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ORIGINAL ARTICLE

Bevacizumab in recurrent ovarian cancer

Mehmet Sait Bakir[1], Ozer Birge[2], Ceyda Karadag[3], Yusuf Ilhan[4], Hasan Aykut Tuncer[5], Sema Sezgin Göksu[6], Tayup Simsek[7]

[1]Akdeniz University, Department of Obstetrics and Gynecology, Division of Gynecologic Oncology. Antalya, Turkey. [2]Akdeniz University, Department of Obstetrics and Gynecology, Division of Gynecologic Oncology. Antalya, Turkey. [3]Akdeniz University, Department of Obstetrics and Gynecology, Division of Gynecologic Oncology. Antalya, Turkey. [4]Akdeniz University, Department of Medical Oncology. Antalya, Turkey. [5]Akdeniz University, Department of Obstetrics and Gynecology, Division of Gynecologic Oncology. Antalya, Turkey. [6]Akdeniz University, Department of Medical Oncology. Antalya, Turkey. [7]Akdeniz University, Department of Gynecology Obstetrics, Division of Gynecologic Oncology. Antalya, Turkey.

Summary

Purpose: *The cost-effectiveness of bevacizumab has been the subject of debate, and we aimed to present our own retrospective data on its effect on survival in recurrent epithelial ovarian cancer.*

Methods: *Patients with recurrent ovarian, tubal and primary peritoneal cancer between October 2007 and June 2018 were grouped according to the platinum-free interval. The progression-free and overall survivals of the patients who had received chemotherapy only and chemotherapy with bevacizumab were calculated.*

Results: *Eighty patients had received chemotherapy (CT) only, and 65 had received CT+BV. In platinum-sensitive recurrent epithelial ovarian cancer (PSREOC) patients, the median progression-free survival (PFS) months was 7 months (95% CI; 5.5-8.4) in the group who had received CT only and 13 months (95% CI; 5.8-20.1) in the group who had received CT+BV (p=0.001) and for CT+BV HR (Hazard Ratio):0.39 (95% CI; 0.24-0.64) (p=0.001). The median PFS of platinum-resistant recurrent epithelial ovarian cancer (PRREOC) patients who had received CT only was determined as 2 (95% CI; 1.4-2.5) and as 10 (95% CI; 6.8-13.1) months for patients who had received CT+BV (p=0.001), for patients who had received CT+BV HR: 0.31 (95% CI; 0.17-0.58) (p=0.001). In both PSREOC and PRREOC patients, there was no difference between CT + BV and CT group in terms of overall survival (p=0.978 and p=0.738, respectively).*

Conclusion: *A significant effect of bevacizumab on the progression-free survival of both platinum-sensitive and platinum resistant recurrent ovarian cancers has been demonstrated; however, this effect failed to impact overall survival. Therefore, it could be recommended to use bevacizumab, considering the cost-effectiveness in undeveloped and developing countries.*

Key words: *recurrent epithelial ovarian cancer, platinum-sensitive, platinum resistance, bevacizumab, cost-effectiveness*

Introduction

Based on the latest data among all cancers 295414 (1.6%) new cases and 184799 (1.9%) deaths from ovarian cancer have been reported, and it is ranked 8th among cancers of women both in incidence (3.4%) and mortality (4.4%). [1]. Since ovarian cancer develops silently and insidiously and does not cause early symptoms, it is mostly diagnosed in stages 3 and 4. The standard treatment of ovarian cancer is cytoreductive surgery, followed by adjuvant platinum-based chemotherapy [2,3]. Despite this aggressive treatment, recurrence occurs in approximately 70% of the patients within 2-3 years [4]. If recurrence occurs 6 or more months after the completion of adjuvant chemotherapy, it

Corresponding author: Mehmet Sait Bakir, MD. Akdeniz University, Department of Obstetrics and Gynecology, Division of Gynecologic Oncology. Antalya, Turkey. Akdeniz University, Pinarbasi Mah. Dumlupinar boulevard 07070 Kampus Konyaalti, Antalya, Turkey.
Tel: +90 242 2274400, Email: sabakcil@gmail.com
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is defined as platinum-sensitive recurrent ovarian cancer. Due to the fact that the median overall survival is approximately 12 months in platinum-resistant patients [6], the platinum-free interval is the most important factor affecting the success of treatment in recurrent ovarian cancer [5]. Therefore, in recent years, new treatment modalities, especially biological agents, have been studied to provide hope for patients with recurrent ovarian cancer.

Angiogenesis has an important role in the growth and metastasis of solid organ tumors [7,8]. Epithelial ovarian cancer cells secrete excessive amounts of vascular endothelial growth factor (VEGF) [9]. In studies conducted, it has been found that decreased VEGF production is associated with a decrease in tumor vascularity and an increase in survival [10]. Bevacizumab (BV) is the first monoclonal antibody studied in ovarian cancer, and it inhibits angiogenesis by binding to all isoforms of VEGF-A. Although it is used in metastatic colorectal and lung cancer, solid organ tumors such as the kidney, breast and brain tumors [11,12], its use in ovarian cancer has become popular in recent years. It was first used as 11th line chemotherapy in a patient with recurrent serous high-grade ovarian cancer in March 2005 and increased survival for 6 months [13]. In the following years, many randomized controlled studies have shown that it is effective in epithelial ovarian cancers in both frontline [14,15] treatment and the treatment of platinum-sensitive [16,17] and platinum-resistant recurrent ovarian cancer [18]. Under the influence of these studies, the European Medicines Agency (EMA) and the US Food and Drug Administration (FDA) approved the use of BV in epithelial ovarian cancers after 2014 [19,20]. In June 2018, the FDA approved BV for the frontline and maintenance treatment of newly diagnosed epithelial ovarian cancer patients. However, unlike standard chemotherapy regimens, the high incidence of complications such as fatal gastrointestinal system complications, venous thromboembolism, hypertension and proteinuria in BV treatment arms has raised concern among clinicians [14-18]. Another matter discussed about BV is that is does not have a significant effect on overall survival. Besides, due to it being a costly treatment in cost-effectiveness studies, its total effect has not been established clearly [21-24].

The cost-effectiveness of BV has been under debate. Although new and effective biological agents have entered our clinical practice in recent years, these treatments are not widely available all over the world. Since BV is the most commonly used biological agent in recurrent ovarian cancer and there is not enough data investigating its efficacy in our country and to improve the appropriate patient selection and to avoid unnecessary morbidity, we herein present our own data in the light of the relevant literature.

Methods

The data of patients with ovarian, tubal and primary peritoneal cancers who had presented to our hospital between October 2007 and June 2018 were collected retrospectively from the hospital's electronic archive. The study was evaluated by the Akdeniz University Faculty of Medicine Clinical Research Ethics Committee and was approved under the decision number KAEK – 212. Patients who had completed 6 cycles of platinum+paclitaxel chemotherapy, who had been diagnosed with first recurrence in stage 2-4 epithelial, ovarian, tubal and primary peritoneal cancer clinically, radiologically and by assessing the CA 125 levels, those older than 18 years of age, those with a life expectancy longer than 3 months, those with an ECOG (Eastern Cooperative Oncology Group Performance status) score of 0-2, those with sufficient bone marrow, kidney and liver functions, those who had agreed to the informed consent form and who had been approved by the Ministry of Health (for BV),were included in the study. R0 (complete resection, no macroscopic tumor), R1 (optimal resection, macroscopic tumor remaining 1 cm or less) and R2 (suboptimal resection, macroscopic tumor residue above 1 cm) were included in the study according to the amount of residual tumor. The patients were divided into two groups according to the platinum-free interval (PFI) as platinum-sensitive and platinum-resistant recurrent epithelial ovarian cancer. Platinum refractory, early-stage (stage 1-2a) epithelial ovarian cancer patients, patients with a second tumor, those with a history of non-epithelial ovarian cancer, those with gastrointestinal obstruction and fistula, patients with bleeding diatheses and coagulation problems, and those with kidney, liver and cardiac failure were not included in the study. Patients candidate for secondary cytoreduction were evaluated in our clinic (for example, patients with single site and / or resectable recurrence, no ascites over 500 cc, PFI over 6-12 months, no peritoneal carcinomatosis and medically fit). While some of the platinum-sensitive recurrent ovarian cancer patients had only received platinum-based chemotherapy regimens (carboplatin+paclitaxel, cisplatin+paclitaxel, carboplatin+gemcitabine), some had received BV (15 mg/kg) in addition to chemotherapy. Some of the patients with platinum-resistant ovarian cancer had only received pegylated liposomal doxorubicin, gemcitabine, paclitaxel, and some had been administered BV in addition to these chemotherapies. The chemotherapy response rate for both groups was determined according to the WHO recommended criteria [25]: 1) progressive disease (PD), 2) stable disease (SD), 3) partial response (PR) and 4) complete response (CR). Overall response rate (ORR) = CR + PR. The chemotherapy patients were followed up at 3-month intervals with clinical examination, panabdominal CT and/or PET-CT. The cut-off

Table 1. Clinical and pathological characteristics of the cases

	CT + BV (n= 65)	*CT alone (n= 80)*	*Total (n= 145)*	*p value*
Age (years)	57.5 (±9.6)	55.8 (±9.6)	56.6 (±9.6)	0.291
Stage, n (%)				0.444
2	1 (0.7)	4 (2.8)	5 (3.4)	
3	58 (40.0)	67 (46.2)	125 (86.2)	
4	6 (4.1)	9 (6.2)	15 (10.3)	
Tumor diameter(cm), n (range)	6.5 (1.5-34)	6.25 (0.5-30)	6.5 (0.5-34)	0.211
Histology, n (%)				NA
Serous	58 (40.0)	49 (33.8)	107 (73.8)	
Endometrioid	4 (2.8)	10 (6.9)	14 (9.7)	
Clear cell	2 (1.4)	2 (1.4)	4 (2.8)	
Mucinous	1 (0.7)	2 (1.4)	3 (2.1)	
Mix	10 (6.9)	7 (4.9)	17 (11.8)	
Residual tumor, n (%)				0.066
R0	35 (24.1)	58 (40.0)	93 (64.1)	
R1	27 (18.6)	20 (13.8)	47 (32.4)	
R2	3 (2.1)	2 (1.4)	5 (3.5)	
Secondary cytoreduction, n (%)				0.314
Yes	13 (9.0)	11 (7.6)	24 (16.6)	
No	52 (35.9)	69 (47.6)	121 (83.4)	
Treatment response, n (%)				0.009
CR	33 (22.8)	21 (14.5)	54 (37.2)	
PR	20 (13.8)	27 (18.6)	47 (32.4)	
SD	9 (6.2)	21 (14.5)	30 (20.7)	
PD	3 (2.1)	11 (7.6)	14 (9.7)	
Chemotherapy cost ($)	15.134 (1.599-103.472)	2.555 (170-14.615)	5.000 (170-103.472)	0.001
Progression(months), n (%)				
Platinum sensitive				0.004
≥24 months	9 (10.8)	1 (1.2)	10 (12)	
<24 months	28 (33.7)	45 (54.2)	73 (88)	
Platinum resistance				0.012
<12 months	17 (27.4)	30 (48.4)	47 (75.8)	
≥12 months	11 (17.7)	4 (6.5)	15 (24.2)	
Life status, n (%)				0.195
Dead	32 (22.1)	48 (33.1)	80 (55.2)	
Alive	33 (22.8)	32 (22.1)	65 (44.8)	
Chemotherapy drugs, n (%)				NA
C / C + P + BV			36 (55.3)	
C / C + G + BV			21 (32.3)	
PLD + BV			8 (12.4)	
C / C + P			46 (57.5)	
C / C + G			18 (22.5)	
PLD			16 (20)	
BV treatment numbers	12 (2-46)	12 (2-46)		
Follow-up (Months)		56 (6-162)		

CT: Chemotherapy, CR: Complete response, BV: Bevacizumab, PR: Partial response, C / C: Carboplatin / Cisplatin, SD: Stable disease, P: Paclitaxel, PD: Progressive disease, G: Gemcitabine, PLD: Pegylated liposomal doxorubicin.

for progression-free survival (PFS) for patients with platinum-sensitive recurrent epithelial ovarian cancer (PSREOC) was taken as under and over 24 months and for patients with platinum-resistant recurrent epithelial ovarian cancer (PRREOC) as under and over 12 months. According to the Response Evaluation Criteria in Solid Tumors (RECIST) [26], radiological progression was as follows: when the tumor reappears, and according to the Gynecologic Cancer InterGroup (GCIP) [27] criteria, an increase in CA 125 levels and a deterioration of the overall health condition or the time of the patient's death due to any cause. The time interval in which the patient died of any cause with the diagnosis of recurrence was taken as the overall survival (OS) time.

Statistics

For the descriptive statistics, with an assessment of the normal distribution average, the standard deviation, median, min-max values and frequencies were used. Statistical significance between the categorical variables was evaluated using the x^2 test. Parametric (Student's t-test) or non-parametric (Mann Whitney U test) were used for the numerical data in two different groups, based on the normality status. PFS and OS were compared using the Kaplan-Meier and log-rank analysis. The effect on survival in patients who had received chemotherapy only or chemotherapy+BV was calculated using the Kaplan Meier and log-rank test. The effect of patients using BV on survival was calculated using univariate Cox regression analysis since only the efficacy of bevacizumab was evaluated. Statistical analyses were carried out using the 23rd version of SPSS. The p values in all tests were two-sided and p values less than 0.05 were accepted as statistically significant.

Results

The mean age of patients who had received BV was 57.5 (±9.6) years, and the mean age was 55.8 (±9.6) years in those who had not received BV. The clinical characteristic risk factors of the patients are presented in Table 1. In our study, 80 patients had received chemotherapy only and 65 chemotherapy+BV. The median follow-up duration was 56 months (range 6-162). Among the patients, 125 (86.2%) had stage 3 (p=0.444) and 107 (73.8%) had serous histology. There was no significant difference between the two groups in terms of tumor diameters at the time of diagnosis (p=0.211). The median number of BV cycles used was 12 (range: 2-46). There were 20.7% patients in the chemotherapy+BV group in terms of the amount of residual tumor (R1 + R2), while there were 15.2% patients in the chemotherapy alone group (p=0.06). The chemotherapy regimens of both groups are given in detail in Table 1. While the overall response rate (CR+PR) was 81.5% (53/65) for the chemotherapy+BV group, it was 60% (48/80) for the group receiving only chemotherapy (p=0.009). The average cost of patients who had received chemotherapy only was statistically lower than in patients who had received chemotherapy+BV (p=0.001). While 46 patients with platinum-sensitive recurrent epithelial ovarian cancer (PSREOC) had received chemotherapy only, the remaining 37 patients had received chemotherapy+BV treatment (p=0.004). Progression occurred in 10 (12%) patients of the PSREOC after 24 months. While 34 patients with platinum-resistant recurrent epithelial ovarian cancer (PRREOC) were given chemotherapy only, 28 patients received chemotherapy+BV (p=0.012). Progression developed in 47 (75.8%) of the PRREOC patients before 12 months. Hypertension was the most common adverse event in the chemotherapy+BV group (18.4%). In addition, observed were gastrointestinal perforation in 2 patients (3%), thromboembolic events in 2 patients (3%) and myocardial infarction in 1 patient (1.5%) in the chemotherapy+BV group. However, in the chemotherapy alone group, 5 patients developed hypertension and 1 patient had thromboembolic event. Comparison of adverse events according to chemotherapy treatments is given in detail in Table 3. There was no difference between the two groups in terms of the number of patients who died during follow-up (p=0.195). In PSREOC patients, the median PFS was 7 months (95% CI; 5.5-8.4) in the group who had received chemotherapy only and 13 (95% CI; 5.8-20.1) months in the group that had received chemotherapy+BV (p=0.001) and for chemotherapy+BV the hazard ratio (HR) was 0.39 (95% CI; 0.24-0.64) (p=0.001). While the median OS of PSREOC patients was 80 months (95% CI; 37-122) in the group that had received chemotherapy only, it was 81 months (95% CI; 68-93) in the group that had received chemotherapy+BV (p=0.978); for those who had received chemotherapy+BV treatment, HR was 0.99 (95% CI; 0.54-1.79) (p=0.979). The PFS analysis of the patients according to the platinum-free interval is presented in Table 2 and Figure 1. The median PFS of PRREOC patients who had received chemotherapy only was 2 months (95% CI; 1.4-2.5) and 10 months (95% CI; 6.8-13.1) for patients who had received chemotherapy+BV (p=0.001); for patients who received chemotherapy+BV, HR was 0.31 (95% CI; 0.17-0.58) (p=0.001). With regard to OS, the median OS of patients who had received chemotherapy only was 53 months (95% CI; 36-69) and 43 months (95% CI; 30-55) in patients who had received chemotherapy+BV (p=0.738). With regard to mortality in patients who received chemotherapy+BV, HR was 1.12 (95% CI; 0.55-2.27) (p=0.741) (Table 2, Figure 1).

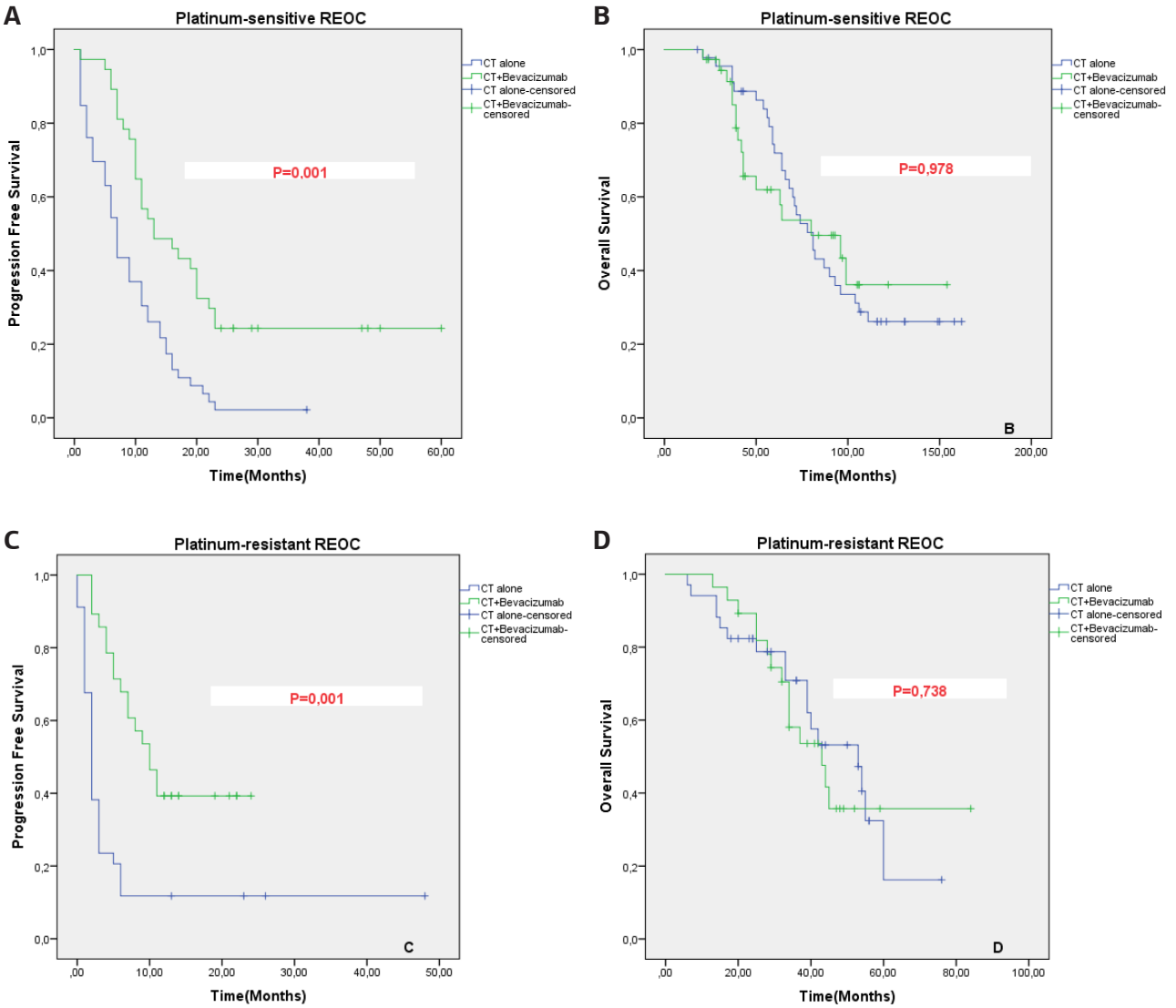

Figure 1. A: Progression-free survival in patients with platinum-sensitive recurrent ovarian cancer using only chemotherapy and chemotherapy + BV. **B:** Overall survival in patients with platinum-sensitive recurrent ovarian cancer using only chemotherapy and chemotherapy + BV. **C:** Progression-free survival for patients with platinum-resistant recurrent ovarian cancer using only chemotherapy and chemotherapy + BV. **D:** Overall survival for patients with platinum-resistant recurrent ovarian cancer using only chemotherapy and chemotherapy + BV.

Table 2. Progression free and overall survival analysis of patients according to platinum free

	PFS				*OS*			
	Month (95%CI)	*p value*	*HR (95%CI)*	*p value*	*Month (95%CI)*	*p value*	*HR (95%CI)*	*p value*
Platinum sensitive		0.001	0.39 (0.24-0.64)	0.001		0.978	0.99 (0.54-1.79)	0.979
CT+BV	13 (5.8-20.1)				80 (37.5-122.4)			
CT alone	7 (5.5-8.4)				81 (68.4-93.5)			
Platinum resistant		0.001	0.31 (0.17-0.58)	0.001		0.738	1.12 (0.55-2.27)	0.741
CT+BV	10 (6.8-13.1)				43 (30.4-55.5)			
CT alone	2 (1.4-2.5)				53 (36.2-69.7)			

CI: Confidence interval, CT: Chemotherapy, BV: Bevacizumab, PFS: Progression free survival, OS: Overall survival.

Table 3. Comparison of adverse events due to chemotherapy

Type of adverse events	*CT alone (n=80) n (%)*	*CT plus BV (n=65) n (%)*
Hypertension	2 (2.5)	3 (4.6)
Grade ≤2	3 (3.7)	9 (13.8)
Proteinuria	0 (0)	2 (3)
Gastrointestinal perforation	0 (0)	2 (3)
Fistula/abscess	0 (0)	1 (1.5)
Bleeding	0 (0)	1 (1.5)
Thromboembolic events	1 (1.2)	2 (3)
Arterial	0 (0)	1 (1.5)
Venous	1 (1.2)	1 (1.5)
Cardiac disorde (myocardial infarction)	0 (0)	1 (1.5)

Discussion

The use of biological agents has been increasing in recent years, and new agents are emerging routinely. BV is molecularly the oldest. It was first used in ovarian cancer and inhibits angiogenesis by bonding with VEGF [13]. BV may affect the biological behavior of microscopic residual tumors that remain after surgery. Since preclinical studies have demonstrated that the tumor growth increases, local invasion is observed, and distant metastasis occurs due to discontinuation of antiangiogenic agents [28-30], VEGF secretion in the tumor is also important in the development and persistence of ascites. Due to the fact that angiogenesis returns to normal with the addition of BV in tumors inclined to cause ascites, the amount of ascites decreases with its addition. This effect occurs for both pleural and pericardial effusion in ovarian cancer [18]. For example, in the AURELIA study, the rate of paracentesis was 2% in the group in which BV had been added and 17% in the other group [18]. With this effect, the reduction of symptomatic ascites improved the patients' quality of life. The addition of BV to chemotherapy has a synergistic effect and decreases the VEGF that increases as an effect of the chemotherapeutic agent (e.g., carboplatin). The overall response rate was higher in the group that received BV in our study compared to the group that received chemotherapy only. Due to these effects, BV has been used alone or in addition to chemotherapeutic agents in the frontline, maintenance and recurrence treatments of ovarian cancer. In the ICON 7 [14] and GOG 218 [15] randomized controlled studies, a significant increase in median PFS was observed in patients with advanced-stage epithelial ovarian cancer who had undergone debulking surgery with the addition of BV to the standard chemotherapy treatment. However, this positive effect did not manifest for OS [14,15]. Since the response to platinum is under 10% in platinum-resistant recurrent ovarian cancer, a long platinum-free interval (PFI) affects the survival positively. Therefore, BV is being tested to increase the survival of recurrent ovarian cancer patients.

In the randomized controlled trial (RCT) AURELIA designed for this purpose, one group of PRREOC patients was delivered single-agent paclitaxel, PLD, gemcitabine treatment, and BV was added to these chemotherapy agents in the other group [18]. The median PFS was 6.7 months for the group in which BV had been added and 3.4 months for the other group, HR: 0.42 (95%; CI: 0.32-0.53). However, there was no statistically significant difference for OS [18]. In our study, the use of BV in PRREOC patients increased the median PFS by 8 months (p=0.001) (median PFS was 2 and 10 months, respectively) in patients who had received chemotherapy+BV for progression (HR: 0.31; 95% CI; 0.17-0.58, p=0.001). There was no statistically significant difference between the two groups in terms of OS, and the HR for death in patients who had received chemotherapy+BV was 1.12 (95% CI; 0.55-2.27, p=0.741). The results of our retrospective single-center study were similar to the results of the AURELIA study.

The other two RCTs performed with BV in recurrent ovarian cancer are the OCEANS [16] and GOG 213 [17] studies, conducted with platinum-sensitive patients.

In the OCEANS randomized controlled study, BV was used in addition to chemotherapy in PSREOC patients until progression, and the median number of cycles was 12 (range: 1-43). In the 24-month follow-up, PFS was 4 months longer in the group that had received BV (8.4 months and 12.4 months, respectively), HR was 0.48 and 95% CI: 0.39-0.61 [16]. There was no statistically significant difference between the two groups in terms of median OS in the data published after reaching the sufficient follow-up period (32.9 months in the chemotherapy only group, 33.6 months in the chemotherapy+BV group (HR: 0.95) [27].

In the GOG 213 randomized controlled trial, in PSEROC patients, BV was added to the standard chemotherapy regimen until progression, and the median number of BV cycles was 16. The median PFS was 3 months longer in the chemotherapy+BV group compared to the chemotherapy only group (median PFS 13.4 months and 10.4 months, respectively) (HR:0.61 (95% CI; 0.52-0.72); p<0.0001). The median OS of the group that had received

chemotherapy+BV was 5 months longer and was statistically of borderline significance (HR: 0.829; 95% CI 0.683-1.005), p=0.056) [17]. When we look at the PSREOC patients in our study, the median PFS of the group that had received chemotherapy+BV was 6 months longer than the other group (7 months for the chemotherapy only group, 13 months for the chemotherapy+BV group) (p=0.001), for chemotherapy+BV (HR: 0.39, 95% CI; 0.24-0.64, p=0.001). However, similar to the two RCTs published before, there was no difference between the groups in terms of OS. For patients who had received chemotherapy+BV, HR was 0.99;95% CI;0.54-1.79) (p=0.979). The results of the platinum-sensitive recurrent ovarian cancer part of our study were similar to the OCEANS study.

In all of the randomized controlled studies mentioned above, severe complications (for example, sudden death, venous thromboembolism, gastrointestinal complications, brain hemorrhage, etc.) were more frequent in the patient groups that had received BV [14-18]. However, it has been shown that BV is tolerated well in BV maintenance treatments [16,17]. In our study, like in previous published articles, it is seen that serious complications are more common in the group receiving BV. In our study the gastrointestinal perforation rate was 3% lower than the rates in the literature. In this case, we can say that the number of patients is low or the rate of gastrointestinal perforation is not as high as expected, because this rate was stated as 4% in the AURELİA study [18].

After the survival results of the AURELİA study came out, it was stated that BV puts an economically serious burden on the health system and it should be taken into consideration that it is not cost-effective while arranging this treatment [21]. The use of bevacizumab at a standard dose of 15 mg / kg was found to be unsuitable in terms of cost effectiveness, and lower doses were thought to be economically feasible. In ICON 7 randomized controlled trials, adding 7.5 mg / kg to the standard frontline chemotherapy regimen as adjuvant therapy was investigated, but it was not found to be cost effective [22]. Based on the results of the AURELİA study, it has been shown that the addition of BV to the standard chemotherapy regimen is not cost-effective for patients with recurrent ovarian cancer in the Canada population as a result of the cost-effective model made from the Canada [31]. Finding biomarkers that reveal which patients will benefit with BV facilitates the selection of appropriate patients and minimize unnecessary morbidity which will relieve clinicians and country's economies. In our study, the cost of the chemotherapy+BV group was also higher. With the influence of published randomized controlled trials, the European Medicines Agency (EMA) and the US Food and Drug Administration (FDA) approved it for the frontline, maintenance and recurrence treatments of ovarian cancer, although it does not improve the OS satisfactorily.

As for the limitations of our study, since it was retrospective, a natural bias may be observed in the selection of patients. According to randomized controlled studies published previously, the number of our patients may be small because it comes from a single center. According to the quality of life questionnaire, the situation of both groups was not clear because of its retrospectiveness.

Conclusion

A significant effect of BV on the PFS of both platinum-sensitive and platinum-resistant recurrent ovarian cancers has been demonstrated. However, this effect failed to positively impact OS. Therefore, it could be recommended to use BV considering its cost-effectiveness in undeveloped and developing countries.

Conflict of interests

The authors declare no conflict of interests.

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