotherapy and surgery may be achieved only in 20–25% of stage III patients. Seventy-five to eighty percent of patients who have residual disease or disease recurrence need further treatment with a second-line choice of cytotoxic agents. First-line treatment includes taxanes, with cisplatin or carboplatin [3]. These agents can be re-administered in cases of a late recurrence of the disease. Often, for second-line treatment, other agents are selected on the basis of their efficacy and toxicity profiles. One of the newer agents is topotecan, which has shown effectiveness as second-line chemotherapy [4–6]. The major problem with topotecan is the 5-day administration, which is followed by a high percentage of serious myelotoxicity (neutropenia) [4, 7, 8]. During recent years, in attempts by several investigators, topotecan has been used in combination with other agents as second-line treatment [9, 10]. Weekly administration has also been attempted. This once-weekly mode of

treatment in other tumors has shown much less myelotoxicity without a reduction in effectiveness [11–13].

In the present trial, we administered topotecan weekly in combination with paclitaxel. Paclitaxel has also been applied in a weekly mode of administration [14]. The maximum tolerated dose (MTD) of this combination was defined in a previous phase I/II study [15]. The primary endpoint of the present study was to determine the efficacy of the regimen and the secondary endpoints, tolerance and survival.

Patients and methods

Eligibility criteria

Patients >18 years old with a histologically or cytologically confirmed diagnosis of ovarian cancer and with bidimensionally measurable disease, pretreated by chemotherapy, were enrolled in this study. Other eligibility criteria included a World Health Organisation (WHO), performance status (PS) of 0–2, life expectancy of at least 3 months, adequate bone marrow reserves (granulocyte count ^{3} 1,500/dl, platelet count ^{3} 120,000/dl) normal renal (serum creatinine concentration < 1.2 mg/dl) and liver function tests (total serum bilirubin concentration < 3 mg/dl, provided that serum transaminases and serum proteins were normal), normal cardiac function with no history of clinically unstable angina pectoris or myocardial infarction, or congestive heart failure within the previous 6 months. Patients with active infection, malnutrition or a second primary tumor (except for a non-melanoma skin epithelioma or in situ cervix carcinoma) were excluded from the study. Up to two prior chemotherapy treatments were allowed. The study was approved by our institutional review boards and all patients gave their written informed consent to participate.

Treatment

All patients were treated on an outpatient basis. The chemotherapy agents used were topotecan and paclitaxel on a weekly basis for 3 consecutive weeks every 28 days. The plan was to give three courses (each course included three once-weekly infusions). The doses were based on the MTD defined by a previous phase I/II study [15]. Topotecan (Hycamptin; Glaxo Smith Kline, 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, NY, USA) was infused after topotecan and after premedication with dexamethasone 8 mg and both H_1 and H_2 receptor antagonists to prevent hypersensitivity reactions. Both treatments were given on day 1. The dose of topotecan was 1.75 mg/m^2 and of paclitaxel 70 mg/m^2. Dose adjustment criteria were based on hematological parameters.

Patient evaluation

Pretreatment evaluation included complete medical history and physical examination, full blood count including differential leukocyte and platelet counts, a standard biochemical profile (and creatinine clearance when necessary), electrocardiogram, chest X-rays, ultrasound of the upper abdomen and computed tomography (CT) scans of the chest, upper and lower abdomen. Additional imaging studies were performed upon clinical indication. Full blood counts with differential were performed weekly; in cases of grades 3 or 4 neutropenia or thrombocytopenia full blood counts were evaluated daily. A detailed medical and physical examination was completed before each course of treatment (three once-weekly infusions for three consecutive weeks), in order to document the symptoms of the disease and treatment toxicities. Biochemical tests, ECG and chest X-rays were performed every 3 weeks and CT scans at the end of the third cycle (nine infusions).

Definition of response

A complete response (CR) was considered to be the disappearance of all measurable disease confirmed at 4 weeks at the earliest; partial response (PR), a 30% decrease, also confirmed at 4 weeks at the earliest. In stable disease (SD), neither PR nor progressive disease (PD) criteria were met; PD, a 20% increase of tumor burden and no CR, PR or SD documented before increased disease. Response data were based on the response evaluation criteria in solid tumors (RECIST) [16]. A two-step deterioration in PS, a >10% loss of pretreatment weight or increasing symptoms did not by themselves constitute PD; however, the appearance of these complaints was followed by a new evaluation of the extent of the disease. All responses had to be maintained for at least 4 weeks and be confirmed by an independent panel of radiologists.

Statistical design

This was an expected two-step phase II study. According to the trial design, 30 patients were to be enrolled

during the first part of the study and if an objective response rate of less than 15% had been achieved, the treatment would have been abandoned; otherwise, 15 additional patients were to be enrolled. The primary endpoint of the study was to determine the efficacy of the regimen and the secondary endpoints, tolerance and survival. The duration of response was calculated from the day of the first demonstration of response until PD. TTP was calculated from the day of entry into the study until documented PD. Overall survival was calculated from the day of enrollment until death. The estimation of survival distribution was done by Kaplan–Meier method.

Results

Patients' demographics

From January 2004 until January 2006, 45 patients were enrolled in this multicenter trial. Forty-four patients were evaluable for response and toxicity and one patient stopped treatment after the first infusion, of her own volition. The patients' characteristics are shown in Table 1. The median age was 60 years (range 39–82), PS 0–2 and the patients were mainly stage III (a, b, c subclassification included); all had been pretreated with first-line chemotherapy (carboplatin or cisplatin plus paclitaxel). Twenty patients had repeated treatment on first recurrence or on disease progression 3–12 months after first-line treatment; chemotherapy in these patients included carboplatin with cyclophosphamide or with gemcitabine or with anthracycline or with docetaxel. Five patients had extra-abdominal disease (lung metastases or pleural effusion) and the remaining 39 had abdominal spread of the disease with or without ascites.

Compliance with treatment

A total number of 103 cycles with a median of 2 cycles (3 infusions per cycle) were given (range 1–3 cycles). Analytically, the number of weekly drug infusions was 309 (median 7.02, range 3–9). Hematologic toxicity (grade 3 or 4 neutropenia) affected 5 (11%) patients who had a 1-week treatment delay and hemopoietic growth factor administration. In cases of grade 3 or 4 febrile or afebrile neutropenia, we reduced both drug doses by 25% in subsequent cycles, rhG-CSF was administered and the next scheduled treatment was postponed for 1 week; this applied to 5 (11%) patients. Toxicities were graded according to WHO guidelines [17]. Grade 1–2 thrombocytopenia was observed in three patients and anemia (grade 1–2) in ten patients. No patient withdrew from treatment because of toxicity. At the time of analysis, 13 patients (29.5%) were still alive and 31 dead. The cause of death was due to disease progression. The median follow-up time was 12 months (range 4–24 months).

Table 1 Patients' characteristics

		No.	%
Patients enrolled		45	100
Patients evaluable		44	98
Age (years)			
Median	60		
Range	39–82		
Disease stage			
III		39	89
IV		5	11
Performance status (WHO)			
0		2	4.5
1		37	84
2		5	11
Prior chemotherapy			
Carboplatin or cisplatin + paclitaxel		44	100
Second-line chemotherapy[a]			
Carboplatin + cyclophosphamide		5	11
Carboplatin + gemcitabine		5	11
Carboplatin + anthracycline		4	9
Carboplatin + docetaxel		6	14
Surgery		22	50

[a] Second-line therapy includes responders and non-responders to first-line therapy

Toxicity

Forty-four patients were evaluable for toxicity. Serious hematologic toxicity (neutropenia grade 3–4) was seen in five patients (11%). Low-grade anemia was observed in ten patients and low-grade thrombocytopenia in three patients. Alopecia was also seen in 31 patients and asthenia in 14. Nausea/vomiting and diarrhea were rare (Table 2). Toxicity did not differ between patients with a PS of 2 and those with a PS of 0–1. Patients with neutropenia required a 1-week postponement of treatment and hemopoietic growth factor support.

Response to treatment and survival

Responses were analyzed on an intention-to-treat basis. There was one complete remission (2%) out of the 44 evaluable patients; this patient's evaluation was pathologically confirmed and the duration of response was 12+ months. Sixteen (36%) patients achieved PR. The total CR and PR was 39%. Three patients with PR had had prior chemotherapy twice, whereas 14 of the

Table 2 Serious hematological and non-hematological toxicity, all cycles

	Grade			
	1–2	3	4	Total
	n(%)	*n*(%)	*n*(%)	*n*(%)
Neutropenia	–	3 (7)	2 (4.5)	5 (11)
Anemia	10 (23)	–	–	–
Thrombocytopenia	3 (7)	–	–	–
Nausea/vomiting	4 (9)	–	–	–
Diarrhea	2 (4.5)	–	–	–
Neurosensory	15 (34)	–	–	–
Muscular pain	9 (20.5)	–	–	–
Asthenia	14 (32)	–	–	–
Allergy	–	–	–	–
Alopecia	15 (34)	16 (36)	–	–
Cardiotoxicity	–	–	–	–
Nephrotoxicity	–	–	–	–

responders had previously received only one line of chemotherapy. Patients who were resistant to cisplatin or carboplatin chemotherapy showed SD or disease progression with the present chemotherapy regimen. Nineteen patients had SD (43%) and eight had disease progression (18%) (Table 3). The median duration of response was 4 months (range 2–12+ months) and TTP median duration was 5 months (range 3–12+ months) (Fig. 1). The median survival time was 9 months (range 2–24+ months) (95% CI: 7.9–10.2) (Kaplan–Meier Fig. 2). All responders showed an improvement in PS.

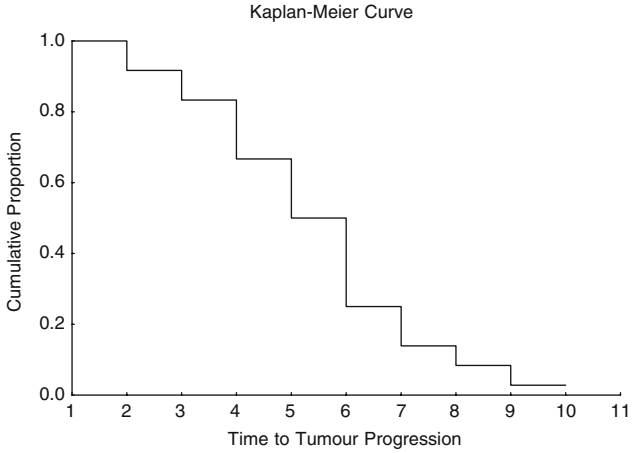

Fig. 1 Time to tumor progression (Kaplan–Meier)

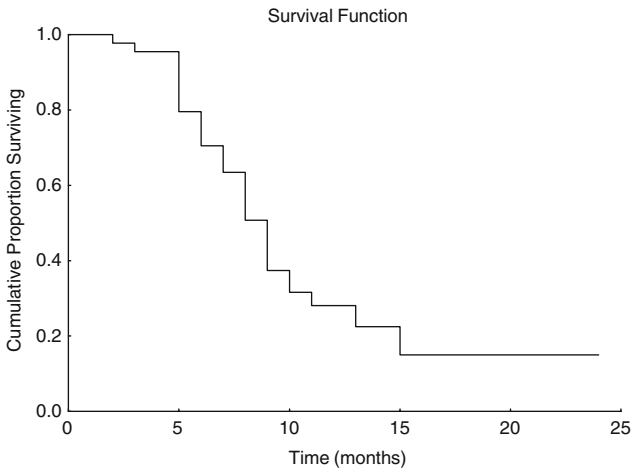

Fig. 2 Kaplan–Meier survival time

Discussion

Advanced ovarian cancer has shown quite a high responsiveness to first-line treatment. The majority of patients present recurrent disease at various times after response to treatment or a long-standing residual disease. These factors dictate the necessity for second-line treatment, mainly chemotherapy and occasionally surgery or both. Quite a number of trials have tested several cytotoxic agents or combinations with some effectiveness and prolongation of life [18–23]. Topotecan has been shown to be one of the eligible agents as monotherapy or in combination [24, 25]. Although 5-day topotecan administration is effective, 46% myelotoxicity (grade 3 neutropenia) and 12% (grade 4 neutropenia) are intolerable [26, 27]. The 1.5 mg/m^2 of topotecan administered daily as a single agent and the high percentage of neutropenia may have been due to the 5-day daily administration of this agent [27]. When combined with other agents such as cisplatin, etoposide, ifosfamide or doxorubicin, the result was 76.9% in cycle reduction due to hematological toxicity (67.4%) and renal toxicity (7.2%) [12]. Weekly administration of topotecan has been indicated as an alternative to topotecan's standard daily × 5 schedule [27]. The topotecan–paclitaxel combination with cisplatin has been tested in extensive small-cell lung cancer [12] showing that this combination is well tolerated and also effective.

In a phase-II study, topotecan at a high dose of 4 mg/m^2 was administered weekly for 3 consecutive weeks in recurrent or persistent epithelial ovarian cancer. The patients had been pretreated with a cisplatin-based chemotherapy combination; there was serious

Table 3 Response rate and survival

	n	%
Complete response	1	2
Partial response	16	36
Overall response	17	39
Stable disease	19	43
Progressive disease	8	18

Median survival time (months): 9 (95% CI: 7.9–10.2)

thrombocytopenia but effectiveness was as high as a 47.8% response rate. The median progression-free survival was 4.9 months [28].

CA 125 was detected in all patients, but was significantly reduced in all responders. Five/17 patients with SD also had a reduction in CA 125 levels, but this was not significant.

In the present study, the response rate was 39%, toxicity 11% (mainly neutropenia grades 3–4) and asthenia 32%. In a very small number of patients, treatment was postponed. The median TTP was not long at 5 months.

As mentioned before, quite a high percentage of patients with stage III ovarian cancer have residual disease after first-line chemotherapy or following second-line treatment. Patients with residual disease are mainly considered for treatment when there is disease progression. At that stage, if surgery is not effective, the cure rate is non-existent. The decision for another series of chemotherapy should, apart from the prolongation of life, be related to quality of life. The regimen used in this study could be considered as fitting in this category. The fact that the toxicity of a weekly cytotoxic regimen combination is much less myelotoxic has been proven in clinical testing. Five-day consecutive administration directly hits bone marrow cells, and this does not occur with the weekly administration. Neuropathy is not increased by low-dose weekly administration of paclitaxel. We did, however, observe low-grade fatigue.

In conclusion, the combination of topotecan and paclitaxel administered on a weekly basis is a well-tolerated chemotherapy schedule. The 38% response rate is quite high for pretreated ovarian cancer patients. This mode of treatment, in comparison to 5-day topotecan administration, is not less effective, but it is much less myelotoxic.

References

1. McGuire WP, Hoskins WJ, Brady MF et al (1996) Cyclophosphamide and cisplatin compared with paclitaxel and cisplatin in patients with stage III and stage IV ovarian cancer. N Engl J Med 334:1–6
2. Piccart MJ, Bertelsen K, James K et al (2000) Randomized intergroup trial of cisplatin-paclitaxel versus cisplatin-cyclophosphamide in women with advanced epithelial ovarian cancer: three-year results. J Natl Cancer Inst 92:699–708
3. McGuire WP, Ozolos RF (1998) Chemotherapy of advanced ovarian cancer. Semin Oncol 25:340–348
4. Kudelca AP, Tresukosol D, Edwards CL et al (1996) Phase II study of intravenous topotecan as a 5-day infusion for refractory epithelial ovarian carcinoma. J Clin Oncol 14:1552–1557
5. Creemers GJ, Bolis G, Gore M et al (1996) Topotecan an active drug in the second-line treatment of epithelial ovarian cancer: results of a large European phase II study. J Clin Oncol 12:3056–3061
6. ten Bokkel Huinink W, Gore M, Carmichael J et al (1997) Topotecan versus paclitaxel for the treatment of recurrent epithelial. J Clin Oncol 15:2183–2193
7. Bookman MA, Malmstrom H, Bolis G et al (1998) Topotecan for the treatment of advanced epithelial ovarian cancer: an open label phase II study in patients treated after prior chemotherapy that contained cisplatin or carboplatin and paclitaxel. J Clin Oncol 16:3345–3352
8. Hoskins P, Eisenhower E, Beare S et al (1998) Randomized phase II study of two schedules of topotecan in previously treated patients with ovarian cancer: a National Cancer Institute of Canada Clinical Trials Group Study. J Clin Oncol 16:2233–2237
9. Ardizzoni A, Hansen H, Dombernowsky P et al (1997) 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 15:2090–2096
10. Belinson J, Kennedy A, Webster K et al (1999) 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. Proc Am Soc Clin Oncol 18:369a
11. Franci G, Panza N, Comella P et al (1999) Cisplatin–topotecan–paclitaxel weekly administration with G-CSF support for ovarian and small-cell lung cancer patients: a dose-finding study. Ann Oncol 10:355–361
12. Frasci G, Nicolella G, Comella P et al (2001) A weekly regimen of cisplatin, paclitaxel and topotecan with granulocyte-colony stimulating factor support for patients with extensive disease small-cell lung cancer: a phase II study. Br J Cancer 84:1166–1172
13. Homesley H, Bemigno B, Williams J et al (2001) Weekly topotecan combined with weekly paclitaxel in second or third-line therapy of epithelial ovarian carcinoma. Proc Soc Clin Oncol 20:191b
14. Klaasen V, Wilke H, Strumberg D et al (1996) Phase I study with a weekly 1-h infusion of paclitaxel in heavily pretreated patients with metastatic breast and ovarian cancer. Eur J Cancer 32A:547–551
15. Stathopoulos GP, Rigatos SK, Christodoulou C et al (2004) Weekly administration of topotecan and paclitaxel in pretreated advanced cancer patients: a phase I/II study. Cancer Chemother Pharmacol 54:259–264
16. Therasse P, Arbuck SG, Eisenhauer EA et al (2000) New guidelines to evaluate the response to treatment in solid tumors. J Natl Cancer Inst 92:205–216
17. Miller AB, Hoogstraten B, Stagnet M, Winkler A (1981) Reporting results of cancer treatment. Cancer 47:207–214
18. Bolis G, Scarfone G, Tateo S et al (2001) Response and toxicity to topotecan in sensitive ovarian cancer cases with small residual disease after first-line treatment with carboplatinum and paclitaxel. Gynecol Oncol 80:13–15
19. Gore M, Oza A, Rustin G et al (2002) A randomized trial of oral versus intravenous topotecan in patients with relapsed epithelial ovarian cancer. Eur J Cancer 38:57–63
20. Bhoola SM, Coleman RL, Herzog T et al (2004) Retrospective analysis of weekly topotecan as salvage therapy in relapsed ovarian Cancer. Gynecol Oncol 95:564–569
21. Markman M, Hall J, Spitz D et al (2002) Phase II trial of weekly single-agent paclitaxel in platinum/paclitaxel refractory ovarian cancer. J Clin Oncol 20:2365–2369
22. Morris R, Munkarah A (2002) Alternate dosing schedules for topotecan in the treatment of recurrent ovarian cancer. Oncologist 7(suppl 5):29–35

23. Gordon AN, Fleagle JT, Guthrie D et al (2001) Recurrent epithelial ovarian carcinoma: a randomized phase III study of pegylated liposomal doxorubicin versus topotecan. J Clin Oncol 19:3312–3322
24. Armstrong DK (2002) Relapsed ovarian cancer: challenges and management strategies for a chronic disease. Oncologist 7(suppl 5):20–28
25. Gore M, ten Bokkel Huinink W, Carmichael J et al (2001) Clinical evidence for topotecan-paclitaxel non-cross-resistance in ovarian cancer. J Clin Oncol 19:1893–1900
26. Schiller JH, Adak S, Cella D et al (2001) Topotecan vs observation after cisplatin plus etoposide in extensive stage SCLC E7593—a phase III trial of the Eastern Cooperative Group. J Clin Oncol 19:2114–2122
27. Rowinsky EK (2002) Weekly topotecan: an alternative to topotecan's standard daily x 5 schedule? Oncologist 7:324–329
28. Levy T, Inbar M, Menczer J et al (2004) Phase II study of weekly topotecan in patients with recurrent or persistent epithelial ovarian cancer. Gynecol Oncol 95:686–690