Original Research

Clinical characteristics of relapsed ovarian cancer patients with striking response to the bevacizumab at first relapse

Fatih Kose[1]**, Songül Alemdaroğlu**[2]**, Hüseyin Mertsoylu**[1]**, Ali Ayberk Beşen**[1]**, Ozan Cem Güler**[3]**,**

Seda Yüksel Şimşek[2]**, Gürcan Erbay**[4]**, Cem Önal**[3]**, Hüsnü Çelik**[5]

[1]*Department of Medical Oncology, Baskent University Faculty of Medicine, 01120, Adana, Turkey*
[2]*Department of Obstetrics and Gynecology, Baskent University Faculty of Medicine, 01120, Adana, Turkey*
[3]*Department of Radiation Oncology, Baskent University Faculty of Medicine, 01120 Adana, Turkey*
[4]*Department of Radiology, Baskent University Faculty of Medicine, 01120 Adana, Turkey*
[5]*Department of Gynecological Oncology, Baskent University Faculty of Medicine, 01120, Adana, Turkey*

Summary

Background: Ovarian cancer is fifth leading cause of the cancer related death in women. Platin based doublet regimen plus bevacizumab is standard treatment in relapse. The primary aim of this study is to define clinicopathological characteristics of the relapsed ovarian cancer who derived unexpectedly long benefit from bevacizumab treatment. *Methods*: Total number of 106 patients with relapsed ovarian cancer and treated with bevacizumab (bevacizumab is not reimbursed as a part of adjuvant treatment in Turkey) on their first relapse were included. For the purpose of the study, the patients were placed into two groups, Group A and B, selected on the basis of the rate of PFS 1 (time between first day of adjuvant chemotherapy and first radiological progression) to PFS 2 (time between first day of second line treatment and second radiological progression). The patients included into Group A if PFS 1 greater than PFS 2 and Group B vice versa. *Results*: Group A and B were consisted of 67 (63%) and 39 (37%) patients. At a median follow-up of 32.1 months (5.3–110.8), 56 (52.8%) patients were died. Significant number of patients (78.4%) treated with primary surgery without neoadjuvant treatment and 59 (57.8%) out of the 102 patients had debulking surgery when their cancer relapsed. PFS 1 and 2 were estimated as 16.5 mo (14.1-18.9) *vs.* 13.7 mo (9.9-17.5) and 13.4 mo (8.0-18.6) *vs.* 29.7 mo (21.5-38.0) in group A and B, respectively ($p < 0.001$ and $p < 0.001$). Only parameter that show significant difference between groups was the rate of platin resistant patients; Group A: 13 (19.4%) out of 67 patients *vs.* Group B: 15 (38.6%) out of 39 patients with a *p* value of *0.041*. Binary logistic regression indicates PFS1 is significant inverse predictor (shorter PFS-1 means greater chance of being in group B) of entering Group B [Chi-Square = 16.5, df = 6 and $p = 0.011$ (< 0.05)]. PFS1 is significant at the 5% level [PFS1 wald = 4.33, $p = 0.038$ ($p < 0.05$)]. In multivariate analysis, cox-regression proportional hazard, cytoreductive surgery at second relapse (yes or no) (*p:* 0.028; HR: 0.3, 0.02-0.7, 95% CI) showed significant effect on PFS-2. On the other hand, platin resistance (< 6 mos; yes or no) (*p:* 0.04; HR: 4.0, 1.1-14.4, 95% CI) and secondary surgery outcome (no visible *vs.* visible) (*p:* 0.003; HR: 0.2, 0.07-0.58, 95% CI) showed significant effect on OS. Bevacizumab related adverse effects with greater than grad 3 detected in 13 (15%) and 10 (25%) in group A and B (*p:* 0.77). *Conclusions*: Our findings indicate that bevacizumab produced strikingly high PFS (over 24 months) in significant portion of relapsed ovarian cancer patients whom were mostly platin resistant cases with short PFS-1. This gain specifically achieved in patients who had aggressive secondary surgery with no-visible surgical outcome.

Key words: Ovarian cancer; Bevacizumab; Predictive markers; Relapse.

Introduction

Ovarian cancer is fifth leading cause of the cancer related death in women all through the world. Though systemic treatment options have been expanded with usage of more aggressive surgical debulking techniques in last decades, merely 30% of patients potentially cured in advanced stage [1]. Indeed, over 70% of patients relapsed in first 18 months. Chemotherapy is the still mainstay of the systemic treatment [2]. However, after dissecting the ovarian cancer patient not only based on histopathological features but based on genomic profiling, certain pathways is found to be having particular importance [3].

Although, each one of the pathways is not targetable now, pathway related with DNA repair and VEGF are ef-

fectively druggable targets [4, 5]. Bevacizumab is the first molecular-targeted anti-VEGF approved by the European Medicines Agency (EMA) and the U.S. Food and Drug Administration (FDA). This monoclonal antibody binds specifically to the circulating vascular endothelial growth factor A (VEGFA), which inhibits tumor angiogenesis [6]. The increased expression of VEGFA has been found in most human cancers examined and anti-VEGF treatment is actively used in many cancers including ovarian cancer [7]. At least three phase III randomized trials showed that bevacizumab when added to the chemotherapeutics significantly increased PFS and OS in adjuvan and both cisplatin-resistant and cisplatin-sensitive relapse settings of ovarian cancer [7-9]. However, even as a targeted agent no single

Table 1. — *Demographic and Clinical Characteristics of the study cohort.*

	Group A	Group B	*p* value
Number of patients (n)	67	39	
Age (mean)	60.4	58.3	*p*: 0.31
ECOG 0-1, n, (%)	65 (97.0)	36 (92.3)	*p*: 0.36
CCI ≤ 2, n, (%)	52 (77.6)	32 (82.1)	*p*: 0.63
Ca 125 value (kU/L)	287.8	265.4	*p*: 0.85
Histology subtype, serous, n: 103, (%)	61 (93.8)	33 (86.8)	*p*: 0.49
Neoadjuvant treatment, n: 88, (%)	14 (25.0)	5 (15.6)	*p* : 0.42
Primary surgery outcome, no-visible, n: 77, (%)	38 (76.0)	21 (77.8)	*p*: 0.35
Platin resistant cases, n: 106, (%)	13 (19.4)	15 (38.6)	*p*: 0.041
Second debulking surgery, n: 102, (%)	34 (53.1)	25 (65.8)	*p*:0.22
Secondary surgery outcome, no-visible, n: 59, (%)	22 (63.0)	16 (66.7)	*p*: 0.74
Chemotherapy dose reduction, n: 88, (%)	19 (33.9)	7 (21.9)	*p*: 0.33
Bevacizumab, grade 3-4 side effects, n: 23, (%)	13 (15)	10 (25)	*p*: 0.77
PFS-1, median (range), 95% CI	16.5 mo (14.1-18.9)	13.7 mo (9.9-17.5)	*p* < 0.001
PFS-2, median (range), 95% CI	13.4 mo (8.0-18.6)	29.7 mo (21.5-38.0)	*p* < 0.001
OS, median (range), 95% CI	58.6 mo (32.2-85.0)	48.3 mo (43.5-53.1)	*p*: 0.71

CCI: Charleston Co-morbidity index; ECOG: Eastern Cooperative Oncology Group, PFS: progression free survival; OS: overall survival; p < 0.05 (statistically significant difference).

proven pathological or laboratory biomarker was found to be predict the effectiveness of the bevacizumab in subset analysis of these well-designed phase III studies [10, 11].

The primary aim of this study is to define clinicopathological characteristics of the relapsed ovarian cancer who derived unexpectedly long benefit from bevacizumab treatment.

Patients and Methods

Patients

Current retrospective hospital-based observational case series study was conducted with 106 recurrent ovarian cancer patients treated with single agent chemotherapy + bevacizumab (platin resistant) or platin-based doublet regimen + bevacizumab at Baskent University Faculty of Medicine, Adana Dr. Turgut Noyan Research and Treatment Centre between 2012 and 2018 (Figure 1). For the purpose of the study, the patients were placed into two groups, Group A and B, selected on the basis of the rate of PFS 1(time between adjuvant chemotherapy start date and first radiological progression) to PFS 2 (time between second line treatment and second radiological progression). The patients included into Group A if PFS 1 greater than PFS 2 and Group B vice versa.

Main demographic and clinicopathological characteristics including age, CCI (Charlston comorbidity index), ECOG performance, histology, primary tumor location (over *vs.* tuba), Ca 125 value at recurrence, history of neoadjuvant treatment, success of primary surgery, requirement of salvage surgery at relapse and the success of second surgery were recorded. Initial date of ovarian cancer diagnosis, date of first and second relapse and the death/last control were noted (Table 1).

Statistical analysis

All results were presented as the rate for categorical values or mean/median for continuous variables. To detect significant differences of clinicopathological characteristics between DNM and LM group, Chi-square and/or Fischer-exact test for rates, and t-test for continuous variables were used. Overall Survival (OS) was defined from first relapse to death/last control date and reported in months. Progression free survival (PFS 1) was defined from diagnosis to first relapse. Progression free survival (PFS 2) was defined from first relapse to second relapse. Survival curves were estimated according to the Kaplan-Meier method, and log-rank tests were used for univariate statistical comparisons. Adjusted Hazard Ratio (HR) and 95% confidence interval (95% CIs) were used for estimation. Multivariate analysis was performed using by Cox-proportional hazard analysis for OS and PFS. In multivariate analysis HR and 95% CIs were used for estimation. All statistical data were analyzed using the SPSS version 25.0, and a *p* value of < 0.05 was considered statistically significant.

Results

Characteristics of the patients

Group A and B were consisted of 67 (63%) and 39 (37%) patients. At a median follow-up of 32.1 months (5.3-110.8), 56 (52.8%) patients were died. The median age of patients was 62 (range 30-83) years. There were 101 (95.3%) patients with European Cooperative Oncology Group (ECOG) performance score (0 and 1) in whole cohort. Median CCI index and Ca 125 value were estimated as 2 (0-7) and 93 kU/L (3-3141). High-grade serous histology consisted 94 patients out of 103 (3 missing data) in whole group. Significant number of patients (78.4%)
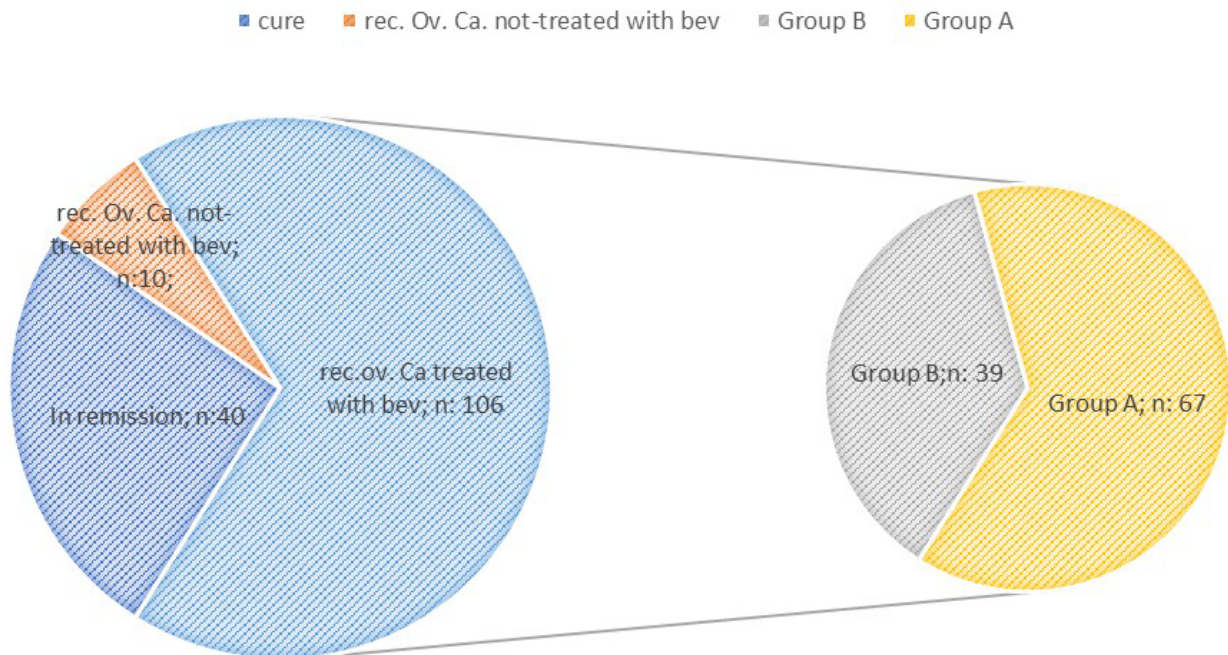
Figure 1. — Basic illustration of the study population and group A and B. Group A: PFS 1 > PFS 2; group B: PFS 2 < PFS 1; Rec. Ov. Ca: recurrent ovarian cancer; Bev: bevacizumab.

treated with primary surgery without neoadjuvant treatment and 59 (57.8%) out of the 102 patients (missing data in 4 patients) had secondary debulking surgery at relapse with decision of the gynecological oncology tumor board. The rates of no-visible disease from the first and salvage debulking surgery were 76.6 and 64.4%, respectively. All patients treated with carboplatin (AUC 5-6) and paclitaxel (175 mg/m^2) /3wks as an adjuvant treatment schema. In relapse, 38 patients were treated with single agent LPD (37.5 mg/m2/3wk) plus bevacizumab (7.5 mg/kg). On the other hand, 68 patients were treated with carboplatin (AUC 5-6) and LPD (37.5 mg/m^2) /3wks plus bevacizumab (7.5 mg/kg). During these treatments, there were dose reduction in cytotoxic chemotherapy in 19 (33.9%) and 7 (21.9%) patients in group A and B, respectively (p: 0.33). Bevacizumab related grad 3 and above side effects detected in 13 (15%) and 10 (25%) in group A and B (p: 0.77).

When we compare the group A and B with descriptive statistics, there are no significant difference with regard to histopathology, outcome of the first and second surgical operation, ECOG performance score, Ca 125 value, CCI, age, chemotherapy dose reduction rate and class side effect related to bevacizumab. However, only parameter that show significant difference was number of platin resistant patients; Group A: 13 (19.4%) out of 67 patients $vs.$ Group B: 15 (38.6%) out of 39 patients with a p value of 0.041. This finding suggested that some of the platin resistant patients can reach higher PFS in second line when compared to first line treatment.

Treatment and outcomes

At a median follow-up of 32.1 months (5.3-110.8), 56 (52.8%) patients were died. PFS 1 and 2 were estimated as 16.5 mo (14.1-18.9) $vs.$ 13.7 mo (9.9-17.5) and 13.4 mo (8.0-18.6) $vs.$ 29.7 mo (21.5-38.0) in group A and B, respectively ($p < 0.001$ and $p < 0.001$). However, OS was estimated as 58.6 mo (32.2-85.0) $vs.$ 48.3 mo (43.5-53.1) in group A and B. Therefore, although, chemotherapy plus bevacizumab produce almost 30 mos of PFS 2 in group B, after progression third or later cytotoxic treatment produced marginal benefit (Table 1).

We included ECOG performance score, age, no-visible rate of primary surgery, cytoreductive surgery in relapse, platin resistance, and PFS1 parameters. (these parameters showed significant difference or $p < 0.35$ with descriptive statistics between group A and B, though PFS2 showed significant difference it is not logical to put in binary logistic regression, so we omit PFS2). Binary logistic regression indicates PFS1 is significant inverse predictor of entering Group B [Chi-Square = 16.5, df = 6 and $p = 0.011$ (< 0.05)]. The other five parameters ECOG performance score, age, no-visible rate of primary surgery, cytoreductive surgery in relapse, platin resistance are not significant. All the six parameters 'explain' 27.3% of the variability of including in group B. PFS1 is significant at the 5% level (PFS1 wald = 4.33, $p = 0.038$ ($p < 0.05$)). The odds ratio (OR) for the PFS1 1.12 (95% CI 1.007-1.247). The model correctly predicted 42.3% of cases in where patients included in Group B and 87.8% of cases in where patients included in Group A, giving an overall percentage correct prediction rate of 72.0.

Table 2. — *Univariate analysis and multivariate analysis of PFS-2 and OS.*

Univariate analysis and multivariate analysis of PFS-2				
Variable	Univariate analysis, Median time (95% CI)	p	Multivariate analysis HR, (95% CI)	p
Histology, n: 103				
serous, n: 94	19.4 (14.5-24.3)	0.025	2.87 (0.3-31.0)	0.385
non-serous, n: 9	6.05 (1.2-11.0)			
Neoadjuvant, n: 88				
Yes, n: 19	9.4 (4.1-14.7)	0.04	3.43 (0.8-15.7)	0.104
No, n: 69	19.4 (15.0-23.8)			
Primary surgery outcome, n: 77				
no-visible, n: 59	20.2 (13.2-27.3)	0.34		
visible, n: 18	19.0 (9.5-28.5)			
Platin resistance (< 6 mo), n: 106				
Yes, n: 28	11.6 (1.7-21.6)	0.014	1.23 (0.4-4.1)	0.737
No: n: 78	21.1 (17.5-24.7)			
Cytoreductive surgery at relapse, n: 102				
Yes, 59	26.5 (16.5-36.5)	0.001	0.3 (0.02-0.7)	0.028
No, 43	14.0 (5.6-22.4)			
Secondary surgery outcome, n: 59				
no-visible, n: 38	29.3 (25.4-33.2)	0.003	0.83 (0.3-2.1)	0.69
visible, n: 21	14.1 (12.0-16.2)			
Univariate analysis and multivariate analysis of OS				
Variable	Univariate analysis, Median time (95% CI)	p	Multivariate analysis HR, (95% CI)	p
Histology, n: 103				
serous, n: 94	48.3 (34.4-62.2)	0.007	0.6 (0.1-4.2)	0.65
non-serous, n: 9	23.0 (20.7-25.3)			
Neoadjuvant, n: 88				
Yes, n: 19	25.6 (21.0-30.3)	0.05	1.4 (0.2-10.1)	0.71
No, n: 69	48.3 (32.5-64.1)			
Primary surgery outcome , n: 77				
no-visible, n: 59	60.3 (39.3-81.2)	0.29		
visible, n: 18	33.0 (21.5-44.6)			
Platin resistance (< 6 mo), n: 106				
Yes, n: 28	25.7 (13.2-38.1)	< 0.001	4.0 (1.1-14.4)	0.04
No: n: 78	60.3 (44.4-76.1)			
Cytoreductive surgery at relapse, n: 112				
Yes, 59	61.4 (44.7-78.1)	< 0.001	0.8 (0.2-3.9)	0.78
No, 43	36.0 (27.4-44.7)			
Secondary surgery outcome, n: 59				
no-visible, n: 38	73.4 (56.6-90.1)	< 0.001	0.2 (0.07-0.58)	0.003
visible, n: 21	37.8 (26.3-49.1)			

PFS-2 and OS were estimated as 18.8 mos (14.4-23.3, 95% CI) and 48.3 mos (33.1-63.5, 95% CI) for whole group (Figure 2). PFS-2 of the Group A and B were found as 13.4 (8.0-18.8, 95% CI) and 29.7 (21.5-38.0, 95% CI) months, respectively ($p < 0.001$). OS of the Group A and B were found as 58.6 mos (32.2-85.0) and 48.3 mos (43.5-53.1, 95% CI), respectively (p: 0.72). Although, PFS-2 significantly higher in Group B compared to group, this difference did not translate into OS and the data showed that Group A patients had numerically higher OS compared to group B. We believe that lower PFS-1 (Table 1) and possible lower response to third or later line treatment in group is the main reason for this. Therefore, this group of patients substantially well responded to the bevacizumab, but they showed marginal response to conventional cytotoxic therapy. In univariate analysis, histology (serous *vs.* non-serous) (p: 0.025), presence neoadjuvant treatment (yes or no) (p: 0.04), platin resistance (< 6 mos; yes or no) (p: 0.014), cytoreductive surgery at second relapse (yes or no) (p: 0.001), secondary surgery outcome (no visible *vs.* visible) (p: 0.003) showed significant effect on PFS-2. Additionally, histology (serous *vs.* non-serous) (p: 0.007), presence neoadjuvant treatment (yes or no) (p: 0.05), platin resistance (< 6 mos; yes or no) ($p < 0.001$), cytoreductive
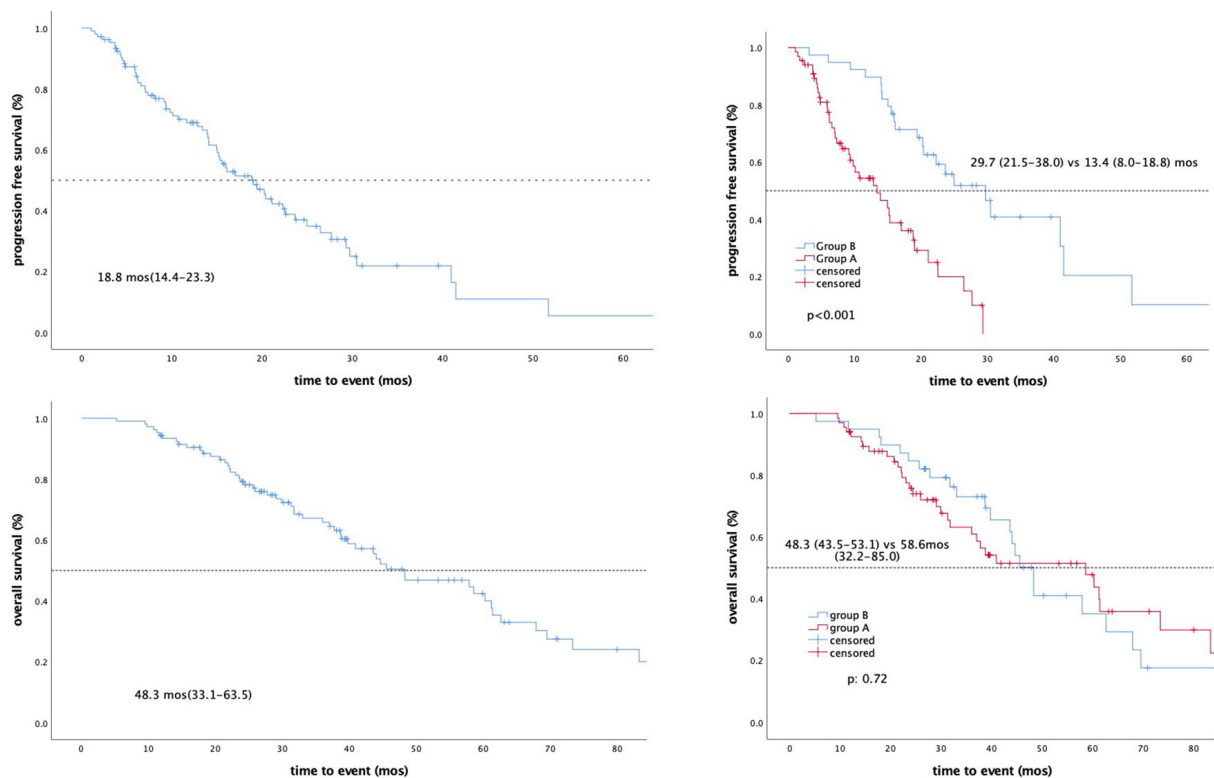
Figure 2. — Kaplan-Meier plots of PFS-2 and OS according to Group A and B and whole cohort of patients. These figures show group B patients showed statistically higher PFS-2 compared to group A but this difference in PFS-2 did not translate to OS.

surgery at second relapse (yes or no) ($p < 0.001$), secondary surgery outcome (no visible *vs.* visible) ($p < 0.001$) showed significant effect on OS (Table 2). In multivariate analysis, cox-regression proportional hazard, cytoreductive surgery at second relapse (yes or no) (*p*: 0.028; HR: 0.3, 0.02-0.7, 95% CI) showed significant effect on PFS-2. On the other hand, platin resistance (< 6 mos; yes or no) (*p: 0.04;* HR: 4.0, 1.1-14.4, 95% CI) and secondary surgery outcome (no visible *vs.* visible) (*p*: 0.003; HR: 0.2, 0.07-0.58, 95% CI) showed significant effect on OS (Table 2).

Discussion

Advanced stage ovarian cancer can be treated either primary surgery followed by adjuvant chemotherapy which produced almost 14-17 mos of median PFS and 30-40 mos of OS or neoadjuvant chemotherapy followed by debulking surgery which produced 12-13 mos of median PFS and 22-30 mos of OS [12-15]. Over 60-70 percent of the advanced stage ovarian cancer relapse and will probably need secondary debulking surgery with secondary systemic chemotherapy plus bevacizumab. According to platin resistance status of the patients platin doublet plus bevacizumab or single-agent chemotherapy plus bevacizumab produced 6.7 to 12.4 months of median PFS and 16.6. to 24.0 months of OS [16]. After two line of treatment, endocrine treatment with tamoxifen, targeted therapy for the patients carrying deleterious germline BRCA1-2 mutation, and further cyto-

toxic chemotherapy can be used with lower effectiveness, 3.4 to 7.0 months of PFS [17]. As clearly shown in the literature, as we moved to later lines of treatment, effectiveness of treatment protocols decrease significantly. Therefore, it is very important to guarantee for the patients taking maximum benefit from each treatment line. In current study, we try to define specific properties of the patients with exceptional profound disease control with bevacizumab in second line setting. Our results showed that in 37% of whole group (group B) of relapsed ovarian cancer patients, treatment with bevacizumab produced more PFS than treatments used even in adjuvant setting for stage IIIC ovarian patients. Interestingly, although, chemotherapy plus bevacizumab produce almost 30 mos of PFS 2 in group B, after progression third or later cytotoxic treatment produced marginal benefit. And median OS of the Group B patients even getting huge benefit from the bevacizumab their OS stays numerically lower than Group A patients [58.6 (32.2-85.0) *vs.* 48.3 mos (43.5-53.1, 95% CI), *p*: 0.72].

Bevacizumab is the first molecular-targeted anti-angiogenic drug which binds specifically to VEGF-A and targets VEGF-A in blood and tumor tissue. Though bevacizumab which has specific target, there are no predictive biomarkers currently available to deciding which patients derive more benefit from the bevacizumab. One of the systematic reviews reported that VEGF gene polymorphism, haplotype analysis of FLT1, plasma levels

of Ang-2 or LDH, and developing HTN after the beva-cizumab treatment may have a role as a potential laboratory and clinical biomarkers. However, none of these results was validated in large randomized trials [9]. Indeed, our retrospective analysis also failed to find any predictive clinical characteristics but give some important clues about clinical characteristics of the ovarian cancer patients whom most benefit from the bevacizumab.

Our analysis showed that 38% or patients in group B were platin resistant relapse, the rate of these patients was significantly higher than group A (15%). Also, binary lo-gistic regression showed that rate of shorter PFS-1 signifi-cantly increases the rate of inclusion into Group B and get most benefit from the bevacizumab treatment (29.7 *vs.* 13.4 mo). And this benefit only could be maximized with forc-ing secondary debulking with no-visible disease. When we think the literature suggest that platin resistance was rela-tive contraindication for the secondary debulking surgery in these patients, our data strongly suggest 38% of these patients may have 29.7 month of PFS-2 if we included aggressive secondary surgery and bevacizumab included chemotherapy regimen. Additionally, these patients even having gBRCA mutation would not be treated with PARP inhibitors, indeed they all excluded from the second line PARP inhibition studies because of platin resistant state [18]. Therefore, our data suggest that in 53% (15/28) of ovarian cancer patients with platin resistant relapse, beva-cizumab could produce over 24 months of PFS, and this gain could be maximized with forcing secondary debulking with no-visible disease.

Our results provide relevant data about clinicopathologi-cal characteristics of the ovarian cancer patients treated with chemotherapy plus bevacizumab at first relapse. However, some limitations are worth noting. The retrospective nature of the present study, the small size of the cohorts admittedly represents limitations which prevent us from drawing gen-eral conclusions. Additionally, our study was limited data for the toxicity data. Finally, some of the patients had con-traindication to bevacizumab treatment (n = 10) and their data not included into study and their clinical course was not mentioned. However, to the best of our knowledge, this is the first study that specifically focused on the patients' characteristics of ovarian cancer patients who gained over 24 months of PFS with bevacizumab.

In conclusion, our findings support that bevacizumab is effective treatment option at first relapse of ovarian can-cer. Even if patient had platin resistant relapse over 50% of these cases may produce over 24 months of PFS when bevacizumab combined with aggressive secondary surgery and no-visible surgical outcome. However, our data also showed that even group B patients gain enormous benefit from the bevacizumab treatment median OS was founded numerically lower than Group A patients. Lack of the re-sponse to third or further line of treatments of these cases was the main reason. Therefore, VEGF pathway is very active in ovarian cancer patients and a deeper understand-ing of primary and secondary resistance to bevacizumab is essential to maximize their efficacy.

Ethics approval and consent to participate

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. Informed consent was ob-tained from all individual participants included in the study. Ethical approval is not required due to retrospective nature of the study.

Acknowledgments

Conflict of Interest

All authors declare no conflicts-of-interest related to this article.

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Corresponding Author:
FATIH KOSE, M.D.
Baskent University Faculty of Medicine, Adana Dr. Turgut Noyan Research and Treatment Centre, Department of Medical Oncology, 01120 Adana Turkey
e-mail: fatihkose@gmail.com