Efficacy and Safety of Combined Chemotherapy Regimens with Bevacizumab in Platinum-sensitive Ovarian Cancers

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ABSTRACT

Objective: To determine the differences in terms of overall survival in platinum-sensitive ovarian cancer (PSOC) patients undergoing various chemotherapy protocols, and to demonstrate patient tolerance, toxicity, and efficacy data with the use of bevacizumab in different protocols.

Study Design: An observational study.

Place and Duration of the Study: Dr. Abdurrahman Yurtaslan Ankara Oncology Training and Research Hospital, Ankara, Turkey, from January 2018 to January 2022.

Methodology: Patients aged 18 and above, who had received treatment for PSOC, were included in the study. Patients with platinum-resistant disease and those for whom bevacizumab usage was contraindicated were not enrolled in the study.

Results: For the 95 patients, the median age was 55 (34-78) years. Median follow-up are 39.7 (39.2-47.5) months. Median progression-free survival (PFS) of the patients are 10.8 (7.3-14.0) months for carboplatin-gemcitabine-bevacizumab (CGB), 10.9 (IQR 5.5-14.3) months in the carboplatin-liposomal doxorubicin-bevacizumab (CLdB) arms, and 6.1 (IQR 5.8-14.3) months in the carboplatin-paclitaxel-bevacizumab (CPB) group (p=0.79). The median overall survivals (OS) are 37.9 (IQR 33.3-46.9) months in the CGB arm, 41.0 (IQR 38.0-50.3) months CPB arm, and 41.3 (IQR 38.1-52.3) months in the CLdB arm (p=0.173).

Conclusion: There was no difference in terms of overall survival among all three chemotherapy protocols. However, due to the difference in toxicity, the treatment should be selected on a patient-specific basis. Additionally, the use of bevacizumab at a dose of 7.5 mg/kg was demonstrated to be equivalent to using 15 mg/kg in terms of overall survival. This lower dose is also important to avoid financial toxicity.

Key Words: *Bevacizumab, Ovarian cancer, Platinum-based chemotherapy, Tolerability, Adverse clinical events.*

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INTRODUCTION

Ovarian cancer ranks fifth in cancer-related deaths in women in the developed countries. According to the current data, 314,000 women worldwide are annually diagnosed with ovarian cancer.[1] Although the frequency of germ-cell ovarian cancers increases at the younger ages, tumours of epithelial origin increase in those over 50 years.[2] Patients who have relapsed 6 months or more after the first-line treatment in ovarian cancer are considered platinum-sensitive (PS) patients. The interval between the first-line treatment and relapse is defined as the platinum-free interval, which is associated with prognosis. Combined chemotherapy regimens are recommended as the second-line therapy in patients with PS-relapsed ovarian cancer,[3] and the priority of giving platinum therapy to these patients is essential.[4] The effectiveness, tolerability, and common toxic side effects of these drugs are important in the selection of the planned combination chemotherapy protocol.

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Different regions have different efficacy, tolerability, and toxicities. Therefore, making the right choice based on the patient is crucial. The OCEAN study, which includes PSOC patients, compared the combination chemotherapy of carboplatin (AUC 4) and gemcitabine (1000 mg/m^2) with chemotherapy plus placebo in one arm, and chemotherapy plus bevacizumab (15 mg/Kg) in the other arm. It showed that the patients receiving bevacizumab had superior median progression-free survival (PFS) of 12.4 months compared to 8.4 months in the placebo group. However, the bevacizumab group also experienced higher rates of hypertension (HT), proteinuria, and bleeding.[5] GOG 0213 investigated the efficacy of chemotherapy regimens in PSOC with carboplatin (AUC 5) and paclitaxel (175 mg/m^2) in one arm, and the addition of bevacizumab (15 mg/Kg) in the other arm. The bevacizumab group demonstrated a significantly superior median PFS of 13.8 months but also experienced higher rates of side effects such as hypertension (12% *vs*. 1%), thromboembolism (4% *vs*. 1%), and gastrointestinal fistula/abscess (15% *vs*. 4%).[6] The AURELIA study evaluated the efficacy of combining chemotherapy with bevacizumab *versus* chemotherapy alone in platinum-resistant recurrent ovarian cancer patients. The chemotherapy treatment options included Paclitaxel (80 mg/m^2), Topotecan (4 mg/m^2), or pegylated liposomal doxorubicin (40 mg/ m^2). The study found that the group not receiving bevacizumab had higher rates of hypertension, gastrointestinal perforation, and thrombotic events compared to the control group.[6]

In the above studies, the addition of anti-VEGF agents to chemotherapy showed significant PFS benefits, however, none have demonstrated a significant overall survival advantage. The choice of protocol to be implemented for patients poses a challenging process for clinicians in terms of efficacy, toxicity, and cost. There is a need for studies to determine which protocol should be applied to patients considering their effectiveness, toxicity, and cost. This study attempted to address this gap by investigating the patient tolerance, toxic side effects, and efficacy differences among the three treatment regimens, *i.e.* carboplatin-gemcitabine-bevacizumab (CGB), carboplatin-liposomal doxorubicin-bevacizumab (CLdB), and carboplatin-paclitaxel-bevacizumab (CPB). The objective of this study was to determine the differences in terms of overall survival in platinum-sensitive ovarian cancer (PSOC) patients undergoing various chemotherapy protocols and to demonstrate patient tolerance, toxicity, and efficacy data with the use of bevacizumab in different protocols.

METHODOLOGY

Between January 2018 and January 2022, a retrospective search at Dr. Abdurrahman Yurtaslan Ankara Oncology Training and Research Hospital was performed, and patients who followed up in the medical oncology clinic were included. The study included patients aged 18 years and above who were diagnosed with ovarian cancer and experienced relapse 6 months or more after adjuvant treatment. The inclusion criteria were PSOC patients with ECOG PS (Eastern Cooperative Oncology Group Performance Status) between 0-2 who received combination chemotherapy with bevacizumab after relapse. Patients with suboptional general condition (ECOG PS ≥3) and contraindications to bevacizumab were excluded from the study.

In the CGB arm, patients received gemcitabine 1000 mg/m^2 every 21 days, carboplatin AUC 4 at Day 1 and 8, and bevacizumab 7.5mg/kg for every 21 days. In the CPB arm, patients received carboplatin 5-6 AUC, paclitaxel 175mg/m^2 and bevacizumab 7.5mg/kg for every 21 days. In the CLdB arm, patients received liposomal doxorubicin (Ld) 30mg/m^2 every 28 days, carboplatin 5AUC, and bevacizumab 7.5mg/kg once every 21 days.

The Statistical Package for the Social Sciences program (SPSS for Windows, Version 25.0, Chicago, IL, USA) was used for analysis. Normality analyses were performed to show the distribution of the variables. Continuous variables were reported using the median (interquartile range) or mean (SD), and categorical variables were reported using the Pearson Chi-square or Fisher's exact test. Survival analyses were performed using the Cox regression and Kaplan-Meier analyses, while survival curves were created by the Kaplan-Meier method. Multivariate analysis was performed for the findings that were significant in the univariate analysis in Cox regression. The log-rank test was used to compare OS and PFS. A p-value of <0.05 was considered significant.

RESULTS

A total of 95 patients diagnosed with recurrent PSOC were included in the study. The median age of patients was 55 (IQR 34-78). The median ages at diagnosis were 57 (IQR 42-71), 53 (IQR 34-78), and 50 (IQR 37-66) years in the CGB, CPB, and CLdB groups, respectively. Ovarian malignancy was the most common cancer type in all groups (ovary, fallopian tubes, and peritoneal). The rates of patients with FIGO stage 3 disease were 75%, 70%, and 81% in the CGB, CPB, and CLdB groups, respectively. The median follow-up time was 39.7 (IQR 39.2-47.5) months. Patients receiving maintenance bevacizumab were 11/26 (42.3%) in the CPB arm, 11/24 (45.8%) in the CGB arm, and 9/22 (40.9%) in the CLdB arm, respectively. Objective response rates (ORR) were 87% in the CPB arm and 83% and 90% in the CGB and CLdB arms, respectively. The median PFS was evaluated as 10.8 (IQR 7.3-14.0) months in the ODD, 6.1 (5.8-14.3) months in the CPB group, and 10.9 (5.5-14.3) in the CLdB arm. In addition, the median OS was 37.9 (IQR 33.3-46.9) months in the CGB arm, and 41.0 (IQR 38.0-50.3) and 41.3 (IQR 38.1-52.3) months in the CPB and CLdB arms, respectively (Table I). Grade 1-2 anaemia, thrombocytopenia, and neutropenia were the most common toxicities in the three regimens in all patient groups. In addition to haematological toxicity, hypertension, allergy, proteinuria, and thrombosis were also observed. When the patients were categorised according to their histopathological subtype, 81 (85.2%) were high-grade serous, 6 (6.3%) were low-grade serous, 2 (2.1%) were clear cells, and 6 (6.25%) were other types.

When patients were compared by the toxicities that developed due to the treatment, 58 patients developed neutropenia. Grade 3 and higher neutropenia was noted in a total of 15 (25, 8%) patients, and 4 (26.6%) of these patients were in the CGB arm, 9 (60%) were in the CPB arm, and 2 (13.3%) were in the CLdB arm. When evaluated in terms of febrile neutropenia (FEN), 5 (19.2%) patients receiving CGB, 10 (21.2%) patients in the CPB arm, and 3 (13.6%) patients receiving CLdB had febrile neutropenia (Table II).

In the survival analyses, there was a significant risk survival difference in patients with and without neoadjuvant treatment (HR: 10.88 1.66-71.40, $p<0.013$, Table III, Figures 1 and 2).

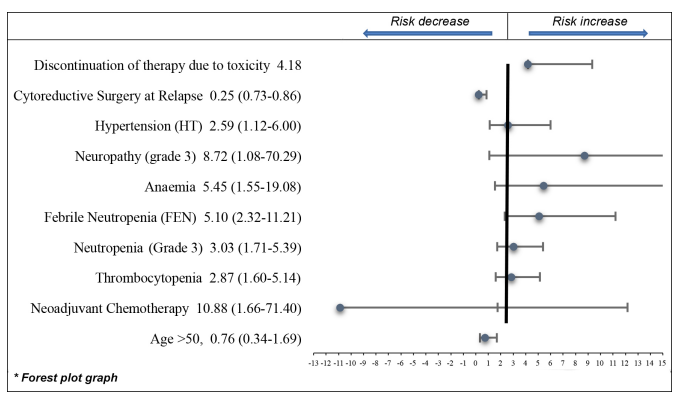

Figure 1: Risk analyses (95% CI).

Table I: Response relationship of demographic characteristics and regimen modalities.

	CGB (n: 26)	CPB (n: 47)	CLdB (n: 22)	p-value
Median age (IQR) years	57 (42-71)	53 (34-78)	50 (37-66)	
Ovarian	16 (67%)	39 (90%)	18 (86%)	
Fallopian	-	2 (5%)	1 (5%)	
Peritoneal	8 (33%)	2 (5%)	2 (9%)	
Pathology				
Low-grade serous	1 (4%)	2 (5%)	5 (24%)	
High-grade serous	23 (96%)	41 (95%)	16 (76%)	
Neoadjuvant chemotherapy				
Yes	21 (87%)	19 (44%)	5 (24%)	<0.013
No	3 (12.5%)	24 (56%)	16 (76%)	
At diagnosis				
FIGO Stage 1	1 (4%)	4 (9%)	1 (5%)	
FIGO Stage 2	1 (4%)	4 (9%)	-	
FIGO Stage 3	18 (75%)	30 (70%)	17 (81%)	
FIGO Stage 4	4 (17%)	5 (12%)	3 (14%)	
Best response				
CR	1 (8%)	17 (39%)	11 (52%)	
PR	18 (75%)	21 (48%)	8 (38%)	
SD	5 (21%)	3 (7%)	2 (9%)	
ORR	83%	87%	90%	
Maintenance bevacizumab				
Yes	11 (46%)	11 (25%)	9 (43%)	
No	13 (54%)	32 (75%)	12 (57%)	
Median maintenance bevacizumab cycle count	9 (2-26)	6 (3-28)	10 (4-20)	
Median PFS	10.8 (7.3-14.0)	6.1 (5.8-14.3)	10.9 (5.5-14.3)	0.79
Median OS	37.9 (33.3-46.9)	41.0 (38.0-50.3)	41.3 (38.1-52.3)	0.173
Bleeding	1 (4%)	1 (2%)	-	0.71
Thromboembolism	1 (4%)	1 (2%)	1 (5%)	0.85
Proteinuria	1 (4%)	2 (5%)	1 (5%)	0.005
Hypertension	6 (25%)	4 (9%)	1 (5%)	0.29
Allergy	4 (17%)	9 (21%)	1 (5%)	0.25

Table II: Chemotherapy and toxicity relationship.

		CGB	CPB	CLdB	p-value
Neutropenia	Grade 1-2	9 (20.9%)	25 (58.1%)	9 (20.9%)	0.157[1]
(n: 58)	Grade 3-4	4 (26.7%)	9 (60.0%)	2 (13.3%)	
Thrombocytopenia	Grade 1-2	12 (20.9%)	25 (58.1%)	11 (20.9%)	0.686[1]
(n: 58)	Grade 3-4	3 (30.0%)	6 (60.0%)	1 (10.0%)	
Thromboembolism	No	26 (28.3%)	44 (47.8%)	22 (23.9)	0.607[1]
(n: 3)	Yes	-	2 (66.7%)	1 (33.3%)	
Anemia	Grade 1-2	14 (25.2%)	26 (46.4%)	16 (28.6%)	0.554[1]
(n: 63)	Grade 3-4	2 (28.6%)	5 (71.4%)	-	
Febrile Neutropenia (FEN)	Yes	21 (27.6%)	36 (47.3%)	19 (25.0%)	0.744[1]
(n: 18)	No	5 (27.8%)	10 (55.6%)	3 (16.7%)	
Nausea-vomiting	Grade 1-2	15 (24.5%)	31 (50.8%)	15 (24.5%)	0.671[1]
(n: 64)	Grade 3-4	2 (66.7%)	1 (33.3%)	-	
Neuropathy	Grade 1-2	8 (20.0%)	23 (57.5 %)	9 (22.5%)	0.173[1]
(n: 41)	Grade 3-4	-	-	1 (100%)	
Diarrhea	Grade 1-2	7 (25.9%)	15 (55.6%)	5 (18.5%)	0.781[2]
(n: 27)					
Constipation	No	19 (25.7%)	35 (47.3%)	20 (27.0%)	0.177[1]
(n: 13)	Yes	2 (15.4%)	10 (76.9%)	1 (7.7%)	
Allergic reaction	No	21 (26.3%)	39 (48.8%)	20 (25.0%)	0.873[1]
(n: 15)	Yes	5 (33.3%)	7 (46.7%)	3 (20.0%)	

[1]Fisher's exact, [2]Pearson Chi-square

Table III: Overall survival analysis in all patient groups.

	Univariate analysis		Multivariate analysis	
	HR (95% CI)	p-value	HR (95% CI)	p-value
Age >50 years	0.76 (0.34-1.69)	0.509	0.13 (0.02-0.77)	0.025
Neoadjuvant CT	4.60 (1.74-12.17)	0.002	10.88 (1.66-71.40)	0.013
Thrombocytopenia	2.87 (1.60-5.14)	<0.001	19.88 (1.03-382.0)	0.047
Neutropenia (Grade 3)	3.03 (1.71-5.39)	<0.001	30.21 (1.46-623.0)	0.027
FEN (Febrile Neutropenia)	5.10 (2.32-11.21)	<0.001	4.06 (1.19-13.85)	0.025
Anaemia	5.45 (1.55-19.08)	0.08	0.48 (0.03-0.80)	0.035
Neuropathy (Grade 3)	8.72 (1.08-70.29)	0.017	0.21 (0.04-0.04)	0.058
Hypertension	2.59 (1.12-6.00)	0.026	1.45 (0.40-5.25)	0.56
Recurrent cytoreductive surgery	0.25 (0.73-0.86)	0.028	0.15 (0.30-0.82)	0.02
Discontinuation of therapy due to toxicity	4.18 (1.87-9.34)	<0.001	1.35 (0.39-4.59)	0.63

**Cox regression*

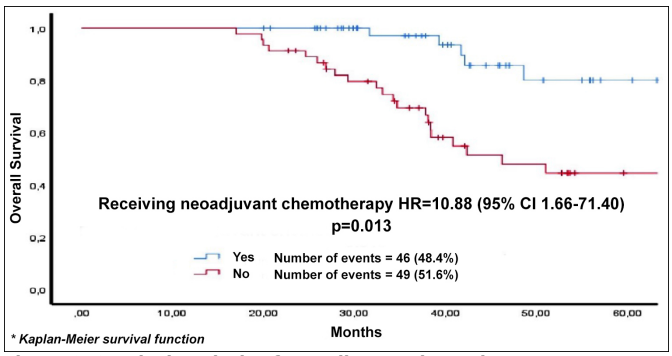

Figure 2: Survival analysis of neoadjuvant chemotherapy.

DISCUSSION

Despite the recent advancements in treatment of ovarian cancer, the long-term survival rates have not yet reached satisfactory levels.[7,8] Ovarian cancer ranks high among the causes of cancer-related deaths in women and remains a significant societal risk. Achieving optimal timing of treatment and tailoring it to personalised treatment modalities can enhance the current survival outcomes. In this regard, while numerous studies have been conducted, further research is still required. Therefore, it is crucial to assess the effectiveness of existing treatment regimens, consider patient-specific tolerability, and manage toxicity.

Several phase 3 studies have been conducted on PSOC. Bevacizumab is an anti-vascular endothelial growth factor (VEGF) monoclonal antibody. The addition of bevacizumab to combination therapies has shown to increase PFS, although it does not have a significant impact on OS. Comparisons between different combination regimens did not reveal a significant difference in OS, and analyses conducted beyond ovarian cancers indicated that adding bevacizumab to chemotherapy was associated with an elevated risk of some fatal side effects.[9] Therefore, further studies are necessary to investigate the toxicity and tolerability profiles specific to ovarian cancer patients and to determine patient-centred treatment approaches.

Because of standard chemotherapy or modified protocols for treating patients with advanced ovarian cancer the median PFS ranges from 16 to 28 months, and median OS from 30 to 60 months.[10] GOG-218 and ICON-7 showed that treatment of bevacizumab combined with carboplatin and paclitaxel as an adjuvant after debulking, followed by maintenance bevacizumab, significantly prolongs PFS in patients with newly diagnosed advanced disease.[11,12] When the survival values were evaluated for all three regimens, it was found that the median PFS for CPB was 6.14 months, and they were close to each other, with 10.87 and 10.94 months for CGB and CLdB. The median OS was 41.0 months in CPB, 37.96 months in CGB, and 41.39 months in the CLdB arm. In the survival analysis, it was interpreted that PFS was due to similar efficacy. In the ICON-7 study, bevacizumab was given at 7.5 mg/kg dose, while the GOG-218, OCEANS, and AURELIA studies administered it at 15 mg/kg. The patient received this dose as the reimbursement institution in the authors' region only provided bevacizumab 7.5 mg/kg. Despite this, PFS times are similar to the literature.[13] Also, median overall survival times were better than what was reported before. Furthermore, some studies show that race has a significant effect on survival.[12] The fact that the OS times in this study gave better results than the literature was thought to be due to ethnic factors.[14]

Although it is thought that the disease will respond to platinum-based combined treatments in PSOC recurrence, it is recommended to decide which platinum to choose on a patient-based and toxicity-specific basis.[15] At ICON-7, grade 3 and higher adverse events were reported in 66% of the bevacizumab arm, compared to 56% in patients receiving standard chemotherapy.[16] Grade 2-3 hypertension was the most common side effect in studies such as GOG-218, ICON-7, and OCEANS.

In this study, the most common side effects among non-haematological side effects were allergic reactions and grade 1-2 hypertension. It was determined that hypertension observed in the patients was controlled with antihypertensive treatments. Although hypertension is the most common side effect observed during the bevacizumab treatment, it rarely leads to treatment discontinuation. In this study, none of the patients required treatment termination due to hypertension. Additionally, studies have indicated a close relationship between serum CA-125 levels and the occurrence of side effects. Specifically, a strong correlation has been found between the development of hypertension and higher serum CA-125 levels in patients receiving bevacizumab. Therefore, it is recommended to closely monitor blood pressure in patients undergoing bevacizumab treatment, especially those with elevated serum CA-125 levels during relapse. However, further studies are needed to evaluate and validate the predictive value of these markers and others in ovarian cancer.[17] In this study, high CA-125 levels before chemotherapy showed a significant difference in the development of hypertension. Studies suggest that hypertension before treatment is associated with increased cardiovascular toxicity in patients receiving bevacizumab therapy.[18]

Gastrointestinal side effects such as perforation were reported to occur more frequently in patients receiving bevacizumab in GOG-218 and ICON-7 than in the chemotherapy arm. The frequency of other adverse events, such as proteinuria and venous thromboembolism, was 7% in both studies.[9] This study had one (1.05%) patient who developed perforation among fatal gastrointestinal side effects. In the follow-up patients, the frequency of thromboembolism was observed as 2-5% between the three arms, and proteinuria was 4-5%. In the OCEANS study, a second-line phase 3 study with a platinum-sensitive patient experience, the more common grade 2-3 adverse events in patients receiving bevacizumab were hypertension, proteinuria, and non-cranial haemor-

rhage.[19] The most common reasons for discontinuation of treatment are thrombocytopenia, hypertension, and proteinuria.[20] In this study, the most common haematological side effects were the development of allergy, hypertension, thrombocytopenia, proteinuria, and non-life-threatening bleeding.

Bevacizumab was administered as 22 cycles in GOG-218, at a dose of 15 mg/kg until disease progression in OCEANS, and in 18 cycles in ICON-7 at different maintenance treatment durations. In ICON-7, there are debates that the relatively low dose of 7.5 mg/kg bevacizumab should be given to high-risk patients (stage 4 or stage 3 patients with suboptimal cytoreduction), which is considered to be below the optimal dose.[21] In this study, patients receiving bevacizumab were continued at a 7.5 mg/kg dose until progression of the disease. Although the 7.5 mg/kg dose of bevacizumab is considered to be a relatively low dose, the detection of progression-free and overall survival rates similar to those in the literature, and the fact that the frequency of grade 3 and higher life-threatening toxicity, such as gastrointestinal perforation, was lower than the studies in the past showed that the administered dose was sufficient.

The maximum treatment benefits for PFS were observed near the time bevacizumab maintenance therapy was stopped at 15 months for GOG-218 and 12 months for ICON-7, with treatment benefit dissipating at approximately 24 months.[19-22] The present study included 26 (27.3%) patients with grade 3 or higher non-haematological side effects. In addition, there was massive bleeding in two (2.1%) patients, cardiac side effects in three (3.2%) patients, thromboembolism in three (3.2%) patients, and severe neuropathy in one (1.1%) patient, who required treatment discontinuation. In patients whose maintenance therapy was discontinued due to toxicity, the median PFS was observed at 12th-13th months. Therefore, the efficacy of bevacizumab continued at the 26th month without a treatment. This suggests that the benefit seen simultaneously with the discontinuation of bevacizumab treatment, contrary to what is believed, especially in patients who develop toxicity, does not disappear, and the effectiveness and benefit continue for longer periods.[21,23]

CONCLUSION

There was no difference in survival between patients in the three protocols. Administration of bevacizumab 7.5 mg/kg, which is a relatively low dose, had similar PFS and OS levels compared to the literature, and the frequency of toxicity was lower. The choice of treatment should be made on a case-by-case basis, considering the toxic characteristics of the planned treatment and patient tolerance.

ETHICAL APPROVAL:
The study was approved by the ethics committee of Health Sciences University, Dr. Abdurrahman Yurtaslan Ankara Oncology Training and Research Hospital with the decision number 2021-04/1140 dated 21.04.2021.

PATIENTS' CONSENT:
Patients' consent was waived as this study was conducted retrospectively.

COMPETING INTEREST:
This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors. The authors have no conflicts of interest to declare that are relevant to the content of this article.

AUTHORS' CONTRIBUTION:
FT, MB, OT: Carried out the conception and design of the research, analysis and interpretation of data, and drafted the manuscript.
MB, FT: Performed the statistical analysis and participated in data acquisition.
All authors have approved the final version of the manuscript to be published.

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