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ORIGINAL ARTICLE

Evaluation of the Efficacy of Bevacizumab-based Therapies in Patients with Platinum-Resistant or -Allergic Metastatic Ovarian Cancer

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OBJECTIVE

This study assessed the efficacy of chemotherapeutic agents used in combination with bevacizumab in patients with metastatic ovarian cancer who could not receive platinum.

METHODS

The study is a retrospective observational study. Kaplan-Meier and Cox regression methods were used for statistical analysis.

RESULTS

The most common metastatic sites among the 60 patients were the peritoneum (91.7%), liver (51.7%), and lung (20%). As a single agent combined with bevacizumab, 29 (48.3%) patients received paclitaxel, 16 (26.7%) received liposomal doxorubicin, and 15 (25%) received gemcitabine. The median progression-free survival was 7.5 months (95% CI, 3.4–11.4), and the median overall survival was 14.4 months (95% CI, 9.3–19.4). Among the factors that affected overall survival, the number of metastasis sites (p=0.01) was statistically significant. The type of chemotherapy used with bevacizumab (p=0.55), age (p=0.057), liver metastasis (p=0.28), lung metastasis (p=0.19), bone metastasis (p=0.13), and brain metastasis (p=0.12) were not statistically significant.

CONCLUSION

Single-agent chemotherapy drugs used with bevacizumab demonstrated similar efficacy against ovarian cancer. Patients' performance scores, previous treatment regimens, and side effect profiles should be considered before administering any specific chemotherapy agent in combination with bevacizumab.

Keywords: Bevacizumab; chemotherapy; metastasis; ovarian cancer; platinum resistance.

INTRODUCTION

Ovarian cancer (OC) is the eighth most common type of malignant tumor and cause of death among women worldwide.[1] Epithelial OC (EOC) constitutes approximately 85%–90% of all diagnosed ovarian tumors and typically occurs in women from 55–65 years old.[2] Diagnosis is typically delayed because patients with early-stage EOC do not present significant symptoms.[3] The standard initial treatment approach for advanced EOC

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is cytoreductive surgery followed by chemotherapy using platinum and taxane-based regimens.[4,5] Despite high response rates following initial treatment of advanced-stage EOC, recurrence occurs in approximately 80% of cases within five years.[6] Treatment of recurrent EOC depends on the amount of time since the previous platinum-based treatment. Patients who experience recurrence or progression within six months of completing platinum-containing chemotherapy are classified as platinum-resistant and exhibit a median overall survival (OS) of approximately 12–18 months. Patients who remain free from disease progression for at least six months after completing platinum-containing treatment are considered platinum-sensitive; they tend to respond favorably to platinum-based drugs. However, patients with platinum-resistant disease or allergic reactions to platinum compounds respond poorly to alternative single-agent chemotherapy regimens.[7,8] Thus, there is a critical need for new treatment options for patients with platinum-resistant EOC.

Angiogenesis promotes tumor growth and metastasis; bevacizumab, a monoclonal antibody that targets vascular endothelial growth factor A (VEGF-A), is a key factor in this pathway.[9] Studies have shown that the combination of single-agent chemotherapy with bevacizumab is an effective treatment strategy for patients diagnosed with platinum-resistant or -allergic metastatic EOC. In particular, the AURELIA study showed that single-agent chemotherapy with paclitaxel, topotecan, and pegylated liposomal doxorubicin (PLD) in combination with bevacizumab was effective in a cohort of 361 patients diagnosed with platinum-resistant EOC. The overall response rate (ORR), as well as the durations of progression-free survival (PFS) and OS, significantly improved when bevacizumab was included in chemotherapy. Moreover, the results were slightly better in the paclitaxel group compared to the others.[10]

Few studies have assessed the efficacy of various chemotherapies combined with bevacizumab in patients with platinum-resistant or -allergic metastatic EOC. Therefore, this study aimed to compare the effectiveness of chemotherapy agents used with bevacizumab in these patients.

MATERIALS AND METHODS

Patient Demographics and Data Collection

This retrospective cross-sectional study was approved by both the academic and ethical committees of our institution. It was conducted in adherence to the principles outlined in the Declaration of Helsinki. The study included patients who were monitored at an oncology center's outpatient clinic between 2010 and 2022. Participants were identified within the institution's database. All patients diagnosed with recurrent platinum-resistant or -allergic EOC and who received non-platinum, single-agent chemotherapy in combination with bevacizumab were assessed. Patients with insufficient data for statistical analysis were excluded from the study. Demographic and clinical information, such as age at diagnosis, family history (in accordance with the International Federation of Gynecology and Obstetrics classification), cancer stage, histological characteristics, prior adjuvant or neoadjuvant chemotherapy, number of bevacizumab cycles administered, number of chemotherapy cycles administered, radiotherapy treatments, surgical procedures, and recorded toxicities, were scrutinized from the medical database. This information was systematically documented and archived for subsequent analysis.

Treatment-related responses were evaluated through a combination of clinical assessments and radiological examinations conducted every 2–3 months. Following the Response Evaluation Criteria in Solid Tumors (RECIST 1.1) guidelines, treatment responses were categorized into four groups: complete response (CR), partial response (PR), stable disease (SD), and progressive disease (PD). These classifications were used to determine the best possible response achieved by patients. The ORR was calculated by summing the CR and PR cases. The disease control rate (DCR) was determined by considering not only CR and PR but also SD cases. Adverse events associated with the treatment were documented during each patient's visit. The severity of these events was systematically assessed and graded in accordance with the Common Terminology Criteria for Adverse Events, version 5. PFS was defined as the duration from the initiation of bevacizumab with chemotherapy to disease progression. OS refers to the time from the start of bevacizumab-based therapy to death. We also conducted a univariate analysis to evaluate the influence of clinical and pathological factors on OS, whose results were included in a multivariate analysis with factors previously identified as significant in the literature.

Statistical Analysis

Statistical analyses were conducted using SPSS software version 25. Continuous variables are presented as medians and the corresponding minimum and maximum values. Categorical variables are expressed as numbers and percentages. Survival curves were constructed using the Kaplan–Meier method. Uni-

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Table 1 Clinical and pathological features of the patients

Characteristics	n	%	Characteristics	n	%
Age at diagnosis			Bone	4	7
<60 years	36	60	Brain	2	3
≥60 years	24	40	The number of metastatic sites		
Family history for ovarian cancer			≤2 sites	33	55
No	57	95	>2 sites	27	45
Yes	3	5	Total number of surgeries prior to bevacizumab		
Pathologic subtypes			No	2	3
Serous	50	83	1	45	75
Others	10	17	2–4	13	22
Grade status			Perioperative chemoterapy before bevacizumab		
Grade 1–2	8	13	No	1	2
Grade 3	52	87	Yes	59	98
BRCA mutation status			Palliative chemoterapy before bevacizumab		
Not examined	45	75	No	12	20
BRCA 1	6	10	Yes	48	80
BRCA 2	0	0	HT before bevacizumab based treatment		
Negative	9	15	No	42	70
Stage at diagnosis			Yes	18	30
Stage 1–2	5	8	CT used in combination with bevacizumab		
Stage 3	42	70	PLD	16	27
Stage 4	13	22	Weekly paxlitaxel	29	48
Sites of metastasis			Gemcitabine	15	25
Liver	31	52	After bevacizumab treatment		
Periton	55	91	CT	32	53
Lungs	12	20	Other (HT, Surgery, RT)	11	18

BRCA: Breast cancer gene; HT: Hormone therapy; CT: Chemotherapy; PLD: Pegylated liposomal doxorubicin; RT: Radiotheraphy

variate analysis was performed using the log-rank test. Multivariate analysis was conducted using the Cox regression model to assess the independent effects of various variables on the outcomes of interest.

RESULTS

Patient Characteristics and Treatment Modalities

A total of 60 patients with primary platinum-resistant or -allergic metastatic EOC were included in this study. The median age of these patients was 57 years, with a range from 26 to 76 years. The majority (83%) of patients were diagnosed with serous adenocarcinoma, whereas the remaining (17%) were classified into other pathological subgroups, including clear-cell, endometrioid, and mucinous subtypes. Table 1 presents an overview of the clinical and pathological characteristics of the patient cohort. Notably, 58 out of 60 patients (97%) underwent primary surgery before initiating bevacizumab-based treatment. All of them, except for one patient, received perioperative chemotherapy. Forty-eight patients (80%) received palliative chemotherapy. Among those who were administered a chemotherapeutic drug in combination with bevacizumab, 16 (27%), 29 (48%), and 15 (25%) received PLD, weekly paclitaxel, and gemcitabine regimens, respectively. The median number of chemotherapy cycles administered in combination with bevacizumab was 9, with a range from 2 to 55 cycles. On average, these patients underwent 10 bevacizumab cycles, though this number ranged from 1 to 55 cycles.

Patients were then classified by treatment response: 3 patients (5%) achieved CR, 26 patients (43%) achieved PR, 11 patients (18%) exhibited SD, and 20 patients (33%) exhibited PD. The ORR was 48%, and the DCR for all patients was 67% (Table 2). Five patients (8%) experienced grade >2 hypertension. Gastrointestinal system (GIS) perforation occurred in one patient (2%), and another (2%) developed a fistula. Thromboembolic events, hemorrhage, and heart failure were reported in three patients (5%), one patient (2%), and one patient (2%), respectively. Febrile neutropenia was observed in six patients (10%) (Table 3). Bevacizumab treatment was discontinued in 50 patients (83%) due to disease progression, in six patients

Table 2 Responses to bevacizumab based chemotherapy in recurrent platinum-resistant or -allergic metastatic EOC

	Total n=60	
	n	%
Response ratios		
Complete response	3	5
Partial response	26	43
Stable disease	11	18
Progression	20	33
Objective response ratio	29	48
Disease control ratio	40	66

EOC: Epithelial OC

Table 3 Grade >2 side effects of bevacizumab plus chemotherapy

Variables	n	%
Hypertension	5	8
Proteinuria	2	3
GIS perforation	1	2
Fistula	1	2
Thromboembolic events/hemorrhage	3	5
Febrile neutropenia	6	10
RPLS	0	0
Congestive heart failure	1	2

GIS: Gastrointestinal system; RPLS: Reversible posterior leukoencephalopathy syndrome

(10%) due to treatment-related toxicity, and in two patients (3%) due to an insufficient treatment duration.

Survival Outcomes

The median follow-up periods after recurrent disease and PFS were 40 months and 9.6 months, respectively. The median PFS was 7.5 months (95% CI: 9.437–11.496) as shown in Figure 1. The median OS was calculated at 14.4 months (95% CI: 2.579–9.346) as shown in Figure 2. Factors such as age, pathology type, grade, initial stage, perioperative chemotherapy, pre-bevacizumab radiotherapy, and hormone therapy status had no significant ($p>0.05$) impact on survival rates. The survival rate of patients with multiple metastatic sites was significantly lower ($p=0.010$, $p<0.05$) than those with fewer sites. Among those who underwent different chemotherapy regimens combined with bevacizumab, no substantial differences in OS were found between weekly paclitaxel (19.5 months), PLD (12.6 months), and gemcitabine (18 months) in combination with bevacizumab ($p=0.783$, $p>0.05$) (Tables 4, 5).

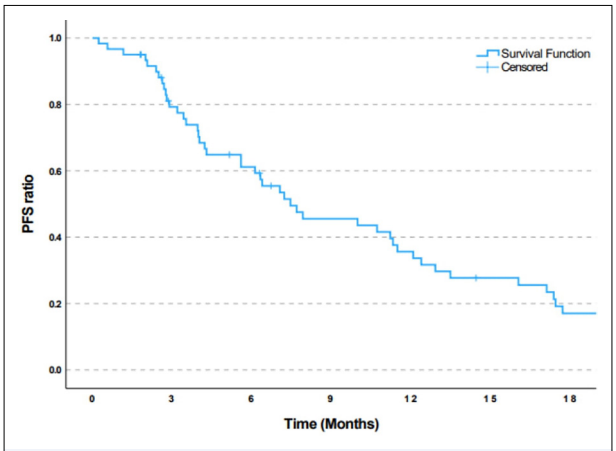

Fig. 1. Kaplan–Meier curve of progression-free survival in patients with platinum-resistant or -allergic metastatic EOC treated with chemotherapy plus bevacizumab.
EOC: Epithelial OC.

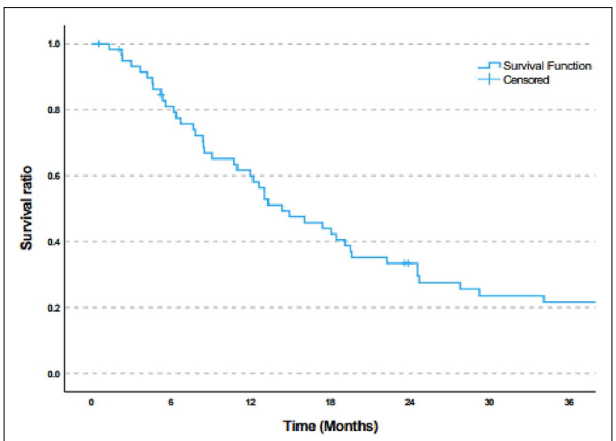

Fig. 2. Kaplan–Meier curve of overall survival in patients with platinum-resistant or -allergic metastatic EOC treated with chemotherapy plus bevacizumab.

DISCUSSION

Carboplatin is the most commonly administered chemotherapeutic agent for managing metastatic EOC. However, some patients with recurring EOC do not respond to, or are allergic to, platinum-based drugs like carboplatin. Although patients who are allergic to platinum can undergo desensitization, this method may not be suitable for all patients. Desensitization requires access to an advanced medical center equipped with a skilled and experienced healthcare team.[11] On the other hand, platinum-resistant patients typically undergo single-agent, non-platinum chemotherapies with bevacizumab. Few stud-

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Table 4 Univariate analysis for survival analysis

	Total n	Ex n	Survivors n	Survival rate (36 month) %	p
Age at diagnosis					
<60	36	29	7	19	**0.016***
≥60	24	23	1	4	
Grade status					
Grade 1–2	8	6	2	50.0	**0.302**
Grade 3	52	46	6	11.5	
Stage at diagnosis					
Stages 1–2–3	47	41	6	12.8	**0.706**
Stage 4	13	11	2	15.4	
Primary surgery before bevacizumab					
No	2	2	0	0	**0.011****
Yes	58	50	8	13.8	
Paliative chemoterapy before bevacizumab					
No	12	10	2	16.7	**0.983**
Yes	48	42	6	12.5	
Liver metastasis					
No	29	25	4	13.8	**0.573**
Yes	31	27	4	12.9	
Peritoneum metastasis					
No	5	5	0	0	**0.074**
Yes	55	47	8	14.5	
Lung metastasis					
No	48	40	8	16.7	**0.182**
Yes	12	12	0	0	
Brain metastases					
No	58	50	8	13.8	**0.001****
Yes	2	2	0	0	
Bone metastasis					
No	56	48	8	14.3	**0.001****
Yes	4	4	0	0	
Number of metastatic sites					
≤2 sites	33	25	8	24.2	**0.064**
>2 sites	27	27	0	0	
CT used in combination with bevacizumab					
PLD	16	15	1	6.3	**0.783**
Weeekly paxlitaxel	29	27	2	6.9	
Gemcitabine	15	10	5	33.3	

*: p<0.05; **: p<0.01

ies have compared the efficacy of various chemotherapy agents used in combination with bevacizumab.[12–14] The AURELIA trial is the first Phase III clinical trial that directly compared the combination of bevacizumab with single-agent chemotherapy against chemotherapy alone in the context of recurrent, platinum-resistant ovarian cancer. Chemotherapy agents included weekly paclitaxel, PLD, or topotecan. Including bevacizumab in the treatment regimen significantly increased PFS to 6.7 months from 3.4 months in chemotherapy alone. Although the OS was 16.6 months in the bevacizumab group and 13.3 months in the chemotherapy-alone group, this difference was not statistically significant. Notably, the true impact of bevacizumab on OS was obscured and likely diluted by the fact that 40% of patients in the chemotherapy group crossed over to receive bevacizumab monotherapy upon

Table 5 Multivariate cox regression analysis for overall survival

	p	HR	95% CI	
			Lower	Upper
Age				
<60 years vs ≥60	**0.057**	1.958	0.980	3.913
The number of metastatic sites				
≤2 sites vs >2 sites	**0.010***	3.850	1.377	10.763
Liver metastasis				
Yes vs no	**0.282**	0.643	0.287	3.913
Peritoneal metastases				
Yes vs no	**0.991**	1.008	0.258	3.940
Lung metastasis				
Yes vs no	**0.194**	0.545	0.218	1.361
Bone metastases				
Yes vs no	**0.134**	3.107	0.704	13.706
Brain metastases				
Yes vs no	**0.120**	4.421	0.679	28.773
CT in combination with bevacizumab				
Gemcitabine	**0.853**	reference		
Weekly paclitaxel	**0.420**	0.730	0.340	1.568
PLD	**0.287**	0.579	0.212	1.582

*: p<0.05. Multivariate analysis model p-value <0.05 was considered statistically significant. HR: Hazard ratio; CI: Confidence interval

experiencing disease progression. Subgroup analysis revealed that the ORR from combinatorial, bevacizumab-based therapy was most pronounced in the paclitaxel group (53.3% ORR compared to 30.2%).

No significant difference in OS was found between treatments in any of the chemotherapy cohorts. Patients who received PLD or topotecan in addition to bevacizumab had slightly higher OS of 14.1 and 13.8 months, respectively, compared to their single-agent counterparts of 13.7 and 13.3 months. However, a more pronounced effect on OS was observed in the paclitaxel cohort (22.4 vs 13.2 months).[15] In our study, the median PFS duration of 7.5 months agreed with the previous trial (6.7 months). Although not statistically significant, the weekly paclitaxel regimen had a more positive effect on OS compared to other regimens. The median OS was 19.5 months for weekly paclitaxel, 12.5 months for PLD, and 18 months for gemcitabine (p=0.783, p>0.05). The OS of all patients in our study was slightly lower at 14.4 months compared to the 16 months reported in the AURELIA trial. This discrepancy may be attributed to the fact that our study used real-world data, whereas the AURELIA study was conducted on selected patient populations. Another study assessed the efficacy of the combination of bevacizumab and PLD against platinum-resistant EOC; the DCR was 73%, and the PFS was six months.[16] Our findings were similar: a DCR of 67% and a PFS duration of 7.5 months. A Phase II clinical trial investigated the combination of bevacizumab and albumin-bound paclitaxel in patients with platinum-resistant EOC and reported an ORR of 50% and PFS of eight months,[17] similar to the ORR (48%) and PFS (7.5 months) reported here. In our study, approximately 8% of patients presented with grade >2 hypertension. Although some complications such as GIS, thromboembolic events, hemorrhage, and heart failure were observed in a small number of patients, bevacizumab was well-tolerated in most cases; only 10% of patients discontinued treatment due to toxicity. These findings are consistent with results from previous studies.[18]

Limitations of The Study

This study has some limitations. The retrospective design of our study led to a heterogeneous patient group, and some data were incomplete or missing. Retrospective and single-center studies like ours may present selection bias.

CONCLUSION

In this study, we highlighted the effectiveness and safety of combining bevacizumab with single-agent chemotherapy for platinum-resistant or -allergic metastatic EOC. Overall, there were no significant differences between

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treatment modalities for recurrent EOC. Bevacizumab was well-tolerated by most patients and improved patient outcomes. Ultimately, treatment strategies should consider factors like the patient's treatment history, comorbidities, drug side effects, and related variables.

Ethics Committee Approval: The study was approved by the Istanbul University Istanbul Faculty of Medicine Clinical Research Ethics Committee (no: 2022/1652, date: 07/10/2022).

Authorship contributions: Concept – N.K., İ.D., P.S., A.Ay.; Design – N.K., İ.D., P.S., A.Ay.; Supervision – N.K., İ.D., P.S., A.Ay.; Funding – N.K., N.S.O., A.Y.; Materials – N.K., N.S.O., A.Y., B.K., A.A.; Data collection and/or processing – N.K., N.S.O., A.Y., B.K., A.A.; Data analysis and/or interpretation – N.K., İ.D., N.S.O., A.A.; Literature search – N.K., İ.D., N.S.O., A.Y., B.K., A.A.; Writing – N.K., İ.D., N.S.O., B.K., A.A.; Critical review – N.K., İ.D., P.S. A.Ay.

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