JBUON 2014; 19(4): 980-984
ISSN: 1107-0625, online ISSN: 2241-6293 • www.jbuon.com
E-mail: editorial_office@jbuon.com

ORIGINAL ARTICLE

Prolonged progression-free survival with maintenance metronomic oral cyclophosphamide and etoposide treatment in macroscopic residual disease or recurrent/advanced stage ovarian cancer

Mukremin Uysal[1], Mustafa Ozdogan[2], Aysegul Kargi[2], Seyda Gunduz[3], Sema Sezgin Goksu[3], Ali Murat Tatli[3], Deniz Arslan[3], Hasan Mutlu[3], Hasan Senol Coskun[3], Hakan Bozcuk[3]

[1]Afyon Kocatepe University Faculty of Medicine, Department of Medical Oncology, Afyon; [2]Medstar Hospital, Antalya; [3]Akdeniz University Faculty of Medicine, Department of Medical Oncology, Antalya, Turkey

Summary

Purpose: *In ovarian cancer permanent remission may be provided with optimal cytoreductive surgery and adjuvant chemotherapy. However survival is short in patients with residual macroscopic disease after surgery or recurrent ovarian cancer. Applicable maintenance therapies with low toxicity are required to prolong progression-free survival (PFS) for patients with no curative treatment options. In this study, we investigated the effect of maintenance metronomic oral cyclophosphamide and etoposide (CE) in ovarian cancer patients with post operative residual or recurrent disease.*

Methods: *Forty five patients that received metronomic oral CE (cyclophosphamide 50 mg/daily and etoposide 50 mg for 1-5 days, every 21 days) as maintenance therapy for residual disease due to incomplete surgical resection or recurrent advanced-stage ovarian cancer were evaluated. The time between the beginning of oral CE and disease progression was also evaluated.*

Results: *The mean patient age was 58 years, the vast majority had serous adenocarcinoma (78%) and received a mean of 2 (range 1-4) lines of various intravenous regimens for postoperative residual or recurrent disease. Mean duration of oral CE was 11.3 months (range 2.9-29). Median PFS was 10.3 months (range 7.9-12.8). Only 5 patients discontinued treatment due to intolerance and grade 3-4 toxicity was recorded in 3 patients (7%).*

Conclusion: *Maintenance metronomic oral CE treatment was found effective, minimally toxic and sustainable in patients with macroscopic residual or recurrent advanced-stage ovarian cancer. However, randomized and placebo-controlled well designed studies are required.*

Key words: *cyclophosphamide, etoposide, maintenance therapy, metronomic oral therapy, ovarian cancer*

Introduction

Ovarian cancer is the most lethal malignancy among all gynecologic cancers, because it usually does not show symptoms until it reaches advanced stages. Complete clinical remission of about 75% may be obtained with cytoreductive surgery and 6 courses platin-based chemotherapy [1]. However, relapse develops in the majority of these patients who may die within 5 years. According to the report of International Gynecology and Obstetrics Federation (FIGO), 5-year survival rate is 46.7% for stage IIIa, 41.5% for stage IIIb, 32.5% for stage IIIc and 18.6% for stage IV disease [2]. Permanent remission may be achieved in only 1-15% of stage III or IV patients [3]. Most of the patients with macroscopic residual disease or recurrence are incurable. The aim of treatment in these patients is the management of related symptoms, avoid treatment-related toxicity, improve quality of life

Correspondence to: Mukremin Uysal, MD. Afyon Kocatepe University Faculty of Medicine, Department of Medical Oncology, Izmir Karayolu 8.km, 03200, Afyon, Turkey. Tel: +90 2722463322, Fax: +90 272 2462707, E-mail: mukreminuysal@yahoo.com
Received: 17/05/2014; Accepted: 07/06/2014

and prolong survival. Therefore, maintenance therapy is a wise and reasonable way to delay progression in ovarian cancer patients. The main purpose of maintenance therapy is to prolong stable disease status using less toxic anticancer drugs, thereby delaying or preventing symptoms that may arise from recurrent disease. A satisfactory clinical benefit could not be shown in maintenance treatments done with the use of highly toxic drugs and an applicable treatment regimen could not be obtained due to toxicity and technical difficulties. No significant clinical benefit was demonstrated in studies done with the use of paclitaxel, topotecan, platins, and doxorubicin [4-10]. In maintenance therapy, not only anticancer efficacy but also the patient quality of life should be considered. Therefore, selecting oral agents may be more rational in maintenance therapy. Metronomic oral cyclophosphamide and etoposide (CE) is a good treatment option. According to NCCN Practice Guidelines of Oncology, oral etoposide is recommended in platin-resistant recurrent ovarian cancer [11]. In previous studies, an overall response rate of 16-26.8%, median response duration 4.3-8.7 months and approximately 11 months overall survival (OS) time were obtained with oral etoposide therapy in recurrent ovarian cancer [12-14]. Cyclophosphamide is an effective alkylating agent used for a very long time both for solid organ cancers and hematologic malignancies. Previous studies showed that the use of oral cyclophosphamide was effective and feasible in ovarian cancer patients treated with a multi-agent therapy regimen [15,16]. This treatment was also shown to be effective and feasible in a study done with metronomic oral cyclophosphamide and etoposide for breast cancer treated with multi-agent treatment regimen [17]. Herein, we evaluated the results of maintenance metronomic oral CE in advanced-stage ovarian cancer patients who had macroscopic residual disease due to incomplete primary surgical resection and in patients with recurrent ovarian cancer who had received multiple lines of chemotherapeutic regimens.

Methods

Patients with advanced stage-epithelial ovarian cancer who had residual or recurrent disease and received maintenance metronomic treatment between September 2009 and June 2013 were included in this retrospective study. The groups of patients who had received maintenance therapy were composed of (1): patients with advanced-stage epithelial ovarian cancer, those that had undergone incomplete surgical resection and had macroscopic residual disease, those that had responded well to first line paclitaxel/platin treatment, those that had not undergone second look operation; and (2): patients with advanced-stage epithelial ovarian cancer whose primary surgical cytoreduction was optimal, those with cancer recurrence after first-line paclitaxel/platin treatment (patients with platinum-sensitive recurrence after optimal debulking had received one or more lines of salvage i.v. chemotherapy prior to CE oral treatment). Among these patients, those who had complete or near-complete response to chemotherapy, and were administered oral CE for maintenance therapy were included in the study. These patients received oral cyclophosphamide 50 mg/daily and oral etoposide 50 mg/daily for 1-5 days every 21 days. Patients who had severe comorbidities were excluded from the study.

The primary endpoint of this study was PFS. The duration of PFS was defined as the time from oral CE treatment initiation to objective tumor progression. Drug compliance, side effects and tumor progression were assessed at each visit. Elevated CA125 level with positive imaging studies were characterized as tumor progression. OS rate was not calculated as the patients received several therapies after progression.

Statistics

Statistical analyses were performed using the SPSS software (SPSS 11.0 for Windows, SPSS Inc, Chicago, Ill, USA). Factors that could affect PFS of ovarian cancer patients were investigated. PFS was analysed using Kaplan-Meier method with log rank test. A 5% type-I error level was used to infer statistical significance which was set at $p<0.05$.

Results

A total of 45 patients with advanced-stage ovarian cancer who received oral CE as maintenance therapy were evaluated. The characteristics of the patients are shown in Table 1. The mean age of the patients was 58 years (range 38-80). ECOG performance status was 1-2, the incidence of comorbidities was 16% and 78% of the patients had serous adenocarcinoma. While surgery could not be performed or incompletely performed in 2 patients, the remainder relapsed > 6 months (range of time to relapse: 6-61 months; median time from last chemotherapy to relapse 16 months); re-operation was not possible. Information concerning oral CE therapy is shown in Table 2. The patients who were administered oral CE usually had achieved complete or near-complete (82%) or partial (18%) responses to previous therapies and had received a mean of 2 (range 1-4) lines of various parenteral chemotherapy regimens. The mean

Table 1. Demographic characteristics

Characteristics	*N*	*%*
Age, years		
Mean	58	
Min - Max	38-80	
Histologic subtype		
Serous	35	77.8
Endometroid	7	15.6
Clear cell	1	2.2
Choriocarcinoma	1	2.2
Unidentified	1	2.2
Co morbidity		
Yes	7	15.5
No	38	84.4
ECOG PS		
1	35	77.8
2	10	22.2
Operation performed		
Yes	33	73.3
No, or incomplete	12	26.7

ECOG PS: Eastern Cooperative Oncology Group Performance Status

Table 2. Data about oral cyclophosphamide and etoposide treatment

	N	*%*
Number of chemotherapy lines received before oral CE		
Median	2	
Min-Max	1-4	
Response to the regimen before oral CE		
Complete, near-complete response	37	82.2
Partial response	8	17.8
Duration of oral CE use (months)		
Mean	11.3	
Min - Max	2.9-29	
Reason for oral CE discontinuation		
Progression	29	74.4
Intolerance, toxicity	5	12.8
Patient's desire	5	12.8

CE: cyclophosphamide/etoposide

duration of oral CE use was 11.3 months (range 2.9-29). While the cause for discontinuation of oral CE was usually disease progression (74%), 5 patients discontinued due to intolerance.

The therapeutic results are shown in Table 3. Tolerance to oral CE according to these results was good and grade 3-4 toxicity was seen in only 3 (7%) patients. Disease progression was recorded in 35 patients during a 24-month follow up, while

Table 3. Treatment results

Results	*N*	*%*
Hematologic toxicity		
Grade 1-2	12	26.7
Grade 3-4	3	6.7
Current status		
Dead	21	46.7
Alive with progression	14	31.1
Alive, no progression	10	22.2
Median time to progression (months)	10.3 (range 7.9-12.8)	

Table 4. Factors affecting progression-free survival

	Median PFS (months)	*p value*
Comorbidity		
No	11.9	0.64
Yes	9.9	
Initial operation		
Optimal surgery	13.9	0.37
No or incomplete surgery	8.1	
Number of chemotherapy lines received before oral CE		
≤2	11.7	0.57
>2	8.9	
Response to pre-oral CE regimen		
Complete, near-complete response	10.9	0.09
Partial response	4.6	

PFS: progression free survival, CE: cyclophosphamide/etoposide

10 patients still continued treatment.

Median PFS was 10.3 months (range 7.9-12.8) (Figure 1). When factors affecting PFS were analysed, no statistically significant difference was found between patients in terms of comorbidity, surgery (whether surgery was optimal or resulted in residual disease), response to previous therapies, or chemotherapy lines received before oral CE (Table 4). However, PFS was better (but statistically not significant) in patients without comorbidities vs those with comorbidities (11.9 vs 9.9 months, p=0.37), in patients whose initial surgery was optimal vs those with incomplete or being inoperable (13.9 vs 8.1 months, p=0.37), in patients who received ≤ 2 lines of i.v. chemotherapy before oral CE vs those with > 2 lines of i.v. chemotherapy (11.7 vs 8.9 months, p=0.57), and in patients in whom complete or near-complete response was obtained before oral CE (10.9 vs 4.6 months, p=0.09).

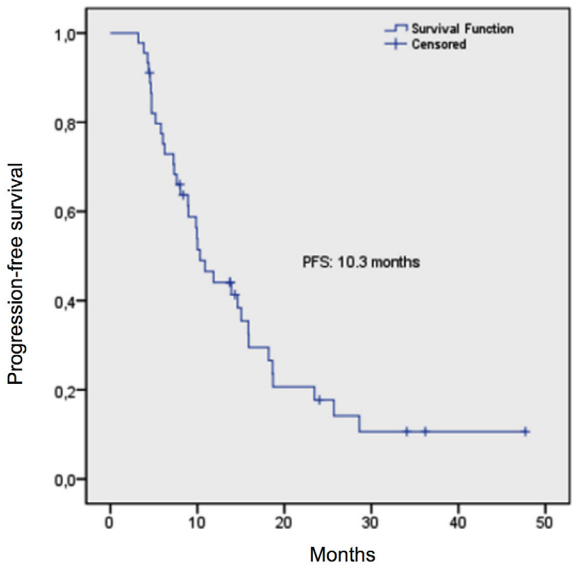

Figure 1. Progression-free survival.

Discussion

Our study included patients who had macroscopic residual disease due to incomplete surgical resection or recurrent advanced-stage ovarian cancer and had received multiple treatments. These patients were incurable and received palliative chemotherapy. Maintenance metronomic oral CE palliative treatment was shown to prolong PFS in this group of patients. Moreover, the metronomic oral CE treatment was well tolerated without severe toxicity, and compliance problems were not experienced by the patients.

Maintaining the adjuvant therapy for 6-12 cycles with the same or other parenteral cytotoxic drug has not been accepted for the treatment of stage III or IV ovarian cancer patients who had achieved maximum cytoreduction [4-9]. Median PFS may reach 18-30 months even if no maintenance therapies are given to these patients, and can result even to cure. On the other hand, median PFS is much shorter in recurrent and advanced-stage ovarian cancer or in patients with macroscopic residual disease due to incomplete surgical resection (mean 8 months/range 4-17, in platin-sensitive groups, and mean 5.4 months/range 1-28 in platin-resistant groups) and permanent remission rate is quite low [18-21].

The main purpose of offering therapy to these patients is to prolong PFS. Therefore, maintenance therapy may be more rational in patients who have macroscopic residual disease due to incomplete surgical resection or recurrent disease. In our study, maintenance therapy was not given as adjuvant chemotherapy in ovarian cancer with maximal cytoreduction, but was given to patients with no prospects for curative treatment, who had macroscopic residual disease, incomplete surgical resection or who relapsed after the first adjuvant therapy.

Although the difference in the expected PFS remained low, maintenance therapies with targeted agents are more favorable in recurrent ovarian cancer due to acceptable toxicity. However, there are no randomized trials comparing targeted agents with cytotoxic chemotherapy; usually, targeted therapies are compared with placebo. In these studies, like bevacizumab vs placebo [22] and abagovomab vs placebo [23] survival was better (approximately 14 months) with maintenance therapies given after the first remission or after adjuvant therapy [22-25]. Yet, the expected PFS is low in recurrent ovarian cancer, when maintenance targeting therapies are given after palliative therapies (less than 9 months) [26]. In addition, this approach is not easily feasible as the cost of the targeted agents is very high, and maintenance is difficult due to fatigue and asthenia accompanying intravenous chemotherapeutic regimens.

On the contrary, metronomic oral CE maintenance therapy is a feasible treatment option due to its low cost, less toxicity and oral administration route. In our study, median PFS was prolonged by 10.3 months in recurrent ovarian cancer patients who had macroscopic residual disease or received multiple therapies. Therefore, metronomic oral CE maintenance therapy may be considered for patients that are chemosensitive and bear high risk of recurrence, and those with residual and recurrent disease. Nevertheless, we cannot ascertain this finding due to the several study limitations among which is its retrospective nature, precluding thus randomization and a placebo patient control group along with standardized patient selection. Only patients who had macroscopic residual disease or received multiple therapies were included in the study. The small number of the patients is also one of the study limitations. Therefore, randomized, placebo-controlled, prospective studies are required in order to verify the effectiveness of maintenance metronomic oral CE treatment in patients with recurrent or macroscopic residual disease and with no chance of curative treatment.

In conclusion, maintenance palliative metronomic oral CE treatment was shown to prolong PFS in patients with recurrent ovarian cancer or macroscopic residual disease due to incomplete surgical resection and with no chance of curative treatment options. Well designated randomized trials that will also include quality of life assessment are required to enlighten this issue.

References

1. Ozols RF. Challenges for chemotherapy in ovarian cancer. Ann Oncol 2006;17 (Suppl 5):v181-187.
2. Heintz AP, Odicino F, Maisonneuve P et al. Carcinoma of the ovary. FIGO 26th Annual Report on the Results of Treatment in Gynecological Cancer. Int J Gynaecol Obst:2006;95 (Suppl 1):S161-192.
3. Herzog TJ. Recurrent ovarian cancer: how important is it to treat to disease progression? Clin Cancer Res 2004;10:7439-7449.
4. Piccart MJ, Bertelsen K, James K et al. Randomized intergroup trial of cisplatin-paclitaxel versus cisplatin-cyclophosphamide in women with advanced epithelial ovarian cancer: three-year results. J Natl Cancer Inst 2000;92:699-708.
5. Nicoletto MO, Tumolo S, Falci C et al. A Randomized Study of Epithelial Ovarian Cancer: Is Chemotherapy Useful after Complete Remission? Int J Med Sci 2004;1:116-125.
6. De Placido S, Scambia G, Di Vagno G et al. Topotecan compared with no therapy after response to surgery and carboplatin/paclitaxel in patients with ovarian cancer: Multicenter Italian Trials in Ovarian Cancer (MITO-1) randomized study. J Clin Oncol 2004;22:2635-2642.
7. Bolis G, Danese S, Tateo S et al. Epidoxorubicin versus no treatment as consolidation therapy in advanced ovarian cancer: Int J Gynecol Cancer 2006;16 (Suppl 1):74-78.
8. Pecorelli S, Favalli G, Gadducci A et al. Phase III trial of observation versus six courses of paclitaxel in patients with advanced epithelial ovarian cancer in complete response after six courses of paclitaxel/platinum-based chemotherapy: final results of the After-6 protocol 1. J Clin Oncol 2009;27:4642-4648.
9. Mannel RS, Brady MF, Kohn EC et al. A randomized phase III trial of IV carboplatin and paclitaxel x 3 courses followed by observation versus weekly maintenance low-dose paclitaxel in patients with early-stage ovarian carcinoma: a Gynecologic Oncology Group Study. Gynecol Oncol 2011;122:89-94.
10. Mei L, Chen H, Wei DM et al. Maintenance chemotherapy for ovarian cancer. The Cochrane database of systematic reviews. 2013;6:Cd007414.
11. NCCN Clinical Practice Guidelines in Oncology: Ovarian cancer. V.2.2013. http://www.nccn.org/professionals/physician_gls/pdf/ovarian.pdf. Accessed January 25, 2014.
12. Rose PG, Blessing JA, Mayer AR, Homesley HD. Prolonged oral etoposide as second-line therapy for platinum-resistant and platinum-sensitive ovarian carcinoma: a Gynecologic Oncology Group study. J Clin Oncol 1998;16:405-410.
13. Alici S, Saip P, Eralp Y, Aydiner A, Topuz E. Oral etoposide (VP16) in platinum-resistant epithelial ovarian cancer (EOC). Am J Clin Oncol 2003;26:358-362.
14. Kucukoner M, Isikdogan A, Yaman S et al. Oral etoposide for platinum-resistant and recurrent epithelial ovarian cancer: a study by the Anatolian Society of Medical Oncology. Asian Pacific J Clin Oncol 2012;13:3973-3976.
15. Watanabe Y, Etoh T, Koike E, Mizuno Y, Wang WM, Hoshiai H. Feasibility study of oral cyclophosphamide salvage therapy for the treatment of heavily pretreated patients with recurrent epithelial ovarian cancer. Int J Clin Oncol 2010;15:468-471.
16. Handolias D, Quinn M, Foo S, et al. Oral cyclophosphamide in recurrent ovarian cancer. Asian Pacific J Clin Oncol 2013,doi10.1111/ajco.12074.
17. Mutlu Hasan BH, Ozdogan Mustafa, Artac M et al. Impressive survival data with semimetronomic oral chemotherapy with old agents in heavily treated metastatic breast cancer patients. J Clin Oncol 2009;27:15s,1082 (abstr).
18. Zanotti KM, Belinson JL, Kennedy AW, Webster KD, Markman M. Treatment of relapsed carcinoma of the ovary with single-agent paclitaxel following exposure to paclitaxel and platinum employed as initial therapy. Gynecol Oncol 2000;79:211-215.
19. Parmar MK, Ledermann JA, Colombo N et al. Paclitaxel plus platinum-based chemotherapy versus conventional platinum-based chemotherapy in women with relapsed ovarian cancer: the ICON4/AGO-OVAR-2.2 trial. Lancet 2003;361:2099-2106.
20. Pfisterer J, Plante M, Vergote I et al. Gemcitabine plus carboplatin compared with carboplatin in patients with platinum-sensitive recurrent ovarian cancer: an intergroup trial of the AGO-OVAR, the NCIC CTG, and the EORTC GCG. J Clin Oncol 2006;24:4699-4707.
21. Vergote I, Finkler N, del Campo J et al. Phase 3 randomised study of canfosfamide (Telcyta®, TLK286) versus pegylated liposomal doxorubicin or topotecan as third-line therapy in patients with platinum-refractory or -resistant ovarian cancer. Eur J Cancer 2009;45:2324-2332.
22. Burger RA, Brady MF, Bookman MA et al. Incorporation of bevacizumab in the primary treatment of ovarian cancer. N Engl J Med 2011;365:2473-2483.
23. Sabbatini P, Harter P, Scambia G et al. Abagovomab as maintenance therapy in patients with epithelial ovarian cancer: a phase III trial of the AGO OVAR, COGI, GINECO, and GEICO--the MIMOSA study. J Clin Oncol 2013;31:1554-1561.
24. Du Bois AF, Jae Weon Kim, Rau J et al. Randomized, double-blind, phase III trial of pazopanib versus placebo in women who have not progressed after first-line chemotherapy for advanced epithelial ovarian, fallopian tube, or primary peritoneal cancer (AEOC): Results of an international Intergroup trial (AGO-OVAR16). J Clin Oncol 2013; 49 ASCO meet, LBA 5503 (abstr).
25. Vergote IB, Jimeno A, Joly F et al. Randomized Phase III Study of Erlotinib Versus Observation in Patients With No Evidence of Disease Progression After First-Line Platin-Based Chemotherapy for Ovarian Carcinoma: A European Organisation for Research and Treatment of Cancer-Gynaecological Cancer Group, and Gynecologic Cancer Intergroup Study. J Clin Oncol 2014;32:320-326.
26. Ledermann J, Harter P, Gourley C et al. Olaparib maintenance therapy in platinum-sensitive relapsed ovarian cancer. N Engl J Med 2012;366:1382-1392.