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Original Research

The effect of bevacizumab maintenance therapy on survival in recurrent epithelial ovarian cancer

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Objective: We aimed to present our own retrospective data about the effectiveness of Bevacizumab (BV) maintenance therapy on survival to achieve optimal treatment in recurrent ovarian cancer. *Methods*: The data of patients with recurrent ovarian, tubal, and primary peritoneal cancer presenting to our hospital between October 2008 and December 2019 were retrospectively gathered from the hospital's electronic archive system. The patients were grouped according to the platinum-free interval state. The patients were divided into two groups of BV maintenance and no BV maintenance and their progression-free and overall survival were calculated. *Results*: A total of 65 patients with recurrent epithelial ovarian cancer were included in the study. Among these, 35 had received bevacizumab therapy alone and 30 received bevacizumab maintenance therapy. According to the platinum-free interval, 37 of the patients had platinum-sensitive recurrent epithelial ovarian cancer and the remaining 28 had platinum-resistant recurrent epithelial ovarian cancer. The median follow-up was 42 (min: 13–max: 135) months. The average age was 56.5 $\pm$ 9.1 in the no bevacizumab maintenance group and 57.5 $\pm$ 9.6 in the bevacizumab maintenance group (*p*: 0.812). Among the platinum-sensitive recurrent epithelial ovarian cancer patients, the median progression-free survival progression-free survival (PFS) was 8 months (95% Confidence Interval (CI); 5.7–10.2) in the no bevacizumab maintenance group and 22 months (95% CI; 18.9–24.1) (*p*: 0.001) in the bevacizumab maintenance group and for the bevacizumab maintenance patients Hazard Ratio (HR): 0.10 (95% CI; 0.03–0.27) (*p*: 0.001). While the median overall survival (OS) of platinum-sensitive recurrent epithelial ovarian cancer patients in the no bevacizumab maintenance group was 64 months (95% CI; 21.6–102.3), it was 86 months (95% CI; NA) (*p*: 0.155) in the group that received bevacizumab maintenance, and for patients who received bevacizumab maintenance therapy, HR: 0.55 (95% CI; 0.18–1.33) (*p*: 0.166). The median PFS for platinum-resistant recurrent epithelial ovarian cancer patients who received no bevacizumab maintenance was determined as 7 (95% CI; 4.8–9.1) and as 19 months (95% CI; 9.2–26.7) (*p*: 0.009) for patients who received bevacizumab maintenance therapy, and for patients who received BV maintenance therapy, HR: 0.17 (95% CI; 0.03–0.71) (*p*: 0.022). In terms of OS, the median OS of platinum-resistant recurrent epithelial ovarian cancer patients who received no bevacizumab maintenance was 34 (95% CI; 31.5–36) months, while it was 45 (95% CI; 42.5–47.4) months in patients who received bevacizumab maintenance (*p*: 0.231); the HR for death in patients receiving bevacizumab maintenance therapy: 0.50 (95% CI; 0.15–1.61) (*p*: 0.247). *Discussion*: While it was shown that bevacizumab maintenance therapy had a significant effect on progression-free survival in both platinum-sensitive and platinum-resistant ovarian cancer, this effect could not be demonstrated for overall survival. Despite this, bevacizumab maintenance therapy can be delivered in recurrent ovarian cancer in addition to standard therapy. Further studies about its effect on overall survival are required.

Keywords

Recurrent epithelial ovarian cancer; Platinum-sensitive; Platinum-resistant; Bevacizumab maintenance; Survival

1. Introduction

In advanced epithelial ovarian cancer, recurrence occurs in 70% of the patients within 2–3 years despite the standard approach of cytoreductive surgery followed by six cycles of adjuvant paclitaxel + carboplatin treatment [1–3]. Maintenance therapies have been studied to reduce recurrent ovarian cancer or to stabilize the disease. Although these treatments prolong the progression-free survival (PFS) and/or overall survival (OS), the toxic effects, cost-effectiveness and the impact of the drugs used on the quality of life have been questioned. Due to these reservations, it has taken time to change clinical practice and gain the trust of clinicians. For example, the Gynecologic Oncology Group (GOG) 178 study compared 12 courses and three courses of paclitaxel as maintenance therapy. While a longer PFS was observed in the group that received 12 courses, it was also found that the toxic side effects were more common in this group, and the study was terminated early [4]. Recently, with a better understanding of the pathophysiology of ovarian cancer, maintenance treatments have shifted towards target agents such as antivascular endothelial growth factor (VEGF) and poly (adenosine diphosphate-ribose) polymerase inhibitors (PARPs). These agents have been investigated in first line [5–7] and recurrence treatments [8–13] in ovarian cancer, and their efficacy has been established. Angiogenesis is of vital importance in both normal ovarian physiology and ovarian cancer pathogenesis. It also has a critical role in tumor growth, ascites development, and metastasis [14–16]. Epithelial ovarian cancer cells secrete excessive amounts of vascular endothelial growth

factor (VEGF) [17], and studies conducted have shown that decreased VEGF production is associated with increased survival by reducing the tumor vascularity [18]. Bevacizumab (BV) is the first monoclonal antibody studied in ovarian cancer, and it inhibits angiogenesis by binding to all isoforms of VEGF-A. BV was approved for use in recurrent ovarian cancer by the European Medicines Agency (EMA) in 2011 and the US Food and Drug Administration (FDA) in 2014, after the positive effect of BV on PFS was proven [19, 20]. In June 2018, the FDA approved BV for the first line and maintenance therapy of newly diagnosed epithelial ovarian cancer patients. The last published study emphasized that BV, which is still indispensable and used together with olaparib in the maintenance therapy of ovarian cancers, is significantly effective, even in patients without a *BRCA* mutation [12]. BV is tolerated well by patients, and it has become standard to add it to carboplatin + paclitaxel therapy and use it as maintenance therapy in advanced-stage ovarian cancer [6, 7, 21–23]. In the first-line treatment, the optimal time for BV maintenance therapy is unclear. The result of the ongoing study is being awaited [24].

We aimed to present our own retrospective data about the effectiveness of BV maintenance therapy on survival to achieve optimal treatment in recurrent ovarian cancer.

2. Material methods

The data of the patients with recurrent ovarian, tubal and primary peritoneal cancer, who had presented to our hospital between October 2008 and December 2019 (135 months), were retrospectively gathered from the hospital's electronic archive system. The study was evaluated by the Akdeniz University Faculty of Medicine Clinical Research Ethics Committee and was approved under the decision number KAEK – 765 (date 8 October 2020). Stage 2–4 epithelial ovarian, tubal, and primary peritoneal cancer patients diagnosed with first recurrence clinically, radiologically and based on CA 125 levels, who had completed six courses of platinum + taxane chemotherapy, who were over 18 years of age, had a life expectancy longer than three months, an ECOG (Eastern Cooperative Oncology Group performance status) score of 0–2, with adequate bone marrow, coagulation, kidney, and liver functions, those who agreed to the informed consent form and who were approved by the Ministry of Health (for BV) were included in the study. The patients were divided into two groups according to the platinum-free interval (PFI) as platinum-sensitive (if recurrence occurred within six or more months after the completion of adjuvant chemotherapy) and platinum-resistant (recurrence within the first six months after completion of adjuvant chemotherapy) recurrent epithelial ovarian cancer. Platinum refractory patients, those who received BV in the first-line treatment, patients with early-stage (stage 1–2a) epithelial ovarian cancer, non-epithelial ovarian cancer, those with a history of gastrointestinal obstruction and fistula, bleeding diathesis and coagulation problems, and those with renal, liver or cardiac failure were excluded from the study. Some of the platinum-sensitive patients with recurrent ovarian cancer were given 2–12 cycles of BV (15 mg/kg) in addition to platinum-based chemotherapy regimens (carboplatin + paclitaxel, cisplatin + paclitaxel, carboplatin + gemcitabine) (chemotherapy (CT) + bevacizumab (BV) group), and some were given BV maintenance therapy (chemotherapy (CT) + bevacizumab (BV) maintenance group) in addition to standard chemotherapy until the disease relapsed or intolerable side effects developed. While some of the patients with platinum-resistant recurrent ovarian cancer were given 2–12 cycles of BV (15 mg/kg) therapy (CT + BV group), some of the patients in this group were given BV maintenance therapy until progression or development of intolerable toxic effects (CT + BV maintenance group). Clinical examination, abdominal CT, and/or PET-CT and tumor markers were assessed in patients who received chemotherapy at 3-month intervals. For patients with platinum-sensitive recurrent epithelial ovarian cancer (PSREOC), a duration shorter and longer than 24 months, and for patients with platinum-resistant recurrent epithelial ovarian cancer (PRREOC), a duration shorter and longer than 12 months, were taken as the cut-off values for progression-free survival. According to the Response Evaluation Criteria in Solid Tumors (RECIST) [25] criteria, the time the tumor reappeared, and according to the Gynecologic Cancer InterGroup (GCIP) [26] criteria, the increase in CA 125 levels, deterioration of the overall health condition, or the time of death due to any cause were used. The period between the patients' initial diagnosis and the time of death due to any cause was accepted as overall survival.

3. Statistical analysis

For the descriptive statistics, the mean, standard deviation, median, min–max values and frequencies were used, considering whether there was a normal distribution or not. Statistical significance between the categorical variables was determined using the chi-square (χ^2) test and the Fisher's exact test. For the numerical data, parametric (Student *t*) or non-parametric (Mann Whitney U) tests were used according to the normality for two different groups. Progression free survival (PFS) and OS were calculated using the Kaplan Meier analysis. The log-rank test was used for the effect of subgroups (platinum-sensitive, platinum-resistant, BV maintenance, non-BV maintenance) on survival. The effect of BV maintenance on patients' survival was calculated using the univariate cox proportional hazards model. Statistical analyses were performed using the 23rd version of SPSS (IBM Corp., Armonk, NY, USA). The *p* values in all tests were two-tailed, and *p* values smaller than 0.05 were accepted as statistically significant.

4. Results

A total of 65 patients with recurrent epithelial ovarian cancer were included in the study. Among these, 35 had received bevacizumab therapy alone, and 30 had received beva-

Table 1. Clinical and pathological characteristics of the cases.

			CT + BV	CT + BV maintenance	Total	*p* value
			n: 35	n: 30	n: 65	
Age (years)			56.5 (±9.1)	58.7 (±10.1)	57.5 (±9.6)	0.812
Stage	2		1 (1.5%)	0 (0%)	1 (1.5%)	NA
	3		30 (46.2%)	28 (43.1%)	58 (89.2%)	
	4		4 (6.2%)	2 (3.1%)	6 (9.3%)	
Tumor diameter			6.5 (1.5–34)	6.7 (2–20)	6.5 (1.5–34)	0.906
Histology	-Serous		30 (46.2%)	28 (43.1%)	58 (89.2%)	NA
	-Edometrioid		3 (4.6%)	1 (1.5%)	4 (6.2%)	
	-Clear cell		2 (3.1%)	0 (0%)	2 (3.1%)	
	-Mucinous		0 (0%)	1 (1.5%)	1 (1.5%)	
Progression (months)	Platinum sensitive	<24 months	15 (40.5%)	13 (35.1%)	28 (75.7%)	***0.005***
		≥24 months	0 (0%)	9 (24.3%)	9 (24.3%)	
	Platinum resistance	<12 months	15 (53.6%)	2 (7.1%)	17 (60.7%)	***0.030***
		≥12 months	5 (17.9%)	6 (21.4%)	11 (39.3%)	
Life status	Dead		18 (27.7%)	14 (21.5%)	32 (49.2%)	0.805
	Alive		17 (26.2%)	16 (24.6%)	33 (50.8%)	
BV cure number			6 (2–14)	20 (12–56)	12 (2–56)	***0.001***
Follow-up (Months)					42 (13–135)	

CT, Chemotherapy; BV, Bevacizumab.

Table 2. Comparison of advers events due to chemotherapy treatments.

Type of advers events	CT plus BV (n = 35)		CT plus BV maintenance (n = 30)	
	n	%	n	%
Hypertension	3	8.5	2	5.7
Grade 2≥	1	2.8	3	8.5
Proteinuria	1	2.8	2	5.7
Gastrointestinal perforation	0	0	1	2.8
Fistula/abscess	0	0	1	2.8
Bleeding	1	2.8	1	2.8
Thromboembolic events	1	2.8	2	5.7
Arterial	0	0	1	2.8
Venous	1	2.8	1	2.8
Cardiac disorder (myocardial infarction)	0	0	1	2.8

cizumab maintenance therapy. According to the platinum-free interval, 37 of the patients had platinum-sensitive recurrent epithelial ovarian cancer (PSREOC), and the remaining 28 had PRREOC. The median follow-up was 42 (min: 13–max: 135) months. The average age was 56.5 ± 9.1 in the CT + BV group and 57.5 ± 9.6 in the CT + BV maintenance group (*p*: 0.812). The clinical characteristic risk factors of the patients have been presented in Table 1. There was no difference in the tumor diameters between the two groups at the time of diagnosis (6.5 and 6.7 cm, respectively, *p*: 0.906). When compared the groups in terms of stage; the highest number of patients in both groups were in stage 3 (intragroup rates of 85.7% and 93.3%, respectively). Most of the CT + BV alone and CT + BV maintenance groups had serous histology (46.2% and 43.1%, respectively). The median number of BV courses in the CT + BV maintenance group was 20 (min: 12–max: 56), which was significantly higher than the number of courses in the CT + BV group 6 (min: 2–max: 14) (*p*: 0.001). In the platinum-sensitive group, 0 (0%) patients in the CT + BV group and 9 (24.3%) patients in the bevacizumab maintenance group had developed progression after 24 months *p*: 0.005. In the platinum-resistant group, 15 (53.6%) patients in the CT + BV group and 2 (7.1%) patients in the CT + BV maintenance group had developed progression before 12 months *p*: 0.030. There was no difference between the two groups regarding the number of patients who died (18 and 14, respectively, *p*: 0.805). Hypertension was the most common adverse effect in both groups (11.3% and 14.2%, respectively). In the CT + BV maintenance group, BV maintenance treatment was discontinued due to myocardial infarction (2.8%) in 1 patient, gastrointestinal perforation in 1 patient (2.8%), arterial thromboembolic event in 1 patient (2.8%) and gastrointestinal fistula in 1 patient. In the BV maintenance group, 1 patient could not

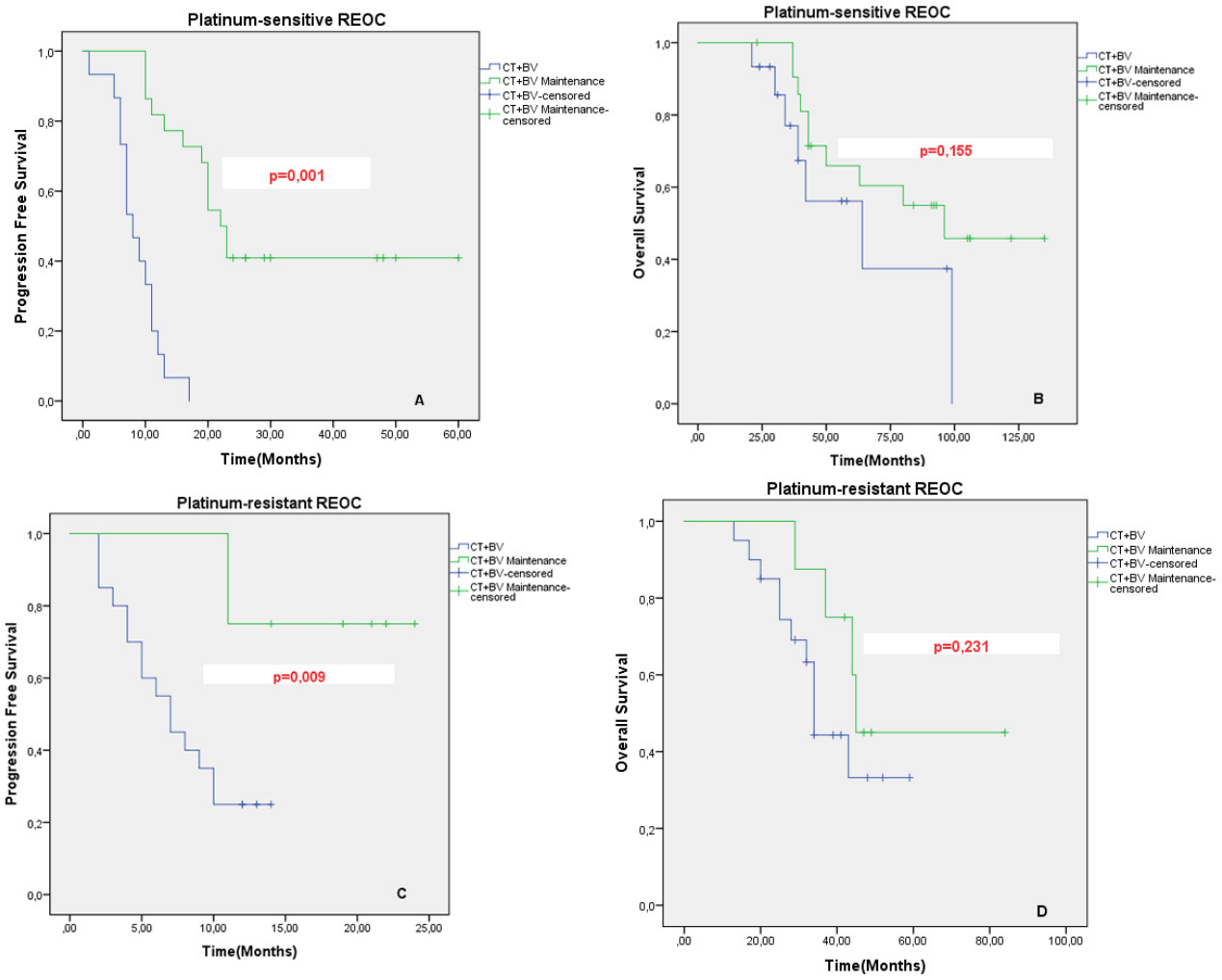

Fig. 1. Kaplan Meier survival analysis of patients receiving and not receiving bevacizumab maintance therapy in recurrent epithelial ovarian cancer. (A) Progression-free survival in patients with Platinum sensitive REOC using CT plus BV and CT plus BV maintenance. (B) Overall survival in patients with Platinum sensitive REOC using CT plus BV and CT plus BV maintenance. (C) Progression-free survival for patients with Platinum-resistance REOC using CT plus BV and CT plus BV maintenance. (D) Overall survival for patients with Platinum-resistance REOC using CT plus BV and CT plus BV maintenance. CT, Chemotherapy; BV, Bevacizumab.

continue BV treatment due to bleeding (2.8%) and 1 patient due to thromboembolic event (2.8%). Comparison of advers events according to chemotherapy treatments is given in Table 2 in detail. Among the PSREOC patients, while the PFS (progression-free survival) was 8 months (95% Confidence Interval (CI); 5.7–10.2) in the CT + BV group, it was 22 months (95% CI; 18.9–24.1) (*p*: 0.001) in the CT + BV maintenance group, and the Hazard Ratio (HR) for the CT + BV maintenance patients was 0.10 (95% CI; 0.03–0.27) (*p*: 0.001). The median OS (overall survival) of PSREOC patients was 64 (95% CI; 21.6–102.3) months in the group that received CT + BV, and 86 (95% CI; NA) months in the CT + BV maintenance group (*p*: 0.155) HR: 0.55 (95% CI; 0.18–1.33) for CT + BV maintenance therapy (*p*: 0.166). The progression-free and the overall survival analysis of the patients based on the platinum-free interval have been presented in (Table 3, Fig. 1). The median PFS for PRREOC patients who had received BV alone was determined as 7 (95% CI; 4.8–9.1) months and as 19 months (95% CI; 9.2–26.7) (*p*: 0.009) for patients who had received BV maintenance therapy; for patients who received BV maintenance therapy, HR: 0.17 (95% CI; 0.03–0.71) (*p*: 0.022). In terms of the OS, the median OS of the PRREOC patients who had received CT + BV was 34 months (95% CI; 31.5–36) and 45 months (95% CI; 42.5–47.4) in patients who had received BV maintenance therapy (*p*: 0.231); the HR for death in patients who had received BV maintenance therapy was 0.50 (95% CI; 0.15–1.61) (*p*: 0.247) (Table 3, Fig. 1).

5. Discussion

Due to the likelihood of recurrence in high-risk patients despite cytoreductive surgery and adjuvant carboplatin + paclitaxel treatment, which is the standard treatment of advanced-stage epithelial ovarian cancer, maintenance thera-

Table 3. Progression free and overall survival analysis of patients according to platinum free interval.

		PFS				OS			
		Month (95% CI)	*p* value	HR (95% CI)	*p* value	Month (95% CI)	*p* value	HR (95% CI)	*p* value
Platinum sensitive	BV alone	8 (5.7–10.2)		1		64 (21.6–102.3)		1	
	BV maintenance	22 (18.9–24.1)	***0.001***	0.10 (0.03–0.27)	***0.001***	86 (NA)	0.155	0.55 (0.18–1.33)	0.166
Platinum resistance	BV alone	7 (4.8–9.1)		1		34 (31.5–36)		1	
	BV maintenance	19 (9.2–26.7)	***0.009***	0.17 (0.03–0.70)	***0.022***	45 (42.5–47.4)	0.231	0.50 (0.15–1.61)	0.247

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

pies with newly developed chemotherapeutic agents have become popular in recent years. The oldest of these targeted therapies and the agent we have the most experience with is bevacizumab [27]. And then PARP inhibitors were used for this purpose. One of the most important prognostic factors that affect survival in ovarian cancer is the platinum-free interval. However, all epithelial ovarian cancers become platinum-resistant over time, and the survival of these patients who receive second line and third-line chemotherapy regimens is very severely affected [28]. The addition of BV to chemotherapy has a synergistic effect that changes the tumor's microenvironment and reduces the VEGF increased by the chemotherapeutic agent (e.g., carboplatin). Due to these effects, BV has been used alone or in combination with chemotherapeutic agents in the first-line, maintenance and recurrence treatments of ovarian cancer [6–10]. In the GOG-0218 and ICON-7 randomized controlled studies (RCTs), the addition of BV (22 courses of BV (GOG 218), 18 courses of BV (ICON 7)) to standard chemotherapy in the first-line treatment has produced a significantly positive effect on PFS compared to placebo in patients at high risk of progression [6, 7]. However, this positive effect was not observed for OS [6, 7]. In our own study, to demonstrate the effectiveness of CT + BV maintenance therapy, patients with stage 3 and 4 high-grade tumors were integrated in particular. Due to these positive aspects of BV maintenance therapy, its effects on recurrent ovarian cancer (both platinum-sensitive and platinum-resistant) required investigation, and the OCEANS [8] and GOG 213 [9] RCTs were designed. The median number of BV cycles used in these studies was 12 (range 1–43, oceans) and 16. In our study, the median number of BV cycles in the group that received BV maintenance was 20 (range 2–56). As also demonstrated in prior RCTs, this shows that our patients tolerated BV well. In the OCEANS randomized controlled study, BV was used in PSREOC patients in addition to chemotherapy until progression or the onset of a toxic effect. During the 24-month follow-up, PFS was four months longer in the BV maintenance group (8.4 months and 12.4 months), HR: 0.48; 95% CI; 0.39–0.61 [8]. In the data published after reaching the adequate follow-up period, there was no difference between the median OS of the two groups (32.9 months in the CT alone group, and 33.6 months in the CT + BV group, HR; 0.95) [29].

In the GOG 213 [9] randomized controlled study, PSREOC patients were delivered BV in addition to the CT regimen until progression or the onset of a toxic effect. The median PFS was three months longer in the group that received CT alone than the CT + BV group (Median PFS 10.4 months, 13.4 months, respectively) HR: 0.61 (95% CI; 0.52–0.72) $p < 0.0001$. The median OS of the group that received CT + BV was five months longer, and this was statistically significant; HR: 0.829 (95% CI; 0.683–1.005); $p = 0.056$ [9]. In the PSREOC group of our study, recurrence occurred before 24 months in all patients who had not received BV maintenance. In the PSREOC group that had received BV maintenance, the progression time was prolonged, and in 9 patients, recurrence occurred after 24 months. The analyses we performed showed that PFS was statistically significantly longer in the PSREOC patient group that received BV maintenance (8 months vs. 22 months, respectively). In the group that received BV maintenance therapy, HR: 0.10 (95% CI; 0.03–0.27) (*p*: 0.001). In terms of OS, it appears that patients who received BV maintenance therapy lived longer, but this was not statistically significant (*p*: 0.155). However, the risk of death was decreased in the group that received BV maintenance therapy (HR: 0.55 (95% CI; 0.18–1.33) (*p*: 0.166)). The fact that its effect on OS is not as substantial as its effect on PFS shows that there are important points in the treatment that are unknown. In particular, establishing the *BRCA* status and the homologous recombination deficiency (HDR) positivity status are essential for maintenance therapy. In the most recent RCTs published, it has been observed that the combined use of BV therapy with PARP inhibitors has a significant contribution to PFS, even in those without *BRCA* mutations [12]. The effect of PARP inhibitor + BV maintenance therapy should be investigated in future studies. Considering the cost-effectiveness and the conditions of the country, BV maintenance therapy can be delivered in platinum-sensitive epithelial ovarian cancer (EOC) patients with high-risk epithelial ovarian cancer in select patients, since it is possible to improve the patient's quality of life by prolonging the progression time and reducing the relapse related stress on the patient and their physician. Therefore, the European Medicines Agency (EMA) and FDA recommend adding BV (as initial and/or maintenance therapy) to standard first-line chemotherapy [19, 20]. The prognosis of platinum-resistant EOC (PRREOC) patients is rather poor. The response to platinum is under 10% in these patients [10]. Agents such as single-agent paclitaxel, pegile lipozomal doksorubisin (PLD), gemcitabine, topotecan or etoposide are

recommended as chemotherapy for these patients. The AURELIA randomized controlled trial (RCT) was designed to investigate the effectiveness of BV added to the single-agent chemotherapies listed above on survival in PRREOC patients [10]. In this study, PFS was positively affected, but no difference was found in OS [10]. In our study, the number of patients who developed recurrence before 12 months was significantly lower in the group that received BV maintenance (15 vs. 2, respectively). It was observed that PFS was significantly longer in the PRREOC patients who received BV maintenance (19 months versus 7 months). For the BV maintenance group, HR: 0.17 (95% CI; 0.03–0.71) (p: 0.022). Like the AURELIA study, our study also showed that BV maintenance made no difference in OS (p: 0.231). Although not statistically significant, the risk of death was found to be lower in the BV maintenance group; HR: 0.50 (95% CI; 0.15–1.61) (p: 0.247). Since the treatment of platinum-resistant recurrent EOC patients is troublesome, there is a serious need for treatments that could provide hope. The positive effect of BV maintenance therapy on survival is very valuable for these patients. This treatment modality can be delivered to select PRREOC patients when feasible. Considering that mortality is still high despite the aggressive treatment of ovarian cancer, the contribution of BV to PFS cannot be ignored. Because this effect of BV has pushed clinicians to focus on target therapy, ultimately contributing to the development of better treatment modalities (such as PARP inhibitors). It should not be forgotten that better results can be obtained in the future by investigating the factors that have limited effect on overall survival. In all of the randomized controlled studies mentioned above, serious complications (such as sudden death, venous thromboembolism, gastrointestinal complications, brain hemorrhage, etc.) were more common in the patient groups that received BV [6–10]. However, it has been shown that BV is tolerated well in BV maintenance therapies [8, 9]. The optimal number of courses in BV maintenance therapy is unclear. The results of the Arbeitsgemeinschaft für Gynäkologische Onkologie (AGO)-OVAR17 NCT01462890; BOOST study designed for this purpose that will compare 22 and 44 cycles of BV maintenance in first-line treatment are being awaited [24].

With regard to the limitations of our study, a bias may be observed in patient selection naturally due to its retrospective design. The complication data of the patients who received CT + BV and CT + BV maintenance were not known in detail. The number of patients who had undergone secondary cytoreduction was unclear in both groups. The *BRCA* status and the HDR positivity of the patients were unknown.

6. Conclusions

In conclusion, while it was shown that bevacizumab maintenance therapy had a significant effect on progression-free survival in platinum-sensitive and platinum-resistant recurrent ovarian cancer, this effect could not be shown on overall survival. In spite of this situation, BV maintenance therapy can be delivered in recurrent ovarian cancer in addition to standard therapy. Further studies regarding its effect on OS are required.

Author contributions

MSB and ÖB conceived and designed the study; MSB, ÖB performed the study; MSB, CK and SD analyzed the data; HAT and TS contributed materials and evaluation; MSB wrote the paper. All authors contributed to editorial changes in the manuscript. All authors read and approved the final manuscript.

Ethics approval and consent to participate

The study was evaluated by the Akdeniz University Faculty of Medicine Clinical Research Ethics Committee and was approved under the decision number KAEK – 765 (date 8 October 2020). Consent was obtained from all patients.

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Conflict of interest

The authors declare no conflict of interest.

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