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Role of Salvage Chemotherapy with Topotecan and Cisplatin in Patients with Paclitaxel- and Platinum-Resistant Recurrent Ovarian or Primary Peritoneal Cancer: A Phase II Pilot Study

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Background and Objectives: We assessed the role of salvage chemotherapy with topotecan and cisplatin in patients with platinum- and paclitaxel-resistant advanced and recurrent ovarian or primary peritoneal cancer, based on the reported in vivo and in vitro synergism between these two drugs.
Methods: Twenty patients were entered in this phase II trial from November 1997 to November 1998. They received cisplatin at 50 mg/m^2 on day 1 with topotecan at 0.6 mg/m^2 from day 1 to 5 every 28 days. In 70% of patients (14/20), this combination represented at least a third line of therapy.
Results: A clinical response rate of 13.3% (two partial responses) was obtained in the 15 patients with evaluable disease. Sixty percent of patients (9/15) had stable disease and 26.7% (4/15) had progression. The median progression-free interval and survival were 4 months and 7 months, respectively. The 20 patients evaluable for toxicity received a mean of four chemotherapy cycles. Dose reductions were required in 45% of patients despite the administration of growth factors. The major dose-limiting toxicity was a 50% occurrence (10/20) of grade 4 thrombocytopenia and 30% (6/20) grade 4 neutropenia. There was one septic death.
Conclusions: These data suggest that combination therapy with topotecan and cisplatin has minimal activity in platinum- and paclitaxel-resistant advanced and recurrent ovarian or primary peritoneal cancer at the doses utilized in this trial.
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KEY WORDS: **paclitaxel; cisplatin; topotecan; recurrence; ovarian cancer; primary peritoneal cancer**

INTRODUCTION

Ovarian cancer is the fifth most common cancer in women, and there are 25,400 new cases in the United States annually, with 14,500 deaths in 1998 [1]. Of these patients, 70% to 80% have advanced-stage disease at the time of diagnosis, and optimal cytoreductive surgery followed by platinum-based chemotherapy remains the reference standard of therapy. Patients with advanced ovarian cancer have a response rate of 73%–77% following first-line therapy with paclitaxel and cisplatin with a median progression-free interval of 16–18 months and a median survival of 35–38 months [2,3]. Unfortunately, most patients will have recurrence, and an important prognostic predictor is whether the recurrence is <6 months (platinum-resistant) or >6 months (platinum-sensitive) from completion of chemotherapy. Patients with platinum-resistant tumors have a response rate of <10% when retreated with platinum compounds [4]. The

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current alternatives include paclitaxel in both standard and dose-intense schedules, topotecan, gemcitabine, liposomal doxorubicin, and oral etoposide [5–16]. The overall response rates remain low, 18%–30%; and the choice of chemotherapy is often determined by factors such as ease of administration, toxicity profile, performance status, and prior chemotherapy [5–16].

Topotecan is a camptothecin derivative that acts by binding to the topoisomerase I (topo-I)–DNA complex and prevents the religation of DNA during replication, causing cell death [17]. Phase II trials of topotecan at 1.5 mg/m^2 administered from day 1 to day 5 every 21 days in patients with recurrent ovarian cancer have demonstrated overall response rates from 13% to 27%, almost all being partial responses [6–9]. In the largest reported phase II study, Creemers et al. [7] had a response rate of 6% in 34 patients with platinum-refractory disease and 18% in 28 patients with platinum-resistant disease with no complete responses. However, eight of 30 patients (27%) with platinum-sensitive disease responded to topotecan, and there was one complete responder [7]. The International Topotecan Study Group trial showed a response rate of 13% and 14% with topotecan after first and second failures of therapy, respectively, with paclitaxel and platinum [8]. Results were recently reported [10,11] of a phase III randomized trial comparing topotecan at the above dose with paclitaxel at 175 mg/m^2 over 3 h every 21 days in 226 patients with recurrent ovarian cancer and history of prior therapy with cisplatin. In the topotecan arm, the overall response rate was 21% (13% in platinum-resistant and 29% in platinum-sensitive tumors), with a progression-free interval of 19 weeks. The paclitaxel arm had a response rate of 14% (7% in platinum-resistant and 20% in platinum-sensitive tumors), with a median progression-free interval of 15 weeks. This difference was not statistically significant, but grade 3/4 hematological toxicity was significantly greater in the topotecan arm.

In vitro and in vivo studies have demonstrated synergism between topotecan and cisplatin [18,19]. The separate mechanisms of action with different toxicities of these two drugs make this a promising combination. Phase I studies with topotecan and cisplatin in solid tumors have prompted the establishment of this protocol to treat patients with recurrent ovarian and primary peritoneal cancer with platinum- and paclitaxel-resistant disease [20,21].

MATERIALS AND METHODS

Twenty patients with advanced or recurrent ovarian or primary peritoneal cancer with platinum- and paclitaxel-resistant disease were eligible for this study. Both platinum- and paclitaxel-resistant disease were defined as either progression of disease while on therapy or recurrence within 6 months of completion of therapy with these drugs. Eligibility criteria required the patients to have a Gynecologic Oncology Group (GOG) performance score of ≤ 2, baseline leukocyte count >3000, platelet count >100,000, serum creatinine <1.5 mg/dl, serum bilirubin <1.5 mg/dl, and liver function tests <3 times the laboratory standard value. Patients were required to have a life expectancy of at least 2 months and no major medical problems that would preclude the use of these drugs. Informed consent was obtained after satisfactory understanding of the potential risk and benefits.

Patients received cisplatin at 50 mg/m^2 over 1 h after adequate hydration with normal saline on day 1, followed by topotecan at 0.6 mg/m^2 over 30 min from day 1 to day 5 every 28 days. Granulocyte- or macrophage-stimulating factors were initiated for grade 3 or 4 neutropenia. Chemotherapy was withheld for a white cell count <3,000/mm^3 and for platelet count <100,000/mm^3, and counts were repeated biweekly until they met the criteria for the next course of chemotherapy. Toxicity was assessed using the GOG scoring system. Patients with persistent grade 4 neutropenia or grade 4 thrombocytopenia had initial reduction in the dose of topotecan by increments of 20% and then in the dose of cisplatin by 20% if necessary. Persistent grade 4 thrombocytopenia after dose reduction required a change in the topotecan schedule, with reduction from 5 to 4 days of therapy. Complete response was defined as total disappearance of all clinically or radiologically measurable tumor with normalization of Ca-125 (<35) for at least 1 month. Partial response was defined as a 50% reduction in the sum of the two perpendicular diameters of all measurable tumors for at least 1 month. Progression of disease was defined as appearance of new lesions or an increase of >50% in the sum of two perpendicular diameters of any existing lesion. The term "stable disease" was used for any response that fell between progression and a partial response. Data accrued from November 1997 to November 1998 were used for analysis.

RESULTS

Twenty patients, 17 with advanced and recurrent ovarian cancer and 3 with recurrent primary peritoneal cancer, who were platinum- and paclitaxel-resistant were enrolled in this phase II trial. The mean age of patients was 60.2 years (range, 39–78) (Table I). For 14 patients (70%), this combination of topotecan and cisplatin represented at least a third line of therapy. All 20 patients had prior therapy with cisplatin and paclitaxel, and another three patients had received single-agent topotecan at 1.2 mg/m^2 from day 1 to day 5 every 28 days. One of these three patients with prior exposure to topotecan had a partial clinical response on this combination therapy and the other two had stable disease. Eighteen of the 20 patients had a papillary serous histology, and both responders belonged to this group.

TABLE I. Patient Characteristics (n = 20): Topotecan–Cisplatin in Recurrent Ovarian Cancer

Characteristic	No. of patients[a]
Mean age, years (range)	60.2 (39–78)
GOG performance status	
0	13
1	6
2	1
Cancer type	
Epithelial ovarian	17
Primary peritoneal	3
Original FIGO stage	
IIB	1
IIC	1
IIIA	1
IIIB	1
IIIC	14
IVB	2
Histopathology	
Papillary serous	18
Clear cell	1
Endometrioid	1
Recent surgery	12
Optimal cytoreduction (<1 cm)	3
Line of chemotherapy	
2nd	6
3rd	6
4th	4
5th	3
6th	1

[a]Unless specified otherwise. GOG, Gynecologic Oncology Group; FIGO, International Federation of Gynecology and Obstetrics.

TABLE II. Clinical Response with Topotecan–Cisplatin (n = 15 Evaluable Patients)

Response	No. of patients	%
Partial response	2	13.3
Stable disease	9	60
Progression	4	26.7

TABLE III. Toxicity Data (n = 20): Topotecan–Cisplatin in Recurrent Ovarian Cancer

	GOG grade				
Toxicity	0	1	2	3	4
Leukocytes	2	4	2	6	6
Erythrocytes	4	1	7	6	2
Platelets	3	3	3	1	10
Sensory neuropathy	17	1	1	1	
Nausea/vomiting	10	5	3	2	

GOG, Gynecologic Oncology Group.

Fourteen of these 20 patients had undergone surgery in the 6 weeks prior to initiation of chemotherapy, and only in three patients was optimal cytoreduction (<1 cm) feasible. Fifteen patients with measurable disease were evaluable for response and two had a partial response (13.3%, >1 to >3 months). Nine of 15 (60%) patients had stable disease and 4 of 15 (26.7%) had progression of disease (Table II). The median progression-free interval and survival were 4 months (range, 1 to ≥8.5) and 7 months (range, 5 to ≥12.5), respectively. Eight of these patients are still alive with disease. Of the three patients who had optimal cytoreduction and were treated with this combination chemotherapy, two are still alive. The median progression-free interval was 5.5 months (range, 5–12) and overall survival was 9 months (range, 5 to ≥12) in these patients.

In total, 83 cycles of chemotherapy were administered to these 20 patients, with a mean of four cycles (range, 1–8). Six patients received at least six cycles of chemotherapy. Toxicity data were available for all 20 patients, and the dose-limiting toxicities were 50% (10/20) grade 4 thrombocytopenia and 30% (6/20) grade 4 neutropenia (Table III). One of the patients with stable disease died with sepsis after her eighth course of chemotherapy. Nine patients required dose reductions in topotecan, three by 40%, and four of these nine required an additional 20% reduction in the dose of cisplatin. Eighteen of the 20 (90%) patients eventually required granulocyte-stimulating factors during the course of this regimen. This chemotherapy was well tolerated, with two patients reporting grade 3 nausea and vomiting; there was just one cycle delay in administration of this chemotherapy.

DISCUSSION

Topotecan inhibits topo I–mediated DNA functions, especially DNA repair. It stabilizes the cleavable complex of topo I–DNA during the single-strand break that allows for DNA uncoiling and increases its half life. Subsequently, these complexes interact with DNA replication forks, causing irreversible double-stranded breaks in the DNA and cell death [22]. This makes the combination of topotecan with other DNA-damaging agents, such as alkylating agents and cisplatin, attractive. Prior exposure with cisplatin leads to formation of cisplatin-induced DNA interstrand crosslinks, and its interaction with the topo I–DNA adducts leads to a greater interference in DNA repair.

In vitro and in vivo studies combining cisplatin have demonstrated synergistic antitumor activity in different human cancer cell lines, and both drugs can be administered at or near their individual maximum tolerated doses in tumor-bearing animals [18]. Recently, Romanelli et al. [19] demonstrated an additive effect when cisplastin and topotecan were administered sequentially and a synergistic effect when administered simultaneously in an in vitro system using cisplatin-sensitive IGROV-1 and cisplatin-resistant IGROV-1/Pt 0.5 ovarian cancer cell lines. They demonstrated this synergy in vivo using a simultaneous administration schedule in IGROV-1 tumor xenografts [19]. Phase I studies by Can-

cer and Leukemia Group B (CALBG) in 37 patients with advanced solid tumors recommend topotecan at 1 mg/m^2 from day 1 to day 5 following cisplatin at 50 mg/m^2 on day 1 without filgrastim every 21 days or topotecan at the same dose with 75 mg/m2 of cisplatin on day 1 with filgrastim as the ideal doses for phase II studies [21]. In that study, only 27% of all courses could be administered at the planned 21-day interval, but all patients were retreated by 28 days. Four of 28 (14%) assessable patients responded to this therapy (one complete response, three partial responses). However in the phase II trials initiated by the CALBG for patients with extensive newly diagnosed small cell cancer of the lung, 3 of 12 patients on the cisplatin/topotecan arm died of treatment-related sepsis, leading to suspension of patient accrual in this arm [23].

Another phase I study, by Rowinsky et al. [20], demonstrated that dose-limiting grade 4 neutropenia and thrombocytopenia can be substantially reduced by limiting the cisplatin dose to 50 mg/m^2 and topotecan to 0.75mg/m^2 from day 1 to day 5 every 21 days and that administration of growth factors did not substantially improve tolerance beyond the above recommended doses. They also demonstrated by pharmacokinetic studies that the hematological toxicity was sequence-dependent and that topotecan clearance was impaired by the subclinical renal tubular damage caused by prior cisplatin administration. However, they recommended the cisplatin/topotecan sequence for clinical trials on the basis of its mechanistic rationale for maximal synergy to allow interaction between the topo I–DNA adducts and polymerase molecules engaged in DNA repair following prior exposure to cisplatin, as shown in animal models.

On the basis of these data, we elected to administer cisplatin at 50 mg/m^2 on day 1 followed by topotecan at 0.6 mg/m^2 from day 1 to day 5 every 28 days in these heavily pretreated patients with recurrent ovarian cancer. Eighteen of 20 (90%) patients required administration of growth factors, nine patients (45%) required further dose reductions in topotecan, and 4 patients (20%) required dose reductions in cisplatin. The dose-limiting toxicity was a 50% incidence of grade 4 thrombocytopenia and a 30% incidence of grade 4 neutropenia, with one septic death. Although 60% (9/15) of patients had stable disease, there were two patients (13.3%) with a partial response. Median progression-free interval and overall survival for the group were 4 and 7 months, respectively.

These results are identical to response rates of 13%–14% in patients with platinum- and paclitaxel-resistant ovarian carcinomas treated with single-agent topotecan [8] and to the 13% response rate in platinum-resistant tumors achieved on the topotecan arm of the phase III study comparing it with paclitaxel with similar progression-free intervals [10,11]. The fact that most of the heavily pretreated patients in this study had large-volume disease and ultimately received much less than the recommended doses of the drugs may be a factor in the minimal response seen in this study.

In conclusion, combination chemotherapy with cisplatin and topotecan has antitumor activity similar to that of single-agent topotecan in platinum- and paclitaxel-resistant epithelial ovarian carcinoma at the expense of higher hematological toxicity.

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