JBUON 2020; 25(4): 1928-1934
ISSN: 1107-0625, online ISSN: 2241-6293 • www.jbuon.com
Email: editorial_office@jbuon.com

ORIGINAL ARTICLE

Half-dose bevacizumab experience in relapsed ovarian cancer patients in Turkey due to formal regulations: similar effectiveness with lower rate of hypertension

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Summary

Purpose: *Ovarian cancer is the fifth leading cause of cancer related death in women. Platin-based doublet regimens plus bevacizumab is standard treatment in relapse. Due to formal regulation of Turkish Ministry of Health, adjuvant bevacizumab has not been reimbursed and clinicians can use bevacizumab at a dose of 7.5 mg/kg/3wk in platin-resistant and sensitive relapse settings. The primary aim of this study was to evaluate 7.5 mg/kg/3wk bevacizumab dosing in platin-resistant and sensitive relapse ovarian cancer and compare these findings with the current literature.*

Methods: *A total 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.*

Results: *At a median follow-up of 32.1 months (5.3-110.8), 56 (52.8%) patients died. Progression-free survival (PFS) and overall survival (OS) were estimated at 18.8 months (14.4-23.3) vs 29.7 months (24.3-35.1) of the whole group overall survival. We observed that 78.4% of patients treated with primary surgery without neoadjuvant treatment and 59 (57.8%) out of the 102 patients with debulking surgery relapsed. A significant number of patients (81%) treated with primary surgery without neoadjuvant treatment and 59 (76.6 %) had secondary debulking surgery at relapse. In relapse, 38 patients were treated with single agent liposomal doxorubicin (LPD) plus bevacizumab. On the other hand, 68 patients were treated with carboplatin and LPD plus bevacizumab. Multivariate analysis failed to show any clinicopathological characteristics with significant effect on PFS. However, cytoreductive surgery at relapse showed significant effect on OS. Bevacizumab-related toxicities were detected in 23 (21.7%) patients; hypertension, pulmonary embolism, perforation, and other toxicities (nephrotic syndrome in 2, osteonecrosis in 2, cerebrovascular and cardiac ischemia in 3 patients) were seen in 12 (11.3%), 3 (2.8%), 1 (0.9%) and 7 (6.6%) patients, respectively.*

Conclusions: *In conclusion, our findings showed that 7.5 mg/kg/3week dosing of bevacizumab in relapsed ovarian cancer could have similar effectiveness compared to standard 15 mg/kg/3week dosing. Increase of OS and PFS in patients treated with primary and secondary debulking surgery with no-visible disease was more pronounced. No new safety information was observed but lower rate of grade 3 or above hypertension with similar rate of severe vascular and intestinal complications were detected.*

Key words: *ovarian cancer, bevacizumab, financial burden, effectiveness, toxicity*

Introduction

Ovarian cancer is the fifth leading cause of cancer related death in women worldwide. Despite the addition of novel systemic treatment options and more aggressive surgical debulking techniques in the last decades, a merely 30% of patients are potentially cured in advanced stages [1].

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Received: 05/04/2020; Accepted: 30/04/2020

Indeed, over 70% of patients relapse in the first 18 months. Chemotherapy is still the mainstay of systemic treatment [2]. However, operating an ovarian cancer patient based only on histopathological features is not sufficient, while based on genomic profiling, certain pathways are found to have particular importance [3].

Although each one of the pathways is not targetable, the pathways related with DNA repair and VEGF are effectively 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 malignancies 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 adjuvant, cisplatin-resistant and cisplatin-sensitive relapse settings of ovarian cancer [7-9]. These pivotal studies used bevacizumab at a dose of 15mg/kg/3weeks. However, due to formal regulation of Turkish Ministry of Health, adjuvant bevacizumab is not reimbursed and use bevacizumab in a dose of 7.5 mg/kg/3 weeks at platin-resistant and sensitive relapse settings.

The primary aim of this study was to evaluate the efficacy of bevacizumab at a dose of 7.5 mg/kg/3 weeks in platin-resistant and sensitive relapse of ovarian cancer and compare these findings with the current literature.

Table 1. Demographic and clinical characteristics of the study cohort

Characteristics	*n (%)*
Age (mean)	61.2
ECOG 0-1	101 (95.3)
CCI >2	63 (59.4)
Serum albumin (gr/dL),	106 (4.1)
Ca 125 (kU/L)	106 (267.9)
Histology subtype, serous	94 (91.3)
Neoadjuvant treatment	19 (21.6)
Primary surgery outcome, no-visible	59 (76.6)
Platin resistant cases	33(31.1)
Second debulking surgery	59 (57.8)
Secondary surgery outcome, no-visible	38 (64.4)
Chemotherapy dose reduction	26 (29.5)
Bevacizumab, grade 3-4 side effects	23 (21.7)
PFS, median (range), 95% CI	18.8 mo (14.4-23.3)
OS, median (range), 95% CI	29.7 mo (24.3-35.1)

CCI: Charlston Co-morbidity index; ECOG: Eastern Cooperative Oncology Group, PFS: progression free survival; OS: overall survival

Methods

Patients

A 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, "Dr. Turgut Noyan Research and Treatment Centre", Adana, between 2012 and 2018.

The main demographic and clinicopathological characteristics including age, Charlston comorbidity index (CCI), ECOG performance status, histology, 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. The initial date of ovarian cancer diagnosis, date of first and second relapse and the death/last control were noted (Table 1).

Statistics

All of the results were presented as the rate for categorical values or mean/median for continuous variables. Overall survival (OS) was defined from first relapse to death/last control date and reported in months. Progression-free survival (PFS) was defined from first relapse to second relapse. Survival curves were estimated according to the Kaplan-Meier method, and log-rank test was used for univariate statistical comparisons. Adjusted Hazard Ratio (HR) and 95% confidence interval (95% CIs) were used for estimation of survival parameters. 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

Patient characteristics

The whole cohort consisted of 106 patients and the median follow-up was 32.1 months (range 5.3-110.8). During follow-up 56 (52.8%) patients died. The median age of the patients was 61.2 years (range 30-83). There were 101 (95.3%) patients with Eastern Cooperative Oncology Group (ECOG) performance score (0 and 1) in the whole cohort. Median CCI index and Ca 125 value were estimated as 2 (0-7) and 133 kU/L (19-1247). High-grade serous histology was found in 94 out of 103 patients (3 missing data) in the whole group. A significant number of patients (81%) were treated with primary surgery without neoadjuvant treatment and 59 (76.6 %) out of the 102 patients (missing data

in 4 patients) had secondary debulking surgery at relapse after decision of the gynecological oncology tumor board. There were 33 (31.1%) patients who relapsed before the 6th month after the last dose of adjuvant chemotherapy and were characterized as platin-resistant relapse. The rates of no-visible disease from the first and salvage debulking surgery were 76.6 and 64.4%, respectively. All patients were treated with carboplatin (AUC 5-6) and paclitaxel (175 mg/m^2/3 weeks as an adjuvant treatment schema. In relapse, 38 patients were treated with single agent liposomal doxorubicin

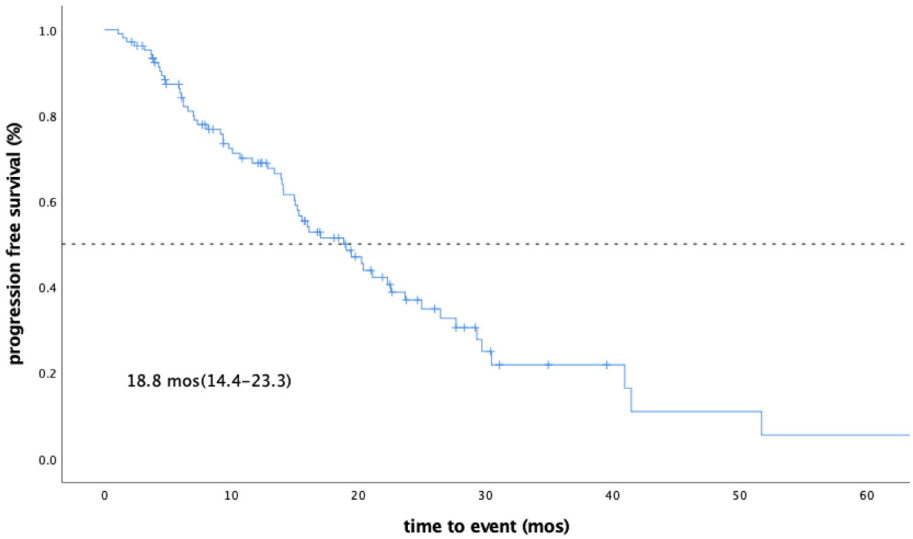

Figure 1. Kaplan-Meier estimates of progression-free survival for the whole group (n=106).

Table 2. Univariate and multivariate analysis of PFS

Variables	*Univariate analysis, Median time (95% CI)*	*p*	*Multivariate analysis HR, (95% CI)*	*p*
ECOG 0 and >1				
0, 23	23.7 (9.0-38.3)	**0.04**	0.82 (0.28-2.34)	0.70
>1, 83	15.2 (13.3-17.0)			
Histology, n:103				
non-serous, n:9	6.05 (1.2-11.0)	**0.03**	1.31 (0.27-6.36)	0.39
serous, n:94	19.4 (14.5-24.3)			
Neoadjuvant, n:88				
Yes, n:19	9.4 (4.1-14.7)	**0.04**	2.75(0.58-13.0)	0.20
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(<6mo), n:106				
Yes, n:33	11.6 (3.4-19.8)	**0.01**	0.69 (0.21-2.24)	0.53
No: n:73	21.1 (17.0-25.2)			
Cytoreductive surgery at relapse, n:102				
Yes, 59	26.5 (16.5-36.5)	**0.001**	0.61(0.23-1.64)	0.33
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**	0.61 (0.23-1.64)	0.61
visible, n: 21	14.1 (12.0-16.2)			
Class side effect of bevacizumab, n:106				
No, 83	16.0 (11.7-20.2)	0.124	1.22(0.40-3.68)	0.73
Yes, 23	23.7 (11.9-35.4)			

Bold numbers denote statistical significance

(LPD) (37.5 mg/m^2/3 weeks) plus bevacizumab (7.5 mg/kg). On the other hand, 68 patients were treated with carboplatin (AUC 4-5) and LPD (37.5 mg/m^2) /3 weeks plus bevacizumab (7.5 mg/kg). During these treatments, dose reduction of chemotherapeutics was necessary in 26 (25%) patients. Bevacizumab-related grade 3 and above side effects were detected in 23 (21.7%) patients.

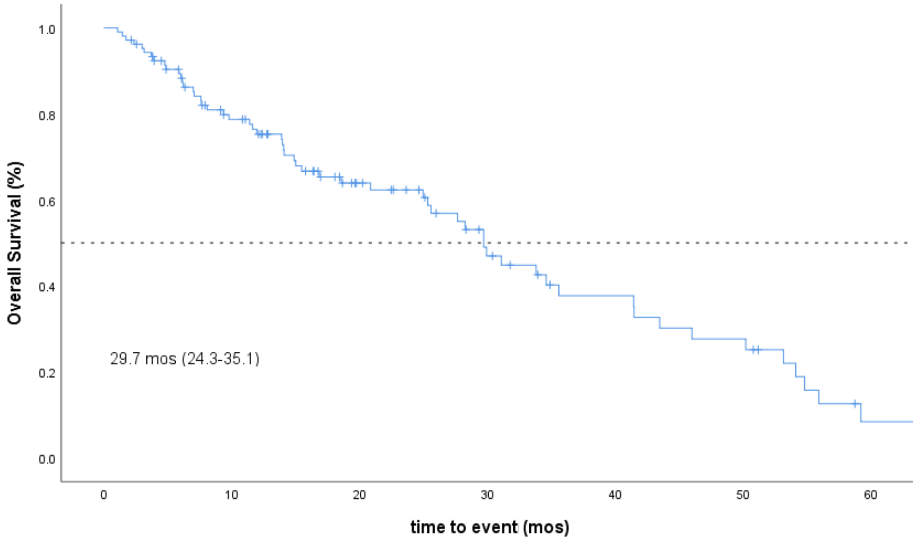

Figure 2. Kaplan- Meier plots of overall survival in the whole cohort (n=106).

Table 3. Univariate and multivariate analysis of OS

Variables	*Univariate analysis, Median time (95% CI)*	*p*	*Multivariate analysis HR, (95% CI)*	*p*
ECOG 0 and >1				
0, 23	Not reached	**<0.01**	0.61 (0.19-1.98)	0.41
>1, 83	25.3 (14.4-36.2)			
Ca 125 value(median), 106 kU/L, spearman correlation test	Sign, 2-tailed, Correlation, -0.345	0.01	1.00 (0.99-1.01)	0.39
Histology, n:103				
non-serous, n:9	6.1 (5.9-6.4)	**0.02**	3.2 (0.35-29.4)	0.30
serous, n:94	29.9 (23.4-36.5)			
Neoadjuvant, n:88				
Yes, n:19	14.0 (5.9-22.1)	**0.02**	3.2(0.67-15.5)	0.15
No, n:69	29.9 (26.0-33.9)			
Primary surgery outcome, n:77				
no-visible, n:59	29.7 (10.2-49.2)	0.64		
visible, n: 18	29.9 (not counted)			
Platin resistance (<6mo), n:106				
Yes, n:28	28.3 (9.6-47.0)	**0.02**	0.53 (0.13-2.15)	0.38
No: n:78	31.1 (17.8-44.4)			
Cytoreductive surgery at relapse, n:112				
Yes, 59	35.6 (22.3-48.8)	**<0.01**	**0.01(0.01-0.32)**	**<0.01**
No, 43	16.9 (4.9-28.8)			
Secondary surgery outcome, n: 59				
no-visible, n:38	41.5 (16.9-66.1)	**<0.01**	0.6 (0.2-1.7)	0.38
visible, n: 21	18.6 (0.00-37.8)			
Class side effect of bevacizumab, n:106				
No, 83	29.7 (24.2-35.2)	0.173	0.63(0.19-2.15)	0.46
Yes, 23	35.6 (20.9-50.3)			

Bold numbers denote statistical significance

Treatment and outcomes

At a median follow-up of 32.1 months (range 5.3-110.8), 56 (52.8%) patients died. Median PFS and OS were 18.8 months (range 14.4-23.3) vs 29.7 months (range 24.3-35.1) in the whole group (Figure 1 and 2).

In univariate analysis, ECOG performance status (0 vs >1) (p:0.04), histology (serous vs non-serous) (p:0.03), administration of neoadjuvant treatment (yes vs no) (p:0.04), platin resistance (<6 months; yes vs no) (p:0.01), cytoreductive surgery at second relapse (yes vs no) (p:0.001), second surgery outcome (no visible vs visible disease) (p:0.003) showed significant effect on PFS (Table 2). Additionally, ECOG performance status (0 vs >1) (p<0.01), Ca-125 at recurrence (Spearman correlation test) (p:0.01, 2-tailed, -0.345), histology (serous vs non-serous) (p:0.02), administration of neoadjuvant treatment (yes vs no) (p:0.02), platin resistance (<6 months; yes vs no) (p:0.02), cytoreductive surgery at second relapse (yes vs no) (p<0.01), secondary surgery outcome (no visible vs visible) (p<0.01) showed significant effect on OS (Table 3). In multivariate Cox regression analysis (results of univariate analysis with p<0.3 were included), statistical analysis failed to reveal any clinicopathological characteristics showing significant effect on PFS. However, Cox multivariate analysis (results of univariate analysis with p<0.3 were included) cytoreductive surgery at relapse showed significant effect on OS (p<0.01; HR:0.01, 0.01(0.01-0.32), 95%CI) (Tables 2,3).

During the active treatment period, dose reductions of carboplatin and LPD were necessary in 26 (29.5%) and 15 (20.8%) patients. Grade 3 or higher hematological and non-hematological toxicities and hand-foot syndrome were seen in 21 (20.8%), 11 (11.9%) and 11 (12.8) patients, respectively. Bevacizumab-related toxicities were detected in 23 (21.7%) patients and included hypertension, pulmonary embolism, gastrointestinal perforation, and other toxicities (nephrotic syndrome in 2, osteonecrosis in 2, cerebrovascular and cardiac ischemia in 3 patients) seen in 12 (11.3%), 3 (2.8%), 1 (0.9%) and 7 (6.6%) patients, respectively. Univariate and multivariate analysis failed to show significant effect of chemotherapy-related toxicities, dose-reductions and class side effect of bevacizumab on PFS and OS (p>0.05) However, patients who developed bevacizumab-related class side effects showed numerically higher PFS and OS [23.7 (range 11.9-35.4) 95%CI vs 16.0 months (range 11.7-20.2), 95%CI, p: 0.124] and 35.6 (range 20.9-50.3) vs 29.7 months (range 24.2-35.2), 95%CI, p:0.173), respectively. The treatment of 21 patients (20.8%) was discontinued because of grade 3 or higher toxicities.

Discussion

Relapsed ovarian cancer patients are treated according to platin resistance status (>6 vs<6 months) either with platin doublet plus bevacizumab or single-agent chemotherapy plus bevacizumab which produced 6.7 to 12.4 months of median PFS and 16.6. to 24.0 months of OS [10]. After two lines of treatment, endocrine treatment with tamoxifen, targeted therapy for the patients carrying deleterious germline BRCA1-2 mutation, and further cytotoxic chemotherapy can be used with lower effectiveness, i.e. 3.4 to 7.0 months of PFS [11].

In our study, at a median follow-up of 32.1 months (range 5.3-110.8), 56 (52.8 %) patients died. PFS and OS were estimated as 18.8 (range 14.4-23.3) vs 29.7 months (range 24.3-35.1) in the whole group. PFS of the platin-resistant and platin-sensitive relapse were 11.6 (range 3.4-19.8) and 21.1 months (range 17.0-25.2), respectively. OS of the platin-resistant and platin-sensitive relapse were 28.3 (range 9.6-47.0) and 31.1 months (range 17.8-44.4), respectively. Therefore, our data suggested that bevacizumab 7.5 mg/kg/3weeks could be as effective as bevacizumab 15 mg/kg/3weeks in ovarian cancer. Multivariate analysis showed that PFS and OS benefit was consistent in the whole group, but the patients treated with aggressive primary and secondary debulking surgery with no-visible disease displayed significantly more benefit from the bevacizumab. In two pivotal trials OCEANS and AURELIA, bevacizumab did not increase the chemotherapy related side effects like fatigue, hematological toxicity and delayed or acute type emesis, but added class side effect like hypertension, arterial and venous embolism, and vascular complications [7,10]. In the current study, we reported lower rate of grade 3 or above hypertension (20% vs 11.3%, respectively). However, our data showed similar rates of pulmonary embolism, gastrointestinal perforation, and other toxicities (nephrotic syndrome in 2, osteonecrosis in 2, cerebrovascular and cardiac ischemia in 3 patients) seen in 3 (2.8%), 1 (0.9%) and 7(6.6%) patients, respectively. Consequently, lower rates of severe hypertension and similar rates of other serious side effect could be expected in ovarian cancer patients treated with bevacizumab 7.5 mg/kg/3weeks.

On the other hand, bevacizumab showed linear pharmacokinetics in the range of 0.3 to 10 mg/kg dosing and reached stable concentration in 10-12 weeks. No dose adjustment is recommended for any patient characteristics or organ dysfunction [12]. Bevacizumab dosing is different in distinct tumor types which are not completely evidence-

based. For example, 5 mg/kg/2weeks along with chemotherapy in colon cancer, 10 mg/kg/2weeks in glioblastoma, and 15 mg/kg/3weeks in ovarian cancer were used [7-9]. Bevacizumab metabolism and excretion from the body is not delineated, but it is most likely cleared by reticuloendothelial system. Half-life is 21 days and reaches steady plasma concentration in 100 days. Studies with various chemotherapeutics reported that no pharmacokinetic interaction with any type of chemotherapeutics. At least one study in renal cancer showed that escalated doses (15 mg/kg/week vs 15 mg/kg/2weeks) of bevacizumab was feasible but not efficacious than standard dose of bevacizumab [13]. In the current study, our data indicated that bevacizumab dosing with 7.5 mg/kg/3week in ovarian cancer produced substantial survival benefit with low financial toxicity.

Bevacizumab is the first molecular-targeted anti-angiogenic drug which binds specifically to VEGF-A and targets VEGF-A in blood and tumor tissues. Despite bevacizumab has a specific target, there are no predictive biomarkers currently available to deciding which patients derive more benefit from bevacizumab. One of the systematic reviews reported that VEGF gene polymorphism, haplotype analysis of FLT1, plasma levels of Ang-2 or LDH, and developing hypertention after the bevacizumab treatment may have a role as potential laboratory and clinical biomarkers. However, none of these results was validated in large randomized trials [9]. In the current study, we also could not define predictive clinical characteristics, but we also showed that someone should not suggest that bevacizumab is not alternative to aggressive debulking surgery in ovarian cancer. Indeed, the increase of OS and PFS in patients treated with primary and secondary debulking surgery with no-visible disease was more pronounced.

Hypertension is accepted as dose-dependent toxicity, however late presenting hypertention (>6 months) accompanied with high grade venous thromboembolism, osteonecrosis, intestinal perforation and bleeding were not truly dose-dependent toxicities [14]. In the current study, results of safety data coincide almost with the relevant literature. The rate of grade 3 and above hypertension was found to be lower compared to literature but there were similar rates of other serious grade 3 or above side effects like embolism, osteonecrosis, and nephrotic syndrome.

Our results provide relevant data about clinicopathological characteristics and outcome of the ovarian cancer patients treated with chemotherapy plus lower dose of bevacizumab at first relapse. However, some limitations are worth noting. The retrospective nature of the present study and its small size represent limitations which prevent us from drawing general conclusions. Additionally, our study was limited by lack of case data for toxicity. Finally, some of the patients had contraindication to bevacizumab treatment (n=10) and their data were not included into the study, while 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, outcomes, safety of 7.5 mg/kg/3weeks dosing of bevacizumab in relapsed ovarian cancer patients.

In conclusion, our findings showed that 7.5 mg/kg/3weeks dosing of bevacizumab in relapsed ovarian cancer could have similar effectiveness compared to standard 15 mg/kg/3weeks dosing. Bevacizumab is not alternative to aggressive surgical measures in ovarian cancer. Increase of OS and PFS in patients treated with primary and secondary debulking surgery with no-visible disease was more pronounced. No new safety warning was observed but lower rate of grade 3 or above hypertension was seen. Therefore, 7.5 mg/kg/3weeks dosing of bevacizumab may be used in relapsed ovarian cancer with similar effectiveness and low financial toxicity.

Conflict of interests

The authors declare no conflict of interests.

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