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Original Article

Low dose (d1-5/7) oral etoposide regimen in intensively treated platinum-resistant epithelial ovarian cancer: The İzmir oncology group (IZOG) study

Halil Taskaynatan[1], Yuksel Kucukzeybek[2], Yasar Yildiz[2], Tarik Salman[2], Utku Oflazoglu[2], Umut Varol[3], Ahmet Alacacioglu[2], Seray Saray[2], Ozlem Ozdemir[4], Mustafa Oktay Tarhan[5]

[1]Kahramanmaras Necip Fazil City Hospital, Clinic of Medical Oncology, Kahramanmaras, Turkey
[2] Izmir Katip Celebi University, Ataturk Training and Research Hospital, Department of Medical Oncology, Izmir, Turkey
[3]Izmir Demokrasi University, Faculty of Medicine, Department of Medical Oncology, Izmir, Turkey
[4]Izmir Bozyaka Training and Research Hospital, Department of Medical Oncology, Izmir, Turkey
[5]Izmir Dokuz Eylul University, Faculty of Medicine, Department of Medical Oncology, Izmir, Turkey

Abstract

Aim: Oral etoposide dosage is roughly 50-100 mg/m2 on days 1 to 21 every 28 days. However, dosage of 50 mg/day oral etoposide for five days a week is not well published. The present study, aimed to evaluate the efficacy and toxicity profile of low dose oral etoposide regimen (50 mg/day on days 1 to 5 every week) in platinum-resistant epithelial ovarian cancer (EOC).

Material and Methods: This study retrospectively evaluates patients with pathologically confirmed platinum-resistant EOC who were unable to tolerate the standard oral etoposide regimen and were on low dose (d1-5/7) oral etoposide regimen in third line or beyond within the period between 2006 and 2014.

Results: The overall response rate among 33 EOC patients was 15.1% while clinical benefit rate was 42.4% (stable disease in 27.3% and partial response in 15.1%). Median progression-free survival was 4 months (95% confidence interval [CI], 2.8–5.1 months) and median overall survival was 12 months (95% CI, 8.8–15.1 months).

Conclusion: We concluded that low dose oral etoposide (50 mg/day, on days 1 to 5 every week) was effective and well tolerated for platinum-resistant EOC.

Keywords: Epithelial ovarian cancer; oral etoposide; recurrence

INTRODUCTION

The second most prevalent malignancy among gynecologic cancers, ovarian cancer, is the most common cause of gynecologic cancer-related death (1). The most common histological type of ovarian cancer is epithelial carcinoma, among which the serous subtype is the most frequent (2,3). In 2008, approximately 225,000 diagnoses of ovarian cancer and 140,000 ovarian cancer-related death were reported worldwide (4). The fact that the disease is mostly diagnosed in advanced stages contributes to its high mortality rate (5).

Standard first-line treatment regimen for ovarian cancer consists of paclitaxel and carboplatin combination (6). Recurrence is observed in approximately 50% of epithelial ovarian cancer (EOC) cases requiring further chemotherapy (7). So far, there is no optimal standardized treatment strategy for platinum- resistant ovarian cancer. The primary goal of salvage therapy is to maximize disease-free survival, maintain performance status, and improve quality of life by taking chemotherapy toxicities in previous treatments into account (8). Response rates to subsequent chemotherapeutic drugs would be related to effectiveness of drugs, cross-resistance, and platinum sensitivity of tumors. Response rates in platinum-sensitive patients (30-50%) are higher than in platinum-resistant patients (10-30%) (5,9).

The interaction between etoposide and DNA topoisomerase

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Corresponding Author: Halil Taskaynatan, Kahramanmaras Necip Fazil City Hospital, Clinic of Medical Oncology, Kahramanmaras, Turkey **E-mail:** haliltaskaynatan@gmail.com

II causes transient double-strand breaks in DNA. Etoposide stabilizes the DNA topoisomerase II complex, allowing separation of DNA strands and preventing their assembly (10). Inhibition of topoisomerase II is transient and it reverts promptly with decreasing plasma etoposide level (11). Clinical data has clearly shown that daily administration of oral etoposide is superior to single dose administration every three to four weeks (12).

Oral etoposide is administered in various schedules. In previous studies, oral etoposide has been administered 50-75 mg/m2 days 1 to 21 every 28 days (13,14). In platinum-resistant patients receiving standard regimens, response rates are 10-30%; however, grade 3-4 adverse events have been observed in over two-thirds of patients (5,9,15). These patients are expected to be frail usually due to heavy pretreatment and high tumor burden. This study aims to evaluate the efficacy and toxicity profile of low dose oral etoposide regimen (50 mg/day on days 1 to 5 every week) in platinum-resistant EOC intolerant to standard oral etoposide regimen (50-75 mg/m2 on days 1 to 21 every 28 days).

MATERIAL and METHODS

Patients

The medical data of patients admitted to the Medical Oncology Outpatient Clinic of Izmir Ataturk Training and Research Hospital between 2006 and 2014 were retrospectively reviewed. This retrospective study obtained approval by the hospital's local clinical ethics committee. Patients who were ≥18 years of age, with life expectancy of >3 months, without history of other malignancies (except for successfully treated carcinoma in situ of the cervix or basal cell and squamous cell carcinoma), with ECOG (Eastern Cooperative Oncology Group) performance status of ≤2, and adequate hematological, renal, and hepatic function tests were included in the study. Patients who received a standard oral etoposide regimen more than one cycle were excluded. Patients who received a treatment other than the low dose oral etoposide schedule were also excluded. Recurrence of disease documented within six months of platinum-containing therapy is defined as platinum-resistant disease. Accordingly, patients with pathologically-confirmed platinum-resistant EOC who were on low dose oral etoposide in third-line and subsequent therapies were included in the study.

Treatment Plan and Clinical Response Assessment

Standard regimen was planned in all patients. Patients with intolerance to the standard treatment were switched to low dose oral etoposide regimen. Its dose was 50 mg/day for five days every week. Physical examination, serum chemistry analysis, and complete blood count analyses were performed every three weeks. Radiologic assessment was performed at baseline and repeated after two or three months using the same methodology. Tumor size reduction of 30% or more was considered partial response, while lack of clinical evidence after chemotherapy was considered complete response. Tumor with no change or 30% decrease or 20% increase in size was considered stable disease. Increase in tumor size of >20% or new lesion development was considered progressive disease (16,17).

Adverse Events and Survival Assessment

Hematologic and non-hematologic toxicities were evaluated using the Common Terminology Criteria for Adverse Events (CTCAE) version 4.0. Overall survival (OS) was determined as the time period from the initial low dose oral etoposide regimen until death (death for any reason) or the date of analysis. Progression-free survival (PFS) was considered as the time period from the initial low dose oral etoposide regimen until the start of disease progression or the last follow-up visit.

Statistical analysis

IBM SPSS Statistics (IBM Corp. Armonk, NY, USA) for Windows, version 20.0 was used for data analysis. Continuous variables were expressed as mean and standard deviation while categorical variables were expressed as number and percentages. Kaplan-Meier method was used to estimate survival curves and rates. P≤0.05 was considered statistically significant.

RESULTS

In total, 33 patients with EOC were included in this study. Median patient age was 56 (32-76) years. General patient characteristics are presented in Table 1. The most common histologic subtype was serous adenocarcinoma (75.7%) and FIGO (International Federation of Gynecology and Obstetrics) stage IIIC disease was detected at diagnosis in almost half of the patients (48.5%). All patients received at least two lines of chemotherapy before oral etoposide administration and most of the patients (66.7%) received four or five lines of chemotherapy.

Of the patients, 93.9% developed adverse events (AE) of any grade; grade 3 neutropenia and nausea developed in one patient (3%). Grade 4 or higher AEs were not detected in any of the patients. The most common AEs were anemia (84.9%) and neutropenia (60.6%). AEs related to treatment are presented in Table 2.

The overall response rate (RR) among 33 patients with EOC was 15.1% and the clinical benefit rate was 42.4% (stable disease in 27.3% and partial response in 15.1%). Progressive disease was observed in 19 (57.6%) patients. Complete response was not observed in any of our patients. Response rates to oral etoposide treatment are presented in Table 3.

Median PFS was four months (95% confidence interval [CI], 2.8–5.1 months) and median OS was 12 months (95% CI, 8.8–15.1 months). Median follow-up time was 49 (10-144) months. The Kaplan-Meier survival curves for PFS and OS are presented in Figure 1 and Figure 2, respectively.

Table 1. Baseline patient characteristics

Characteristics	Patients with EOC (N=33)
Age, years, median (range)	56 (32-76)
Histopathology, n (%)	
Serous carcinoma	25 (75.7)
Endometrioid carcinoma	2 (6.1)
Clear cell carcinoma	1 (3.0)
Mixed type carcinoma	5 (15.1)
ECOG, n (%)	
0	7 (21.2)
1	15 (45.5)
2	11 (33.3)
FIGO stage at diagnosis, n (%)	
Stage IIA	1 (3)
Stage IIIA	4 (12.1)
Stage IIIB	2 (6.1)
Stage IIIC	16 (48.5)
Stage IV	10 (30.3)
Tumor grade, n (%)	
Well differentiated	4 (12.1)
Moderately differentiated	8 (24.2)
Poorly differentiated	21 (63.6)
Previous lines of chemotherapy, n (%)	
2-3	6 (18.2)
4-5	22 (66.7)
6-7	5 (15.1)

EOC, epithelial ovarian cancer; ECOG, Eastern Cooperative Oncology Group; FIGO, International Federation of Gynecology and Obstetrics

Table 2. Treatment-related adverse events

	Grade 1	Grade 2	Grade 3
Hematologic AEs, n (%)			
Neutropenia	14 (42.4)	5 (15.2)	1 (3)
Anemia	15 (45.5)	13 (39.4)	
Thrombocytopenia	5 (15.2)		
Non-hematologic AEs			
Fatigue	6 (18.2)	8 (24.2)	
Stomatitis	4 (12.2)	2 (6.1)	
Nausea	6 (18.2)	2 (6.1)	1 (3)
Vomiting	4 (12.2)	1 (3)	

AEs, Adverse events

Table 3. Treatment response rates to oral etoposide

	Patients with EOC (n=33) n (%)
CR	-
PR	5 (15.1)
SD	9 (27.3)
PD	19 (57.6)

EOC, epithelial ovarian cancer, CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease

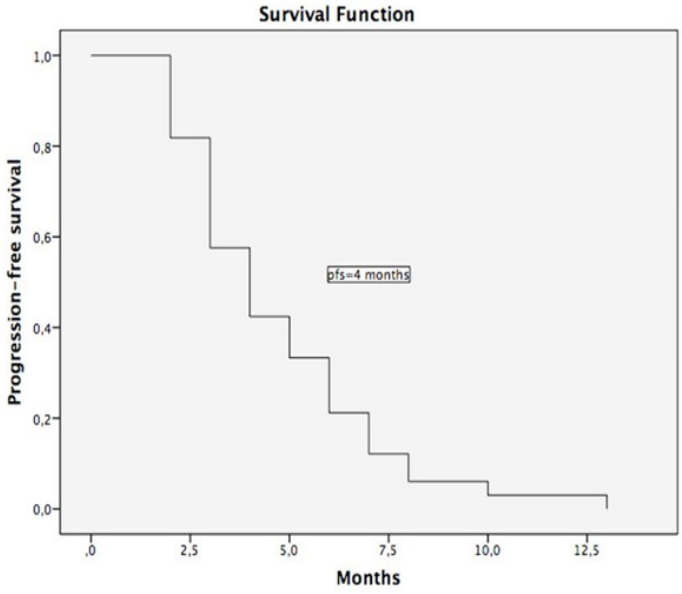

Figure 1. Kaplan-Meier curve for progression-free survival (PFS) in all patients

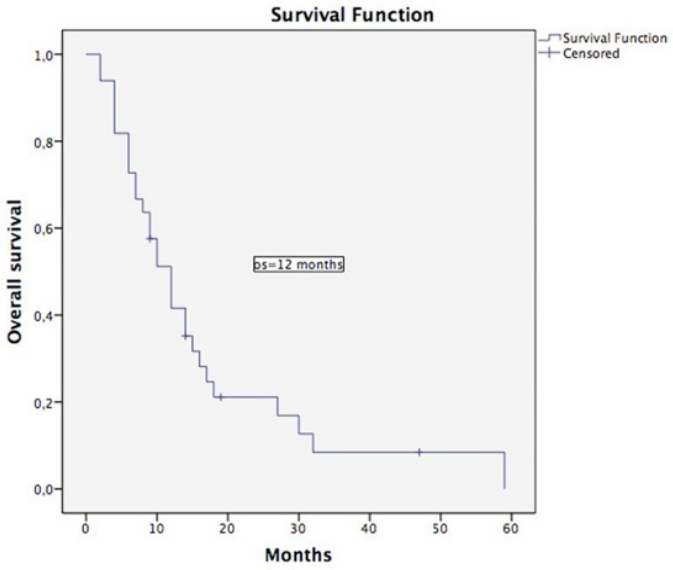

Figure 2. Kaplan-Meier curve for overall survival (OS) in all patients.

DISCUSSION

Optimal treatment schedule for oral etoposide in platinum-resistant EOC has not yet been standardized. Clinical studies have shown that etoposide administration within a multiple day regimen is superior to single dose once every three-four weeks (12). This study, to the best of our knowledge, is the first to evaluate oral etoposide 50 mg/day for five days/week dose regimen for EOC. Median PFS with this regimen was four months and median OS was 12 months, while overall RR was 15.1%. The efficacy outcomes of the present study were comparable to previously reported data (15,18,19).

Based on the data collected from nine different studies, the overall RR to oral etoposide was reported as 20.4% in more than 270 patients with recurrent ovarian cancer (20). According to the largest study conducted by the Gynecologic Oncology Group (GOG) aimed at determining long-term oral etoposide activity, 99 ovarian carcinoma patients were administered oral etoposide at dosage of 50 mg/m2 for 21 days every 28 days (21). Of these ovarian carcinoma patients, 82 were assessable for response, in which 41 were platinum-resistant and 41 were platinum-sensitive. In the platinum-resistant group, overall RR, median PFS, and median OS were reported as 26.8%, 5.9 months, and 10.8 months, respectively (21). As compared with the results of the present study, the overall RR was higher, while median PFS and OS were similar to the GOG study despite the fact that oral etoposide was administered as third-line or beyond (up to six prior regimens) in the current study, whereas patients with more than one previous regimen were excluded from the GOG study and thus patients received long-term oral etoposide solely as second-line therapy (21).

In a study conducted by Thavaramara et al. (22), 38 patients with recurrent/refractory EOC were administered oral etoposide at 75 mg/day dose for 21 days every 28 days. Moosavi et al. (19) evaluated 12 patients with recurrent ovarian cancer who received oral etoposide at 50 mg/day dose for 21 days at four-week intervals. Both studies had similar results to our study regarding objective RR, clinical benefit rate, and OS. In our study, the patients underwent multi-line therapy prior to etoposide and used relatively low doses of etoposide compared with the other studies. Etoposide dosage regimen, response rates, and toxicity data of the studies involving patients with metastatic ovarian cancer who received oral etoposide and those of the current study are shown in Table 4.

Table 4. Studies investigating oral etoposide in ovarian carcinoma in the literature

Author (year)	Dose	Patients (N)	Line of etoposide therapy	RR (%)	CBR (%)	Grade 3-4 Toxicity (%)
Hoskins et al.(1994)[18]	100 mg/day 14 days q[3] weeks	31	Second-line	26	39	6.1*
Kavanagh et al. (1995)[15]	50 mg/m2 21 days q[4] weeks	14	Multi-line	0	23	6[9]**
Rose et al. (1998), the GOG study[21]	50 mg/m2 21 days q[4] weeks	82	Second-line	26.8[x] 34.1[y]	Not achieved	45.4**
Moosavi et al. (2004)[19]	50 mg/day 21 days q[4] weeks	12	Multi-line	20	Not achieved	Not achieved
Thavaramara et al. (2009)[22]	75 mg/day 21 days q[4] weeks	38	Multi-line	25.8	45.2	28.9***
Bozkaya et al.(2017)[23]	50 mg/day 14 days q[3] weeks	52	Multi-line	19.2	40.4	13.4
Current study	50 mg/day 5 days q[1] week	33	Multi-line	15.1	42.4	6

RR, response rate (complete response+partial response); CBR, clinical beneficial rate (complete response+partialresponse+stable response); q, quaque (every).
[x]Platinum-resistant; yplatinum sensitive.
*Grade 3-4 leukopenia; **grade 3-4 neutropenia; ***grade3-4 hematologic toxicity

Oral etoposide may cause gastrointestinal and hematologic AEs. In the present study, neutropenia (3%) and nausea (3%) were to most prevalent grade 3 AEs and none of the patients experienced grade 4 AE. In the study conducted by the GOG (21), grade 3-4 gastrointestinal AEs and neutropenia were encountered in 15.4% and 45.4% of the patients respectively, and three treatment-related deaths occurred. In the study by Thavaramara et al., Grade 3 and 4 hematologic toxicities occurred in 11 patients (28.9%) (22). Lower rates of toxicity observed in the present study compared with the results of other studies may be due to using lower dose of etoposide and two days of rest after every five days of administration.

There are a number of limitations in the present study. This is a retrospective study and therefore prone to common biases associated with similar studies. Toxicity may be

overlooked by retrospective evaluation. In addition, the study included a small number of patients; this limited the statistical power.

CONCLUSION

In conclusion, oral etoposide at dose of 50 mg/day for five days/week was considered an active agent for platinum-resistant EOC. Overall RR, clinical benefit, PFS, and OS of the treatment were comparable to other chemotherapies for EOC. Serious side effects were very rare, especially at 50 mg/day dose. This low dose (d1-5/7) regimen should be considered particularly in heavily pretreated fragile patients who cannot tolerate standard oral etoposide regimen.

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Halil Taskaynatan ORCID: 0000-0002-3671-6540
Yuksel Kucukzeybek ORCID: 000-0003-3173-7999
Yasar Yildiz ORCID: 0000-0002-2912-3835
Tarik Salman ORCID: 0000-0001-7911-6978
Utku Oflazoglu ORCID: 0000-0002-6819-5831
Umut Varol ORCID: 0000-0002-4669-2052
Ahmet Alacacioglu ORCID: 0000-0003-3428-5932
Seray Saray ORCID: 0000-0001-5916-6265
Ozlem Ozdemir ORCID: 0000-0002-3897-3890
Mustafa Oktay Tarhan ORCID: 0000-0002-1380-9736

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