Topotecan as a second-line therapy in patients with ovarian and primary peritoneal cancer: initial response and long-term follow-up

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Summary

The purpose of this study was to evaluate the role of topotecan at a dose of 5-day standard 1.5 mg/m2/day in patients with relapsed ovarian cancer. Two different groups of patients were included. In group 1, 23 patients who had bidemensionally measurable disease were examined, and in group 2, 11 patients were given topotecan after positive second-look laparotomy (SLL) were analyzed. Total number of cycles was 190 with a median value of six cycles. In group 1, three (13%) patients had complete response (CR) and seven (30%) had partial response (PR) with a total response rate of 43%. Six patients (27%) had stable disease (SD), and seven (30%) had progressive disease (PD). Median survival durations for patients with CR, PR, SD, and PD were 35, 14, 15, and two months, respectively. In group 2, two patients had PD during treatment. The remaining nine patients had no measurable disase or marker relapse at the end of treatment period. Median survival duration was 27 months. In conclusion, topotecan had significant antitumor activity as a second-line therapy in relapsed ovarian cancer patients with measurable disease. In a subgroup of patients with positive second-look laparotomy topotecan was also associated with long median survival duration.

Key words: Ovarian cancer; Recurrence; Topotecan; Second-line; Toxicity.

Introduction

Ovarian cancer is the most lethal gynecological cancer. Since there is no effective screening method, and the early signs and symptoms are nonspecific, two-thirds of the patients are first diagnosed at advanced stages. Despite significant advances in initial surgical therapy, and front-line chemotherapy, the vast majority of patients will eventually develop recurrent disease, and become candidates for additional chemotherapy [1]. Topotecan is a semisynthetic, water-soluble analog of camptothecin that inhibits topoisomerase I, a cellular enzyme that relieves torsion in DNA induced by replication, resulting in DNA breaks, fragmentation, and cell death [2, 3]. Topotecan has been demonstrated as one of the most efficient chemotherapeutics in the second-line treatment of ovarian cancer with a response rate of 19-33% in patients with platinum-sensitive tumors, and 12-23% in platinum-resistant or refractory tumors [4-10]. The purpose of this study was to evaluate the role of topotecan at a dose of 5-day standard 1.5 mg/m^2/day.

Materials and Methods

The patients treated with topotecan as a second-line chemotherapy for recurrent epithelial ovarian cancer or primary peritoneal cancer between January 1997 and January 2003 were evaluated. Two different groups of patients were included in the study. In group 1, the patients were required to have bidemensionally measurable disease on physical examination or chest X-ray, ultrasound, abdominal-pelvic computed tomography (CT) scan, or magnetic resonance imaging (MRI) including at least one tumor with a diameter ≥ 2 cm. In group 2, the patients who were given topotecan after positive second-look laparotomy (SLL) were included. Further eligibility criteria included age ≥ 18 years; a Gynecologic Oncology Group (GOG) performance status of ≤ 2; the failure of initial platinum-based chemotherapy; at least 12 weeks' life expectancy; no active concomitant malignant disease and laboratory values of hemoglobin ≥ 9 mg/dl, white blood cell (WBC) count ≥ 3.000/μl, granulocytes ≥ 1.500/μl, platelets ≥ 100.000/μl, creatinine ≤ 1.5 mg/dl, creatinine clearance rate ≥ 60 ml/min, bilirubin ≤ 2.0 mg/dl, and transaminase levels less than two times the upper limit of normal. Initial response to chemotherapy was defined as follows: (1) platinum-refractory, if the disease progressed or remained stable on initial chemotherapy; (2) platinum-resistant, if the patient responded and subsequently relapsed within six months after the completion of initial platinum-based therapy; and (3) platinum-sensitive, if the relapse was seen after six months of completion of initial chemotherapy.

Topotecan was given at a dose of 1.5 mg/m^2/day as a 30-minute IV infusion for five consecutive days every three weeks. In routine follow-up, weekly complete blood cell (CBC) counts, and blood chemistries including liver and renal function tests were performed. If clinically indicated, they were analyzed more frequently. Treatment was given if the neutrophil was count ≥ 1500/μl and the platelet count was ≥ 100,000/μl. When the blood levels were less than these values the course was delayed one week with a dose reduction of 0.1 mg/m^2/day. Dose reduction below 1.0 mg/m^2 was not allowed, and the treatment was stopped if hematologic toxicity persisted after both the dose reduction and supportive therapy. Even in the cases of significant decrements in hemoglobin concentration, chemotherapy

Revised manuscript accepted for publication February 20, 2006

doses were not reduced, and the patients were supported by red blood cell transfusions. Toxicity was assessed acccording to the GOG toxicity criteria [11].

Responses were evaluated as follows: complete response (CR), disappearance of all evidence of disease for at least ≥ 4 weeks; partial response (PR); reduction of ≥ 50% in the sum of perpendicular diameters of each indicator lesion without appearance of new lesions for ≥ 4 weeks; progressive disease (PD), ≥ 25% increase in any lesion or the appearance of any new lesion within eight weeks; stable disease (SD), any condition other than any criteria mentioned above. Progression-free survival (PFS) was defined as the interval from the date of first topotecan chemotherapy to the date of increased parameters of disease or the date of last contact. Overall survival (OS) was defined as the interval from date of first topotecan chemotherapy until death or the date of last contact. Response duration was calculated from the date of response to the date of progression or last contact in patients with CR+PR. Data was obtained from patients' charts, special gynecologic oncology files, and pathology records. For a few patients who live far from our center, follow-up information was taken by the personal physician of these patients, and if indicated they were referred to our clinic.

Results

Overall 34 patients were included in the study. Of these patients, 23 (68%) received therapy for measurable disease ≥ 2 cm (group 1) and 11 (32%) had positive second-look laparotomy (group 2). The median age at the time of chemotherapy was 49 (range 30-73). None of the patients had peformance status greater than 2. Two patients (5.9%) had Stage IC, 29 (85.3%) had Stage IIIC, and three (8.8%) had Stage IV disease at initial surgery. The most common histology was papillary serous type (55.9%). Fifteen patients (44%) had grade 2, and 19 (56%) had grade 3 tumors (Table 1). As a first-line chemotherapy four patients (12%) received endoxan-platinum, and the remaining 30 (88%) had paclitaxel/platinum-based regimens. Responses to the prior platinum-based therapy were as follows: group 1: five patients (21.7%) were platinum-refractory, ten patients (43.5%) were platinum-resistant, and eight patients (34.8%) were platinum-sensitive; group 2: all the patients were accepted as platinum-refractory (Table 2).

Total number of cycles were 190 with a median value of six cycles (range 3-6; mean 5.58). Treatment was continued until progression or unacceptable toxicity. None of the patients received more than six cycles. Treatment was stopped in six patients due to progressive disease at the 3rd, 4th, and 5th cycles. As a hematologic toxicity 23.5% of the patients had grade 4 leukopenia, 76.4% had grade 4 neutropenia, 29.4% had grade 3-4 thrombocytopenia, and 52.9% had grade 3-4 anemia. Neutropenic fever was seen in four patients (11.7%). Non-hematologic toxicities were rare and mild. Dose reduction was required in six patients (17.6%), and one patient was switched to another regimen after the 4th cycle because of significant-persistant toxicity. No patient died due to side effects.

In group 1, three (13%) patients had CR, and seven (30%) had PR with a total response rate of 43%. Six patients (27%) had SD, and seven (30%) had PD. All the patients with CR had Stage IIIC tumor initially, and one was platinum-refractory, one was platinum-resistant and one was platinum sensitive. After topotecan treatment, they had 10, 24, and 35 months PFS, respectively. Median response duration for patients with CR and PR was seven months, and median PFS for patients with SD was three months. Median survival durations for patients with CR, PR, SD, and PD were 35, 14, 15, and 2 months, respectively (Table 3). Seventeen patients died as a consequence of disease at the time of this writing, and five patients were alive with disease for a median duration of 15 months. The remaining one patient was alive without disease for 35 months.

Table 1. — *Characteristics of the patients.*

Characteristics	no. (%)
Total no. of patients	34
Age, years	
Median	49
Range	30-73
Performance status	
0	18 (53)
1	12 (35)
2	4 (12)
FIGO Stage	
IC	2 (5.9)
IIIC	29 (85.3)
IV	3 (8.8)
Histology	
Ovarian cancer	31 (91.2)
Serous papillary	19 (55.9)
Mucinous	3 (8.8)
Endometrioid	6 (17.6)
Clear cell	1 (2.9)
Undifferentiated	1 (2.9)
Mixed type	1 (2.9)
Primary peritoneal cancer	3 (8.8)
Grade	
2	15 (44)
3	19 (56)

Table 2. — *Characteristics of the patients with respect to first-line and second-line chemotherapies.*

	no. (%)
First-line chemotherapy	
Endoxan-platinum	4 (12)
Paclitaxel-platinum	30 (88)
Response to prior platinum based therapy in group 1[a]	
Platinum-refractory	5 (21.7)
Platinum-resistant	10 (43.5)
Platinum-sensitive	8 (34.8)
Total no. of courses	190
No. of courses per patient	
Median	6
Range	3-6
Response to second-line therapy in group 1[a]	
Complete response	3 (13)
Partial response	7 (30)
Stable disease	6 (27)
Progressive disease	7 (30)

[a]The patients with measurable disease ≥ 2 cm.

Table 3. — *Median progression-free survival (PFS), and overall survival (OS) durations after the completion of topotecan chemotherapy.*

	PFS	OS
Group 1[a]		
Responders	7 months	16 months
Complete response	24 months	35 months
Partial response	5 months	14 months
Stable disease	3 months	15 months
Progressive disease	–	2 months
Group 2[b]		
Patients with progressive disease	–	3 months
Patients with non-progressive disease during therapy	4 months	27 months

[a]The patients with measurable disease ≥ 2 cm.
[b]The patients with positive second-look laparotomy.

In group 2, of the 11 patients who were found to be positive histopathologically at SLL, three had microscopic disease, seven had macroscopic disease ≤ 2 cm, and one had macroscopic tumor > 2 cm. Two patients had PD during treatment. The remaining nine patients had no measurable disease or marker relapse at the end of treatment period. Median PFS and OS durations were four and 27 months, respectively. There was no significant difference between two groups ($p = 0.09$). At the time of this writing five patients had died of disease, five patients were alive with disease for a median survival of 32 months, and one patient was alive without disease for 28 months.

Discussion

The majority of ovarian cancer patients are first diagnosed at advanced stages since the tumor is asymptomatic until it has progressed. Today, the first-line therapy includes initial cytoreductive surgery plus adjuvant chemotherapy consisting of platinum and taxanes. Although a big proportion of the patients respond to this therapy, 50-80% of them will eventually relapse [12]. By prolonging the interval between the completion of initial therapy and recurrence, the likelihood of response to second-line treatment increases [13]. Among the many different alternatives in the second-line setting, topotecan has been heavily studied during the last decade for patients with ovarian cancer. First of all, the series using the standard protocol at a dose of 1.5 mg/m^2/day over 30 minutes for five days repeated every three weeks were published. Creemers *et al.* evaluated the results of 92 patients treated with topotecan as a second-line therapy [4]. A total of 552 courses were given with a median of four per patient, and they reported 16.3% response rate. The values for patients with platinum refractory, resistant, and sensitive tumors were 5.9, 17.8, and 26.7%, respectively. Response duration was 21.7 weeks. Kudelka *et al.* observed a 14% response rate with a duration of 8.9 months in 28 platinum-refractory patients [8]. Sixty-one percent of the patients had stable disease, and the overall median survival was ten months. In the study of Bookman *et al.* 139 patients were analyzed; 81% were platinum-resistant and 55% were treated with two different regimens [5]. Overall response rate was 13.7%, with a median response duration and survival values of 18.1 and 48 weeks, respectively. Response rates in resistant and sensitive groups were 12.4 and 19.2%, respectively. McGuire *et al.* reported a 33% response rate with a duration of 11.2 months in 46 platinum-sensitive patients after one or two prior chemotherapies [6]. Swisher *et al.* observed a 14% response rate in 26 platinum-resistant patients [7]. Malik treated 39 patients with a mean of 7.5 cycles, and found a 28% response rate [14]. The mean response duration was 4.6 months, and mean survival was 11.3 months in his study. The large phase III trials added important knowledge to the growing body of literature [15, 16]. In a comparative study with paclitaxel, 112 patients were treated with topotecan at a standard dose for measurable disease as a second-line therapy [15]. The overall response rate was 20.5%; 13.3% for platinum-resistant patients and 28.8% for the sensitive group. The median time to progression was 23 weeks and median survival was 61 weeks. There was no significant difference between the two arms except longer time to progression in the topotecan group. In another study comparing topotecan with liposomal doxorubicin, 235 patients received the standard dose, which resulted in a 17% response rate [16]. Time to progression was 17 weeks, and median survival was 56.7 weeks. Response rates in platinum-refractory and sensitive groups were 6.5 and 28.8%, respectively. In the current study the overall response rate was 43% in patients with measurable disease which were evaluated in group 1. The median response duration and OS values were 7 and 16 months, respectively. All these findings were well-matched with the results of series mentioned above. In addition, the patients with positive second-look laparotomy were also analyzed. Only two of 11 patients in this setting had progressive disease during therapy, and the median PFS and OS values in the remaining nine patients were four and 27 months, respectively. Although it was not the purpose of this study to compare these two groups, the difference did not gain significance.

It has been reported that overall 21% to 61% of patients receiving topotecan chemotherapy had stable disease [4-10]. Cesano *et al.* [17] evaluated four clinical trials including 392 patients treated with topotecan, and found that the stabilization of disease for at least eight weeks was associated with a 53% reduction in death risk when compared with the nonresponders ($p < 0.001$). This value for patients with partial response was 46% without any significant difference from the patients with stable disease. Therefore the stabilization of disease may have clinical benefit according to the results of this analysis. In the present study, 27% of the patients had stable disease and the median survivals for the patients with SD and PR were similar without any significant difference (15 vs 14 months, respectively).

Noncumulative hematologic toxicity is the leading cause of morbidity during topotecan chemotherapy. Neu-

tropenia is the most common side-effect, and at least three-fourths of the patients had grade 4 neutropenia. Although it is very frequent, only 5.4-13% of the patients have neutropenic fever [4, 8, 18]. Sepsis and chemotherapy-related deaths are extremely rare. Thrombocytopenia and anemia are the second most common toxicities. Non-hematologic side-effects are rare. In the present study, the non-cumulative hematologic toxicities were the most frequent, and the rates were parallel to the literature. No patient died of side-effects. Armstrong and O'Reilly stated that in phase I studies the predominant toxicity was noncumulative neutropenia, and in phase II series thrombocytopenia related to prior carboplatin therapy gained significant importance, and neutropenia was more severe than estimated from phase I studies [18]. Both in the present study and in all of the published series these patients were easily managed by supportive therapy, and/or dose reductions. In the current study six patients (17.6%) required dose reductions, and fortunately only one patient could not complete the therapy and switched to another regimen after the 4th cycle.

Many different series have been published dealing with alternate doses and the routes of administration of topotecan [19, 20]. The major purpose of these series was to decrease toxicities without compromising efficiency. Especially weekly topotecan has gained great interest due to lower rates of side-effects and a comparable rate of antitumor efficiency [20]. However, further research is still necessary to determine the optimum dosing regimen.

Conclusion

Topotecan had significant antitumor activity as a second-line therapy in relapsed ovarian cancer patients with measurable disease. Therefore, it is candidate to be a first choice for these patients. In a subgroup of patients with positive second-look laparotomy topotecan was also associated with a long median survival duration.

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