RESEARCH ARTICLE

Oral Etoposide for Platinum-Resistant and Recurrent Epithelial Ovarian Cancer: a Study by the Anatolian Society of Medical Oncology

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Abstract

Background: The aim of this study was to evaluate the efficacy and toxicity of long-term, low-dose oral etoposide as an advanced treatment option in patients with platinum resistant epithelial ovarian cancer. Materials and Methods: For the purposes of this study, 51 patients with histologically-confirmed, recurrent or metastatic platinum-resistant epithelial ovarian cancer (EOC) treated at six different centers between January 2006 and January 2011 were retrospectively evaluated. Patients were treated with oral etoposide (50 mg/day for a cycle of 14 days, repeated every 21 days). Results: Among the 51 platinum-resistant patients, 17.6% demonstrated a partial response and 25.5% a stable response. The median progression-free survival (PFS) was 3.9 months (95% CI, 2.1-5.7), while the median overall survival was 16.4 months (11.8–20.9). No significant relationship was observed between the pre-treatment CA 125 levels, post-treatment CA-125 levels and the treatment response rates (p=0.21). Among the 51 patients who were evaluated in terms of toxicity, grade 1 or 4 hematologic toxicity was observed in 19 (37.3%); and grade 1-4 gastrointestinal toxicity occurred in 15 patients (29.4%). Conclusions: Chronic low-dose oral etoposide treatment is generally effective and well-tolerated in platinum-resistant ovarian cancer patients.

Keywords: Ovarian cancer - oral etoposide - toxicity - PFS

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Introduction

EOC is one of the most common gynecologic malignancies and the fifth most frequent cause of cancer-related deaths in women (Ahmedin et al., 2009). Approximately 70% of the patients present with advanced disease (stage III or IV). In the last decades, a significant improvement in the 5-year survival has been observed; and the survival rate of 36% in 1977 has increased to to a rate of 45% in 2002 (Stephen et al., 2011). This improvement in survival may be the result of more effective chemotherapy options and surgical techniques. The treatment of the condition generally includes a combination of surgery and chemotherapy. Although ovarian cancer is generally sensitive to chemotherapy, patients who are resistant to platinum-based chemotherapy regimens face difficulties in the treatment. The first-line chemotherapy regimens include systemic treatment with paclitaxel and platinum. In the patients with platinum-resistant ovarian cancer; taxane analogues, oral etoposide, pemetrexed and bevacizumab have been observed to be effective on various degrees (Naumann et al., 2011). Ovarian cancer has gradually come to be recognized as a chronic disease which can be treated via multiple and sequential agents.

Oral administration of etoposide provides the most feasible and economic treatment option under outpatient treatment conditions (Toffoli et al., 2004). Etoposide is a cytotoxic agent that inhibits topoisomerase II; and it is an alternative treatment with demonstrated efficacy in platinum-resistant ovarian cancer (Hoskins et al., 1992). Various studies have reported different response rates to the treatment. However, the optimal schedule for the oral administration of etoposide is yet to be determined. In previous studies, the response rates to oral etoposide treatment in patients with platinum-resistant disease were found to be lower than the patients with platinum-sensitive disease (14% vs. 67%, respectively) (Baur et al., 2005).

The CA 125 serum levels are increased in more than 80% of the patients with serous epithelial ovarian cancer. Although it is not a specific diagnostic test (Bast,1985),

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the CA 125 levels provide a way to monitor the treatment response and the progress of the recurrent disease (Rustin et al., 2009).

The present study evaluates the efficacy and toxicity of a prolonged course of chronic low-dose treatment with oral etoposide in advanced-line treatment of 51 patients with platinum resistant ovarian cancer.

Materials and Methods

Eligilibity: For the purposes of this study, 51 patients with histologically-confirmed, recurrent or metastatic platinum-resistant epithelial ovarian cancer treated at six different centers between January 2006 and January 2011 were retrospectively evaluated. All the patients had previously received chemotherapy with paclitaxel and platinum. When the patients had early recurrence of the disease, they were accepted platinum-resistant disease. Platinum-resistant disease was defined as the type of disease in which progression was observed within 6 months as of the completion of platinum-based chemotherapy. Each patient had an Eastern Cooperative Oncology Group (ECOG) performance status (PS) below two and normal hematological, renal and hepatic function tests. Patients had to have a life expectancy of greater than 12 weeks, no other prior malignancy, leukocyte count ≥ 3000/μl, platelet count ≥ 100,000/ μl, and granulocyte count ≥ 1,500/μl; creatinine concentration < 1,3 mg/dL, bilirubin level < 1.5 times the institutional normal, and AST and alkaline phosphatase levels < three times the institutional normal. Informed consent was obtained from all patientss included in this study.

Treatment: In our study, etoposide was administered orally at a total dose of 50 mg for a cycle of 14 days, repeated every 21 days. Third and following lines theraphies were described as advanced line treatment. A complete blood cell count was performed at the beginning of the cycle and therapy was discontinued if the WBC count was less than 3,000/ μl, or the platelet count less than 100,000/ μl, during a treatment course. Treatment was delayed until recovery. Therapy was continued until disease progression or intolerable treatment due of adverse effects.

Response Assessment and Statistical Analysis: Response to therapy was evaluated every cycle if clinically measurable or every two cycles if measured bycomputed tomography. Serologic Response Assessment was performed by Serum cancer antigen 125 level. Serum cancer antigen 125 (CA-125) levels below 35 U/mL were accepted as normal. CA-125 serum analyses were repeated at each cycle and serologic response assessment was performed. The evaluation of the clinical and radiological response and scoring of toxicity were performed according to the RECIST and WHO toxicity criteria (Patrick et al., 2000; WHO., 1979) The Overall response rate was evaluated as complete and partial response rate. Progression free survival (PFS) was designated as the duration from the date of oral etoposide treatment, until the progression or recurrence of the disease or death of the patient. Overall survival (OS) was accepted as the period from the date of oral etoposide treatment until the occurrence of death. The Chi-square test was used for the comparison of the groups. Survival analyses were performed according to the Kaplan-Meier method using two-sided log rank statistics. For serum CA-125 analyses; The variable was investigatedusing Kolmogorov-Simirnov to determine whether or not it is normally distributed. Since serum CA-125 was not normally distributed; nonparametric test (Wilcoxon test) was conducted. The McNemar test was used to compare this proportions between before treatment and after treatment for serum CA-125 values. P-values <0.05 were considered significant.

Results

A total of 51 patients were included in the study. The median age of the patients was 56 years (range: 28-79 years). All the patients had histologically proven epithelial ovarian cancer at stage IV. The median number of the patients using oral etoposide was in fourth line (range: 3-6) chemotherapy; where 47.1% of the patients were in third line chemotherapy and the remaining patients were in fourth- fifth and sixth-line chemotherapy. The median CA 125 value before the initiation of the oral etoposide treatment was 275 U/ml; while this value was 278 U/ml following the treatment. There was no difference between the initial CA-125 values and subsequent CA-125 values (p=0.11). No significant relationship was observed between the pre-treatment CA 125 levels, post-treatment CA-125 levels and the treatment response rates (p=0.21). Peritoneal metastases were present in 29

Table 1. Univariate Analysis of Variables with Influence on Relapse and Characteristics of Patients

Characteristics		N(%)	PFS(Months)	P Value
Age Groups				0.06
	>60	35 (68.6)	2.9	
	<60	16 (31.4)	4.7	
Grade (N=34)				0.34
	Low-Middle	11 (32.3)	2.8	
	High	23 (67.7)	5.9	
Histopathology				0.39
	Serous	46 (90.1)	3.9	
	Non serous	5 (9.9)	4.8	
Metastasis				0.14
	Local	29 (69.0)	4.7	
	Distant	13 (31.0)	2.7	
Line of Therapy				0.2
	≤3	24 (47.0)	4.1	
	>3	27 (53.0)	3.3	
Response to Therapy				<0.001
	Yes	17 (33.3)	7	
	No	34 (66.7)	2.4	

Table 2. Response of the Patients in the Line of Therapy

	Response to therapy Yes n(%)	Response to therapy No n(%)
Third Line	9 (37.5)	15 (62.5)
Fourth Line	3 (42.9)	4 (57.1)
Fifth Line	5 (31.3)	11 (68.7)
Sixth Line	0 (0)	4 (100)

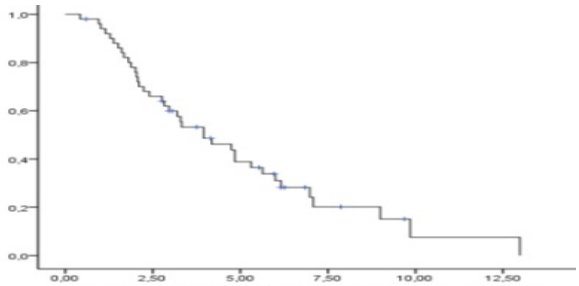

Figure 1. Kaplan-Meier Curve of Progression Free Survival (Months).

patients, while the others had distant metastases. The overall response rate among the 51 platinum-resistant patients was 33.3% (stable response in 15.7% and partial response in 17.6%). Progressive disease was observed in 34 (66.7%) patients. The tumour grade was evaluated in 34 patients and 67% were observed to have high grade (Poorly-differentiated) tumours and 33% of patients were low (Well-differentiated) and middle grade (Moderately-differentiated). Among the patients who responded to the treatment, 72.7% had high-grade tumours (p=0.42). Thus, the PFS rate was better in higher tumour grades. Patient characteristics and treatment response rates are summarized in Table 1-2. The evaluation of the survival results showed that the median PFS was 3.9 months (95% CI, 2.1-5.7). Overall, the median follow-up time was a 16.4 months (11.8–20.9). The median survival rates in the patients below and above the age of 60 was 4.7 and 2.9 months, respectively (p=0.06). Kaplan-Meier Curve of PFS is shown in Figure-1. Grade 1-4 hematologic toxicity was detected in 19 (37.3%) patients. Grade 1-4 gastrointestinal toxicity was observed in 15 (29.4%) patients. No treatment-related deaths occurred.

Discussion

The optimal oral etoposide treatment schedule for the patients with platinum resistant ovarian cancer has not been standardized yet. It is a known fact that the efficacy of etoposide may differ depending on the treatment schedule and a more prolonged administration. Moreover, clinical data have demonstrated that the delivery of etoposide in a multiple-day schedule is distinctly superior compared to a delivery in a single dose every 3–4 weeks (Slevin et al., 1989). Various studies investigating the response to etoposide treatment in platinum-resistant patients describe different response rates of 18%, 20% and 32% (Alici et al., 2003; Garrow et al., 1992; Peter et al., 1998). Also, toxicity rates were between 27.2% and 45.4% in the same studies. Etoposide is effective in recurrent ovarian cancer in terms of acceptable response rates and survival durations, but it has a high rate of toxicity. In the previous studies, an oral dose of 100 mg etoposide was frequently used for 2 to 3 weeks. Interesting side of our study, all the patients were platinum-resistant ovarian cancer and using long-term, chronic low-dose treatment of oral etoposide. In some studies, as also in our study, the preferred oral etoposide dose was 50 mg. In a Phase II study similar to our study, the PFS was found as 5,7 months and the response rate (7.3% complete response and 19.5% partial response rate) was 26.8%; while hematologic toxicity was observed in 41.2% and treatment-related deaths occurred in 3% of the patients (Peter etal., 1998). In certain other studies conducted using a 50 mg dose, the overall response rates were 6% and 16% and the treatment was well tolerated (Maurie et al., 1992; De Wit et al., 1994). In the our present study, the PFS was 3.9 months and the partial response rate was 17.6%. According to the phase II study, we used a lower dose of the etoposide and our study showed a similar effect with the phase II study. The low toxicity rates (37.3%) provided an acceptable treatment advantage in our study. The overall response rate was 17.6% and the higher stable response rate (15.7%) of oral etoposide in our study also presented a significant advantage. In previous studies, especially the early-line treatment response rates were more successful. Thus, treatment with oral etoposide in the earlier stages provides better response rates (Hoskins et al., 1998; Tuxen et al., 1997; Yasumizu et al., 1998). No response to etoposide treatment was observed in the sixth-line therapy in our study; as in the study by Kavanagh et al. where no response could be achieved in fifth line therapy (Kavanagh et al., 1995).

In conclusion, the chronic low-dose oral etoposide regimen is effective in platinum-resistant ovarian carcinoma patients and it is associated with more stable response rates in these patients.

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