LONG TERM ORAL ETOPOSIDE AS SECOND LINE THERAPY IN RECURRENT EPITHELIAL CARCINOMA OF THE OVARY

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Abstract- There is a continuing need to identify new agents that are active in ovarian cancer. Etoposide is a derivative of the plant alkaloid epipodophyllotoxin. The availability of etoposide in oral preparation allows prolonged administration by the oral route. In this study, activity and toxicity of etoposide in women with recurrent ovarian cancer are described from a case series of women with recurrent ovarian cancer who had measurable disease. All patients had prior platinum-based chemotherapy and developed progressive disease. Oral etoposide was given as 50 mg/day for 21 days every 4 weeks until progression of disease or prohibitive toxicity. From December 1999 to January 2004, 32 patients were enrolled in this study. Thirty patients received a total of 133 cycles of etoposide. Median age of patients was 49 years (range, 19 to 75). The median number of etoposide cycles was 4 (range, 1 to 12). There were 5 partial responses (16.6%). The mean response duration was 4.8 months (range, 3.5 to 6); median progression-free interval was 7 months (range, 3 to 13) and median survival time was 12.5 months (range, 1.3 to 36). The major toxicity was leukopenia. One patient required red blood cell transfusions and the main non-hematologic toxicity was nausea and vomiting. There were no treatment-related mortalities. Although etoposide appears to exhibit modest activity in recurrent ovarian cancer after platinum-based therapy, response and survival durations are short.

Acta Medica Iranica, 44(1): 7-12; 2006

Key words: Oral etoposide, recurrent epithelial ovarian cancer, second-line chemotherapy

INTRODUCTION

The current standard of care for patients with optimally debulked ovarian cancer consists of a platinum compound (cisplatinum or carboplatin) and paclitaxel (1). Despite the high incidence of remission following initial therapy, the majority of cancers ultimately recur. The approach to patients with recurrent disease depends, in large part, on the treatment-free interval between the time of the initial therapy and initiation of second-line therapy (1, 2).

There is a continuing need to identify new agents that are active in ovarian cancer. A variety of second-line agents with various response rates are available, including topotecan (14% to 23%), vinorelbine (22%), gemcitabine (29%), paclitaxel (19 to 40%) and liposomal doxorubicin (26%) (3).

Since these second-line agents have produced similar response rates and median survival duration, physicians can consider other factors, such as patients' quality of life, patients' satisfaction, simplicity of the regimen, toxicity and cost in selection of second-line treatment. Clearly, oral agents are least disruptive to the patients' quality of life and are preferable in terms of ease of administration and cost.

Etoposide is a derivative of the plant alkaloid epipodophyllotoxin. It interacts with DNA topoisomerase II, an enzyme which is active during the late S and early G2 phases of the cell cycle and

Received: 18 May 2004, Revised: 7 Feb. 2006, Accepted: 12 Feb. 2006

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produces a transient double strand break in DNA. Etoposide stabilizes the formation of the DNA-topoisomerase II complex, which results in inhibition of rejoining and increased DNA scission (3). The interaction of etoposide with topoisomerase II is reversible and allows DNA annealing following withdrawal of the drug. This mechanism of action is consistent with the schedule dependency of etoposide, which has been demonstrated in both preclinical and clinical studies (4, 5). There is a theoretical advantage to prolonged administration. Indeed, clinical studies have substantiated that multiple drug dosing is superior to single dose administration (4, 6).

The availability of etoposide in oral preparation allows prolonged administration by the oral route. A comparison between studies using intravenously administered etoposide to those using prolonged oral etoposide concluded improved efficacy in several malignancies for prolonged oral administration and stimulated renewed interest in this agent (7). In addition, oral etoposide is appealing in that it is easy to administer. This report describes the result of a phase II prospective study using a 21-day oral schedule of etoposide to assess the activity and toxicity in women with recurrent epithelial ovarian cancer who had prior platinum-based chemotherapy.

MATEIRALS AND METHODS

All patients had histologically confirmed epithelial ovarian cancer with radiological and/or clinical evidence of disease progression. Patients were eligible if they had not previously received etoposide. They were required to have bi-dimensional tumor measurable by physical examination and radiographic study. The patients were required to have at least one square meter of body surface area, adequate intestinal function, no history of other malignancy, Gynecologic Oncology Group (GOG) performance status ≤ 2, and to have had at least 3 weeks elapse since any prior therapy. Pretreatment laboratory eligibility requirements included: leukocyte count ≥ 3000/mm^3, platelet count ≥ 100,000/mm^3, and granulocyte count ≥ 1500/mm^3, creatinine ≤ 2 mg/dl, bilirubin ≤ 1.5 x upper limit of normal and SGOT and alkaline phosphatase ≤ 3 x upper limit of normal. We obtained informed consent from all patients. Patients were excluded for any of the following: 1) prior treatment with etoposide, 2) history of another malignancy, 3) no measurable disease or 4) GOG performance status ≥ 3.

A complete history, physical examination including a pelvic examination, laboratory studies, assessment of performance status and chest X-rays were performed prior to starting the treatment and every 4 weeks after, with the exception of the chest radiograph (unless pulmonary metastases were presented). Computed tomography (CT) scan was performed every 3 months, or sooner in the event of clinical deterioration. A complete blood count (CBC) and differential was performed weekly. All patients were followed for at least 30 days after the final dose of drug or until resolution of any drug treated toxicity.

Etoposide was administered at a dosage of 50 mg/day (one capsule) as a single daily dose on days 1-21 every 4 weeks. Although food has not been shown to interfere with etoposide absorption (8), patients were instructed to take the entire daily dose each morning before breakfast. Antiemetics were not routinely used. During treatment, a CBC, differential, and platelet count were obtained weekly. Etoposide was discontinued if leukocyte count fell below 2000/μl and/or platelets fell below 50000/μl. At the end of each 21-day cycle, etoposide was discontinued and patients underwent an evaluation on day 28. Patients who demonstrated an objective response or stable disease were given another cycle of oral etoposide. However, therapy was not initiated until counts were adequately recovered (*i.e.*, leukocytes > 3000/μl, platelets > 100000/μl). When the counts recovered sufficiently to resume therapy, the next cycle was started at a lower dose. Etoposide was continued until patients demonstrated evidence of tumor progression or experienced unacceptable toxicity. Toxicity evaluations were based upon standard GOG criteria (8). Patients who received one or more courses of drug were eligible for toxicity, regardless of subsequent response or survival.

Patients were considered eligible for response if they completed one course of therapy and lived at least 3 weeks. Tumor response was assessed after 2

cycles of treatment. Standard GOG response criteria were used (8). Responses were determined using the products of the longest perpendicular diameters of all measurable lesions. Complete response (CR) was defined as the total disappearance of all available lesions without the development of any new lesions. Partial response (PR) was defined as at least a 50% reduction in the product obtained from measurement of all lesions, without the progression of any lesion and without the appearance of any new lesions. Both CR and PR had to be documented on two measurement assessments at least 4 weeks apart. Progressive disease was defined as a 50% increase in the product obtained from measurement of any lesion or the appearance of new lesions. Stable disease was defined as any lesion that failed to qualify for CR, PR, or progressive disease on two evaluations at least 4 weeks apart. Response duration was defined as the time from first documentation of objective response until progression. Duration of stable disease was measured from the start of study. Survival was measured from the time of study entry until death.

The data were analyzed using SPSS software. Survival was analyzed by the method of Kaplan and Meier.

RESULTS

From December 1999 to January 2004, 32 patients entered in the study. Two were excluded; one for never receiving therapy, and one was not assessable. The median age of patients was 49 years (range, 19 to 75). The median of performance status was 1 (0 to 2). Histological evaluation showed 26 serous and 4 mucinous adenocarcinomas. One patient had prior whole pelvic radiation.

Patients received a total of 133 courses of etoposide, with a median of 4 and range of 1-12 courses. Other patients' characteristics are shown in table 1. There were 5 partial responses (16.7%), 4 in patients with platinum-sensitive and one in patient with platinum-resistant disease. The median time to recurrence of disease was 10 months (7.5 to 13 months) in platinum-sensitive responders and 6 months in platinum-resistance responders. The mean response duration was 4.8 months (range, 3.5 to 6).

Table 1. Patients' characteristics

Character	Number
Stage	
IIIA	2
IIIB	3
IIIC	16
IV	9
Histology	
Serous	26
Mucinous	4
Prior chemotherapy (courses)	30*
Platinum resistance	16
Platinum sensitive	14

*Range from 3 to 13, median = 9, mean ± SD = 8.5 ± 3.15.

We observed stable disease in 12 patients. Progression of disease was observed after 1 to 8 cycles in 13 patients. The median progression free interval (PFI) was 7 months (range, 3 to 13). The median survival of the whole group was 12.5 months (range, 1.3 to 36).

Toxicities are shown in table 2. They were primarily hematologic. Grade 1 and 2 leukopenia occurred in 12 and 6 patients, respectively. One patient required red blood cell transfusion. Nausea and/or vomiting was the most common non-hematologic toxicity occurring in 7 patients. SGOT and SGPT elevation (grade 1) was seen in one patient. One patient reported hyperpigmentation and hypokalemia occurred in two. Mild mucositis (two patients) and blue-colored nail-beds (one patient) were also reported. There was alopecia in 10 patients. No treatment-related mortalities occurred.

Table 2. Main adverse effects in our study*

	Grade			
Adverse effect	**1**	**2**	**3**	**4**
Leukopenia	12	6	0	0
Granulocytopenia	6	5	0	0
Anemia	7	6	1	0
Thrombocytopenia	0	0	0	0
Nausea/vomiting	7	1	0	0
Diarrhea	2	1	0	0
SGOT, SGPT↑	1	0	0	0
Alk-P↑	1	1	0	0
Mucositis	2	0	0	0
Hypokalemia	2	0	0	0

Abbreviations:↑, elevated; Alk-P, alkaline phosphatase.

Table 3. Summary of studies on oral etoposide in ovarian carcinoma

Author (year)	Dose	No. of patients	Response rate %	CR	PR	Duration (months)
Markkman (1992)	50 mg/m^2/d× 21	18	6	1	1	11
Garrow (1992)	50 mg/m^2/d×21	17	18	0	3	2, 4, 6
Marzola (1993)	50 mg/m^2/d×21	17	6	0	1	9
Dewit (1994)	50 mg/m^2/d×21	28	16	0	4	4, 4, 7, 10
Hoskin (1994)	100 mg/m^2/d×14	31	26*	1	7	2-9
Kavanagh (1995)	50 mg/m^2/d×21	14	0	0	0	
GOG (1998)	50 mg/m^2/d×21	41	34.1†	6	8	1.3-8.7
		41	26.8*	3	8	1.9-14.4

Abbreviations: CR, complete response; PR, partial response; GOG, Gynecologic Oncology Group.
* Platinum-resistance.
†Platinum-sensitive.

DISCUSSION

Patients who had progression after platinum-based therapy may be offered second-line agents. A variety of second-line agents are available for the treatment of recurrent or persistent ovarian cancer (3).

Numerous factors can influence the response to second-line treatments. Because of selection bias, limited numbers of patients in some studies, and differences in response assessment, it is not possible to directly compare response rates in phase II trials. What is apparent is that there is no clear-cut drug of choice that should be used in patients who have recurrent ovarian cancer. However, cure with chemotherapy for these patients is almost never achieved.

Agents with a favorable therapeutic index are more acceptable to patients, easier to administer and less expensive. Etoposide is a semi-synthetic podophyllotoxin derivative which interacts with the topoisomerase II-DNA complex and causes DNA standard breakage (9). The role of prolonged oral etoposide in cancer therapy is still evolving. Its value in small cell carcinoma of the lung (SCLC) has been well established, with response rates as high as 80% in selected patients (10). The anti-tumor activity of oral etoposide is scheduled and dose dependent with prolonged oral administration. Although responses were initially seen with doses as low as 25 mg/m^2, subsequent studies in both lung and ovarian cancer utilizing daily doses less than 50 mg/m^2 have had poor response rate (11-13). However Yasumiza and Kato reported activity with the prolonged oral etoposide regimen (25 mg/d for 21 days, repeated every 4 weeks) in refractory ovarian cancer with a response rate of 42.8% (14). Our study could be compared with others in the literature (Table 3). Markman *et al.* found one responder out of 18 patients (6% response rate with 11 months duration) treated with oral etoposide (50mg/d for 20 days, every 28 days), the treatment program was generally well tolerated, with mild neutropenia being the most common side effect (12). In another study, a similar etoposide schedule was used in 18 ovarian cancer patients who had previously received cisplatin. Only one partial remission lasting 9 months was observed among 17 eligible patients (15). The investigators concluded that oral etoposide was active in both platinum-resistant and platinum-sensitive disease and warranted further study in combination therapy (15, 16). Garrow *et al.* used 50 mg/m^2/d for 21 days every 4 weeks in 17 women with refractory ovarian cancer and achieved three partial responses; the response rate was 18% (17). The largest study using prolonged oral etoposide in ovarian carcinoma is reported by Rose *et al.* (16). The response rates were 26.8% and 34.1% for platinum resistant and platinum-sensitive patients, respectively. This is similar to the result of a phase II trial of prolonged oral etoposide in platinum-resistant ovarian carcinoma using a dose of 100 mg/m^2/d for 14 days every 3 weeks that reported a response rate of 26%

(18). In other studies, data for truly platinum-resistant patients were not presented separately. So a comparison cannot be made (16, 18). Other trials (15, 17, 19), including our study, had small sample size and are difficult to interpret because they have included a mixture of platinum-sensitive and platinum-resistant patients. These studies and ours had variable patients' populations with many prior chemotherapy regimens (12, 17, 20).

In GOG study, patients who had previously responded to platinum based therapy and who were reinduced with their original regimens were classified as having received only one prior regimen (16). The importance of the extent of prior treatment is evident in the different response rates of second-line versus forth line therapy (33% and 4%) (21). As a significant number of our patients had received many courses of chemotherapy, we chose a reduced starting dose (50 mg/day). A response rate as low as 6% has been reported with oral etoposide at a dose of 50 mg/day in a small group of heavily pretreated patients (13). Such reduced dosing may decrease the plasma etoposide concentration to less than 1 μg/ml and limit the activity of this regimen. An association between the duration of plasma levels ≥ 1 μg/ml and activity has been demonstrated in clinical trials (4, 22). However, oral etoposide has the advantage of home administration. The drug is largely protein bound and myelosuppression has also been related to albumin levels less than 3.5 gr/d, which result in increased free etoposide (23). Patients with abnormal renal or liver function despite a normal serum albumin or of advanced age also have decreased etoposide clearance and increased myelotoxicity (23). Anemia in this regimen is common and appears cumulative. Patients who receive prolonged oral etoposide regimens must have their CBC monitored closely. Common non-hematologic toxicities in our study included nausea, vomiting and alopecia, a finding consistent with previous studies (24, 25).

Although response to second-line chemotherapy is not unusual, responses tend to be brief and long-term survival is rare. Thus, the focus of treatment should aim to optimize quality of life and delaying the development of further symptoms. Oral etoposide has the advantages of easy administration, less expenditure and acceptable response with no severe side effects, but the value of maintenance etoposide without evaluation in a phase III trial is uncertain. This would be difficult to perform because of heterogenicity of the patients and small number of eligible patients. Therefore, clinical trials with etoposide should be continued.

Conflicts of Interests

We have no conflicts of interest.

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