Taiwanese Journal of Obstetrics & Gynecology 57 (2018) 819–824

Contents lists available at ScienceDirect

Taiwanese Journal of Obstetrics & Gynecology

journal homepage: www.tjog-online.com

Original Article

Bevacizumab improves overall survival in platinum refractory ovarian cancer patients: A retrospective study

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ARTICLE INFO

Article history:
Accepted 15 January 2018

Keywords:
Bevacizumab
Platinum-refractory
Ovarian cancer
Chemotherapy
Overall survival

ABSTRACT

Objective: The objective of this study was to determine the effectiveness of bevacizumab (BV) in combination with chemotherapeutic regimens for prolonging progression-free survival (PFS) as well as overall survival (OS) in patients with platinum-refractory ovarian cancer.

Materials and methods: We retrospectively reviewed the medical records of platinum-refractory ovarian cancer patients receiving chemotherapy between January 2010 and August 2015 in the Department of Gynecology at the Saitama Medical Center, Jichi Medical University. After excluding for prior malignant disease, 57 patients were enrolled. The study end points included PFS and OS.

Results: Median PFS and OS rates of patients with and without BV were 6.0 (1.9–10.1) and 3.0 (2.1–3.8), and 12.0 (7.7–23.2) and 7.0 (3.7–10.2), respectively, (PFS: $P = 0.005$ and OS: $P = 0.008$). Following univariate analysis, stage, Eastern Cooperative Oncology Group performance status, chemotherapy regimens after platinum-refractory diagnosis, BV treatment status, ascites, and abdominal/gastrointestinal symptom with chemotherapy were significant factors. However, following multivariate analysis, chemotherapy regimens after platinum-refractory diagnosis, BV treatment status, and worsening symptoms with chemotherapy were significant factors. Hypertension and proteinuria rates were significantly more frequent in BV-treated patients, but severe adverse events were not significant. BV significantly improved OS in platinum-refractory ovarian cancer patients.

Conclusion: Our findings may potentially aid in developing treatment strategies for platinum-refractory patients with poor prognoses.

Introduction

Currently, no standard treatment exists for patients diagnosed with platinum-refractory epithelial ovarian cancer. For both platinum-refractory as well as platinum-resistant ovarian cancer, single agent chemotherapy is superior to multiagent chemotherapy. Indeed, previous investigation indicates that multiagent regimens exhibit considerable toxicity without significant improvements in patient survival [1]. Specifically, while the past study demonstrated enhanced progression-free survival (PFS) in platinum-resistant ovarian cancer patients receiving chemotherapy in combination with bevacizumab (BV), overall survival (OS) was not significantly improved [2].

As the disease course of ovarian cancer exhibits extended survival post-progression (SPP), the results presented in the aforementioned investigation [2] may prove difficult to assess for statistical difference in OS [3]. Five years prior to the AURELIA (Avastin Use in Platinum-Resistant Epithelial Ovarian Cancer) trial, a commentary by Broglio et al. proposed that for patient populations demonstrating protracted SPP, statistical significance for OS will likely be lost. To this point, Broglio et al. stated: "For this same scenario to have 80% power to detect a difference in OS, also at the level of a P value less than 0.05, 350 patients were required when median SPP was 2 months, 600 patients when median SPP was 6 months, 1050 when median SPP was 12 months, and 2440 when median SPP was 24 months [3]." Indeed, the results of the AURELIA trial demonstrated overall survival rates of 13.3 months (control arm [182 patients]) and 16.6 months (study arm [179 patients]), respectively.

Therefore, with respect to both platinum-resistant and platinum-refractory ovarian cancer, no definitive reports are available to direct either clinical chemotherapeutic treatments or supportive care. Previous investigation demonstrated that relapsed ovarian cancer may be effectively treated by chemotherapy up until the sixth regimen [4]. However, no discussion regarding platinum sensitivity

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https://doi.org/10.1016/j.tjog.2018.10.009

was included. Further, the 2005 National Institute for Health and Clinical Excellence (NICE) guidelines report differences between OS and PFS. Additionally, platinum-refractory and platinum-resistant disease also presented with differences in OS, reported as 3–5 months and 9–12 months, respectively [5]. Previous retrospective analysis regarding BV treatment in combination with chemotherapy for recurrence or platinum-refractory ovarian cancer indicated a PFS range of 2–11 months [6], which is relatively longer than the aforementioned report. Further, an additional retrospective analysis determined that BV administration was an effective heavy pre-treatment in these patients [7].

The purpose of this investigation was to evaluate the efficacy and safety of BV in patients with platinum-refractory ovarian carcinoma. Specifically, we performed a retrospective analysis of patients diagnosed with platinum-refractory ovarian cancer. As these patients demonstrated relatively short OS, statistical differences in clinical management should be readily detectable. We hypothesized that for platinum-refractory ovarian cancer patients, continuing several chemotherapy regimens would not be clinically effective whereas combination BV chemotherapy may significantly prolong OS in these patients.

Materials and methods

Study design

This investigation was conducted with the approval of the Institutional Review Board of Jichi Medical University, Saitama Medical Center. Specifically, we retrospectively reviewed the medical records of platinum-refractory ovarian cancer patients receiving chemotherapy between January 2010 and August 2015 in the Department of Gynecology at the Saitama Medical Center, Jichi Medical University. The inclusion criteria were patients diagnosed with platinum-refractory ovarian carcinoma using CT according to the Response Evaluation Criteria In Solid Tumors (RECIST) guidelines (version 1.1). The number of prior treatment regimens was not limited. Sixty-four patients were identified, with 57 meeting the specified inclusion criteria. Seven patients were excluded due to previous malignant episodes. Baseline patient characteristics are summarized in Table 1. For analysis, we utilized a chemotherapy data registry maintained by our institute. Only patients ≥20 years of age receiving chemotherapy for platinum-resistant ovarian cancer were included in the analysis. The sole exclusion criterion was a past episode of malignant disease. Informed consent was waived as the data were collected through a retrospective review of patient records. Informed consent was obtained for clinical treatment carried out in the study. The study conformed to the provisions of the Declaration of Helsinki in 1995 and as revised in Tokyo in 2004.

The following data were collected: age; histopathology; disease stage; Eastern Cooperative Oncology Group performance status (PS); and number of prior regimens. Acute and late hematologic and non-hematologic toxicities were recorded based on the Common Toxicity Criteria Version 4.0 and utilized as the primary outcomes.

Both PFS and OS were further utilized as primary outcomes. PFS was defined as the time from “platinum-refractory” diagnosis to the time of disease recurrence, disease progression, or death. PFS data were right-censored at final evaluation for patients lost to follow-up. OS was defined as the time from “platinum-refractory” diagnosis to the date of death. Again, data were right-censored at final evaluation for patients surviving until study termination.

Treatment

Following procurement of informed consent, patients received the respective chemotherapeutic regimen. The utilized doses and schedules are based on those reported by the GOG-0218, OCEANS, and AURELIA trials [2,8,9]. Chemotherapy was continued until the time of disease progression, unacceptable toxicity, or development of adverse events. Chemotherapy dosage guidelines were consistent with standard clinical practice; BV dose reduction was not permitted. In some instances, BV was withheld following the presence of toxicity, and withdrawn for a maximum of 6 weeks to allow for patient recovery. In cases where BV was withheld for longer than 6 weeks, further BV administration was discontinued [9]. Additionally, BV was discontinued in patients following any instance of gastrointestinal (GI) perforation. Further, if the patient demonstrated severe toxicity and was unable to continue chemotherapy, the patient could be started on another chemotherapeutic regimen. Treatment was also discontinued at the onset of disease progression. Treatment on the first day of each cycle was postponed for the following events occurring within 24 h of the scheduled treatment: absolute neutrophil count exceeding 1000/μL; hemoglobin level below 8.0 g/dL; or platelet count below 100,000/μL. Cycles could be delayed for a maximum of 3 weeks until these parameters recovered to their normal range.

Table 1
Baseline characteristics of patients with ovarian, tubal, or peritoneal cancer.

	Total cases (n = 57)
Age (years) (median, range)	58.9+-10.7 (32–78)
Stage n (%)	
I	8 (14.0)
II	2 (3.5)
III	38 (66.7)
IV	9 (15.8)
Histology at diagnosis n (%)	
Serous	25 (43.9)
Endometrioid	4 (7.0)
Clear	16 (28.1)
Mucinous	5 (8.8)
Squamous cell carcinoma	3 (5.2)
others	4 (7.0)
Prior chemotherapy regimens (times) n (%)	
1	35 (61.4)
2	14 (24.6)
3	5 (8.8)
4	2 (3.5)
5	1 (1.8)
ECOG performance status n (%)	
<1	50 (87.7)
2	5 (8.8)
3	2 (3.5)

Values are reported as n (%) or median (range).
BV, bevacizumab; ECOG, Eastern Cooperative Oncology Group.

Regimens

Clinicians selected the chemotherapy regimen for each patient based on a prior regimen, in combination with appropriate premedication according to local standards. Treatment regimens included:

1. Paclitaxel, carboplatin, BV or not (P/C/BV or not)
2. Gemcitabine, carboplatin, BV or not (G/C/BV or not)
3. Paclitaxel, BV or not (P/BV or not)
4. Pegylated liposomal doxorubicin, BV or not (PLD/BV or not),
5. Docetaxel, carboplatin BV or not (D/BV or not)
6. Irinotecan, nedaplatin (CPT/NDP).

Dose of BV was 15 mg/kg triweekly with regimens 1 and 5 and 10 mg/kg biweekly with regimens 2, 3 and 4.

Study assessments

Adverse events were graded using the National Cancer Institute Common Terminology Criteria for adverse events (version 4). Further, BV-specific adverse events as reported in previous clinical trials were determined [2,8,9]. Progression was clinically classified by symptomatic progression. In our analysis, cancer antigen 125 (CA-125) elevation alone was not sufficient to warrant the progression designation. Toxicity was determined during follow-up evaluation. All patients were assessed utilizing computed tomography (CT) every 8–12 weeks from the first day of cycle 1. Cases where treatment was delayed or discontinued were not considered for analysis. CT was also performed in cases where disease progression or adverse events developed.

Statistical analysis

JMP for Windows, version 10.0.0 (SAS Institute Japan, Minato, Japan) was utilized for statistical analyses. Demographic variables are reported as median and range. Adverse events (GI perforation and GI fistula) were analyzed utilizing univariate logistic regression analyses. PFS and OS were analyzed with the Kaplan–Meier method, compared between age, histopathology, stage, and PS, using log-rank tests due to the short study period duration. The Cox proportional hazards model was utilized to adjust for prognostic factors in the analysis, including survival, stage, tumor histology, and PS. For all statistical tests, a two-sided P-value < 0.05 was considered significant. For the hazard ratio, 95% confidence intervals (95% CI) were estimated.

Results

Patient population

Sixteen (28.1%) patients were diagnosed with clear cell carcinoma. Nineteen (87.7%) patients were graded as having PS < 1. The mean age was 58.9 years (range: 32–78 years). Eight (14%) of the 57 patients who had stage I ovarian cancer were diagnosed with early ovarian cancer; they all had stage IC cancer. Five patients had recurrence with peritoneal dissemination and three patients with distant metastasis. Only three patients had a history of more than three prior treatment regimens; all received chemotherapy with BV in this study because they had no bowel wall thickening or bowel obstruction.

Efficacy

The data cutoff date for the primary analysis was set at June 1, 2017. The median (8 months) and range (1–50 months) of the follow-up duration were assessed. Six patients survived until the time of data cutoff for analysis. Regarding PFS, no patient was censored. Regarding OS, only two patients were censored. However, these patients were followed up for 13 and 23 months.

Kaplan–Meier estimates for PFS and OS with or without BV are reported in Figs. 1 and 2, respectively Median PFS rates of patients with and without BV were 6.0 (1.9–10.1) and 3.0 (2.1–3.8), respectively (Fig. 1; P = 0.005). Median OS rates of patients with and without BV were 12.0 (7.7–23.2) and 7.0 (3.7–10.2), respectively (Fig. 2; P = 0.008).

The hazard ratios for PFS and OS in case of various prognostic factors in the univariate/multivariate analysis are shown in Tables 2 and 3. All data are reported in the following format: (Hazard ratio (95% CI), P-value). In the univariate analysis, stage; PS (≤1: 1; 2: 4.38 (1.45–10.85), P = 0.118; 3: 7.25 (1.09–29.13), P = 0.0423); with or without BV therapy (0.45 (0.23–0.84), P = 0.0128); ascites (2.42 (1.23–4.53), P = 0.118); and abdominal/gastrointestinal symptom with chemotherapy (*no change*: 1; *getting better*: 0.69 (0.27–1.51), P = 0.337; *getting worse*: 4.15 (2.11–7.98) P < 0.0001) were significant factors (Table 3). In the multivariate analysis, PS (≤1: 1; 2: 3.67 (1.05–11.42), P = 0.0417; 3: 2.38 (0.34–10.56), P = 0.334); BV or not (0.50 (0.26–0.91), P = 0.0242); and abdominal/gastrointestinal symptoms getting worse with chemotherapy (3.66 (1.79–7.22), P = 0.0006) were significant factors (Table 3).

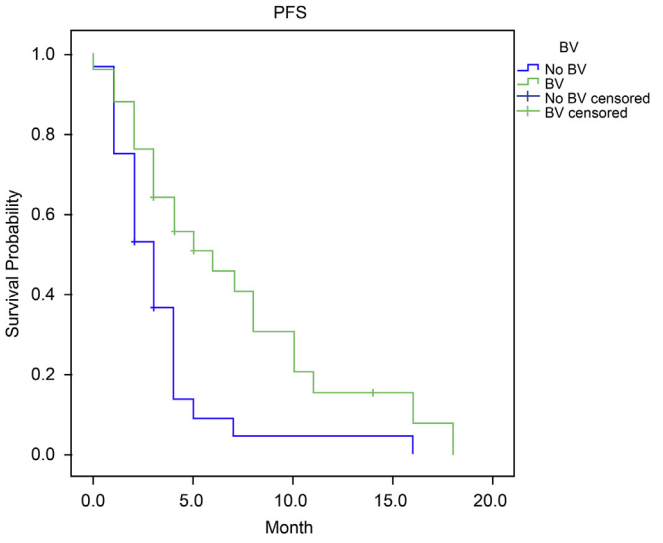

Fig. 1. Kaplan–Meier estimates of progression-free survival in patients with platinum-refractory ovarian cancer receiving chemotherapy with or without bevacizumab (BV).

Safety

Observed adverse events included GI perforation/fistula in three patients (12.0%) receiving BV and in two patients (6.3%) without BV therapy (P = 0.64) (Table 4). Additionally, one patient suffered mortality due to accelerated disease progression and worsening intestinal obstruction. This patient developed a tumor-associated hemorrhagic event on the day following final BV administration. Following hemorrhage, the patient received blood transfusion, and

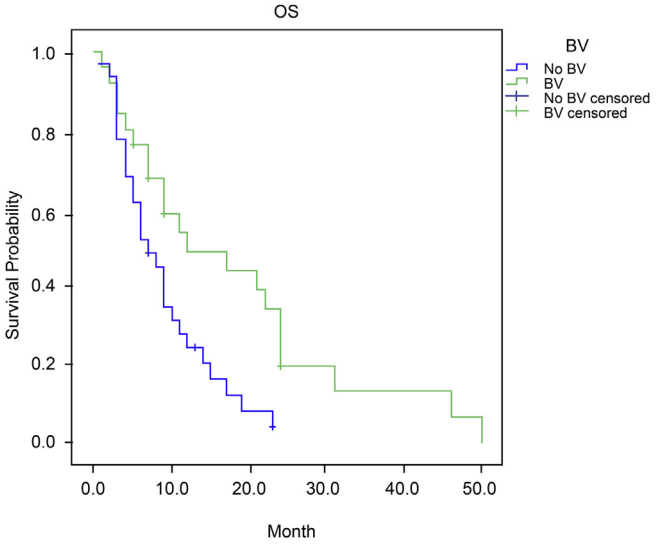

Fig. 2. Kaplan–Meier estimates of overall survival in patients with platinum-refractory ovarian cancer receiving chemotherapy with or without BV.

Table 2
Hazard ratio (HR) for progression-free survival (PFS) based on various prognostic factors in univariate/multivariate analyses.

		PFS HR (95% confidence interval)	P-value		P-value
Stage		univariate		multivariate	
	I	1			
	II	0.59 (0.087–2.44)	0.494		
	III	1.18 (0.57–2.77)	0.666		
	IV	1.29 (0.53–3.92)	0.475		
Tumor histology					
	Serous	1			
	Endometrioid	1.09 (0.31–2.91)	0.911		
	Clear	1.04 (0.54–1.96)	0.812		
	Mucinous	1.50 (0.50–3.68)	0.431		
	Squamous cell carcinoma	1.37 (0.32–3.96)	0.628		
ECOG Performance status					
	1	1		1	
	2	3.09 (1.04–7.45)	0.0434*	1.40 (0.40–4.43)	0.586
	3	6.20 (0.95–23.95)	0.0558	1.81 (0.25–8.37)	0.508
Chemotherapy regimens after platinum refractory (times)					
	0	1		1	
	1	0.57 (0.25–1.54)	0.25	0.50 (0.16–1.39)	0.147
	2	0.35 (0.13–1.02)	0.0538	0.28 (0.095–0.94)	0.0398*
	≥3	0.18 (0.061–0.54)	0.0036*	0.24 (0.072–0.87)	0.0312*
BV					
	No	1		1	
	Yes	0.47 (0.27–0.83)	0.0093*	0.51 (0.27–0.94)	0.0319*
Ascites					
	No	1		1	
	Yes	1.94 (1.00–3.56)	0.0497*	1.95 (0.81–4.41)	0.132
Lung metastasis					
	No	1			
	Yes	1.08 (0.44–2.25)	0.854		
Liver metastasis					
	No	1			
	Yes	1.11 (0.42–2.43)	0.816		
IDS R0					
	No	1			
	Yes	0.99 (0.30–2.46)	0.985		
Symptoms of cancer					
	No change	1		1	
	Improved	0.92 (0.39–1.92)	0.826	1.12 (0.44–2.63)	0.805
	Worsened	3.78 (1.93–7.27)	0.0002*	3.28 (1.51–6.97)	0.0031*

PFS HR, Hazard ratio for progression-free survival; ECOG, Eastern Cooperative Oncology Group; BV, Bevacizumab; IDS: Interval debulking surgery R0.
*P < 0.05.

her condition improved. One week later, the patient developed abdominal pain with abdominal CT indicating the presence of a gastrointestinal obstruction without GI perforation. Unfortunately, the patient's condition deteriorated, leading to her death. Although a direct relationship between the death and tumor hemorrhage could be definitively determined, this event was classified as grade 5. Further, rates of both hypertension and proteinuria were also significantly higher in patients receiving BV therapy. No sigsnificant differences in either hematotoxicity or thromboembolic events were observed.

Discussion

Our data indicate that BV significantly improved PFS and OS for platinum-refractory ovarian cancer. Interestingly, the number of regimens received did not significantly affect OS. Further, worsening of patient symptoms was a significant factor for both PFS and OS. Additionally, the number of regimens received following platinum-refractory diagnosis was not significant for either PFS or OS. Finally, although significant for PFS and OS following the univariate analysis, ascites was not significant for PFS and OS following the multivariate analysis.

The AURELIA study demonstrated that BV therapy significantly improved PFS for platinum-resistant ovarian cancer patients; however, no improvements in OS were observed, which was likely the effect of SPP (2). In the AURELIA study, OS was 13.3 (control arm) vs 16.6 months (study arm), respectively. In our study, the median PFS rate with and without BV was 6.0 (1.9–10.1) and 3.0 (2.1–3.8), respectively (P = 0.005); the median OS rate with and without BV was 12.0 (7.7–23.2) and 7.0 (3.7–10.2), respectively (P = 0.008). As this report investigated patients over relative short time-scales, we were able to detect significance in OS. In previous investigations, BV significantly improved the OS of patients as evidenced by sub-factor analysis for severe prognostic factors, including high disease stage, suboptimal surgery, and ascites [10–12]. In our investigations, all included patients were platinum-refractory, leading to poor clinical prognosis. Our findings, especially in the context of this patient group, indicate the effectiveness of BV in combination with chemotherapy for significant improvements in PFS and OS. However, the optimal timing for the use of BV for ovarian cancer remains to be determined in patients with platinum-refractory malignancies.

Worsening of patient abdominal/gastrointestinal symptoms was a significant factor for both PFS and OS. Indeed, a prior report indicated that a deteriorating gastrointestinal condition significantly correlated with early cessation of chemotherapy [13]. In combination with these findings, our results indicate that in a setting of abdominal/gastrointestinal distress prior to CT/CA-125 assessment, physicians should consider halting chemotherapy altogether. Further, the number of different regimens administered following a platinum-refractory diagnosis did not significantly predict either PFS or OS. In contrast, prior investigation demonstrated significant

Table 3
Hazard ratio (HR) for overall survival (OS) based on various prognostic factors in univariate/multivariate analyses.

		OS HR (95% confidence interval)	P-value		P-value
Stage		Univariate		multivariate	
	I	1			
	II	2.02 (0.29–9.08)	0.424		
	III	1.71 (0.76–4.61)	0.209		
	IV	2.80 (0.96–8.74)	0.0583		
Tumor histology					
	Serous	1			
	Endometrioid	1.83 (0.53–4.92)	0.308		
	Clear	0.95 (0.47–1.91)	0.897		
	Mucinous	1.76 (0.58–4.46)	0.295		
	Squamous cell carcinoma	3.37 (0.76–10.66)	0.099		
	ECOG Performance status				
	1	1		1	
	2	4.38 (1.45–10.85)	0.118	3.67 (1.05–11.42)	0.0417*
	3	7.25 (1.09–29.13)	0.0423*	2.38 (0.34–10.56)	0.334
	Chemotherapy regimens after platinum refractory (times)				
	0	1			
	1	1.50 (0.56–5.24)	0.447		
	2	0.79 (0.28–2.81)	0.688		
	≥3	0.27 (0.084–1.05)	0.057		
BV	No	1		1	
	Yes	0.45 (0.23–0.84)	0.0128*	0.50 (0.26–0.91)	0.0242*
Ascites	No	1		1	
	Yes	2.42 (1.23–4.53)	0.118*	1.62 (0.75–3.28)	0.211
	LANGmeta				
	No	1			
	Yes	1.36 (0.56–2.86)	0.47		
	Livermeta				
	No	1			
	Yes	2.22 (0.84–4.92)	0.101		
	IDS R0				
	No	1			
	Yes	1.03 (0.25–2.86)	0.961		
	Symptoms of cancer				
	No change	1		1	
	Improved	0.69 (0.27–1.51)	0.337*	0.66 (0.26–1.49)	0.337
	Worsened	4.15 (2.11–7.98)	<0.0001	3.66 (1.79–7.22)	0.0006*

PFS HR, Hazard ratio for progression-free survival; ECOG, Eastern Cooperative Oncology Group; BV, Bevacizumab; IDS: Interval debulking surgery R0.
*P < 0.05.

improvements in PFS for ovarian cancer patients receiving chemotherapy even when a fifth treatment regimen was required [4]. However, this analysis did not categorize patients on the basis of platinum sensitivity. Although chemotherapy administration did produce positive results, the authors conclude that routine chemotherapy past the fourth unique treatment regimen did not provide a survival beneficial. Along these lines, the current National Comprehensive Cancer Network (NCCN) guidelines recommend that cessation of treatment after two sequential regimens fails to produce positive results (https://www.nccn.org/professionals/physician_gls/f_guidelines.asp#site).

Although significant in the univariate analysis, ascites did not significantly predict either PFS or OS following the multivariate analysis. In a previous investigation, ascites was demonstrated to be a significant independent prognostic factor for BV effectiveness [10]. However, patients included in that study were all receiving their first treatment. Further, these patients did not exhibit platinum-refractory malignancies, even in the setting of recurrent or persistent disease. One potential confounding factor that was not investigated in our analysis was patient vascular endothelial growth factor (VEGF) receptor status. Indeed, a previous investigation indicated a correlation between total VEGF receptor expression and sub-optimal cytoreduction [14]. An additional study reported that in platinum-resistant patients, overall VEGF

Table 4
Summary of grade ≥3 (and selected grade ≥2) adverse effects of special interest with bevacizumab therapy.

	Total cases (n = 57)		P-value
	BV (n = 25)	No BV (n = 32)	
Hypertension grade ≥2 n (%)	7 (28.0%)	1 (3.1%)	0.0163*
Proteinuria grade ≥2 n (%)	8 (32.0)	1 (3.1%)	0.0072*
GI perforation/fistula (%)	3 (12.0%)	2 (6.3%)	0.64
Bleeding grade 5 n (%)	1 (4.0%)	0	0.439
Thromboembolic event n (%)	1 (4.0%)	1 (3.1%)	1
Cardiac disorders n (%)	0	0	
Hematotoxicity ≥4 n (%)	4 (16.0%)	5 (15.6%)	1

All values are reported as n (%).
BV, Bevacizumab.
*P < 0.05.

expression was increased [15]. Although anti-VEGF therapy may potentially aid in the treatment of platinum resistant/refractory ovarian cancer, this eventuality will require further analysis.

The American Society of Clinical Oncology suggests avoiding direct treatment in the following settings: patients with an Eastern Cooperative Oncology Group (ECOG) PS3/4; no evidence of patient benefit; and general conditions insufficient for inclusion in the clinical trial [16]. In our study, PS was determined to be a significant predictor of OS. Therefore, patients with poor PS scoring may maintain a general condition without adverse effects from cytotoxic chemotherapy. We should, therefore, consider whether administration of chemotherapy is appropriate for a PS2 patient. Additionally, BV was reported to significantly stabilize disease progression, greatly improving patient quality of life [17]. As a result, single-use BV administration may represent a potential clinical option for patients with poor PS scoring. As BV is not particularly cytotoxic, patients could potentially receive chemotherapy continuously. Indeed, a previous phase II clinical trial for platinum-resistant patient treatment with single BV administration reported a median PFS of 4.4 months and an OS of 10.7 months [18]. In this study, 16.3% patients showed resistance to secondary platinum and 47.7% patients had received three or more different chemotherapy regimens. In those patients with poor prognostic factors, a similar OS was observed compared with that in normal platinum-resistant patients (NICE guidelines; (5)). However, the risk of gastrointestinal perforation was significantly higher in patients receiving two prior chemotherapy regimens. Additionally, bowel wall thickening as well as bowel obstruction was detected as a significant risk factor. In cases of single BV application for platinum-refractory patients, caution should be exercise to mitigate these risk factors.

Importantly, ours is the first retrospective study detailing a survival benefit following BV therapy for platinum-refractory ovarian cancer patients. Our results indicate that, in the absence of severe hypertension, bowel obstruction, bowel thickening and intestinal invasion, chemotherapy in combination with BV should be considered for platinum-refractory patients. Indeed, patients receiving BV in our study exhibited a median OS of 12 months.

The major limitation of this investigation was its retrospective nature. Although our retrospective study examined only a relatively small number of cases, we believe that our investigation is potentially useful for predicting patient outcomes for platinum-refractory ovarian cancer using BV. Additionally, retrospective collection and grading of adverse events from the medical records may underestimate their frequency in the general population. In the future, properly powered, randomized clinical trials will be required to assess the efficacy of BV therapy for platinum-refractory ovarian cancer patients. Further, for the high PS patients, stand-alone BV therapy may be optimal.

In conclusion, BV significantly improved PFS and OS for platinum-refractory ovarian cancer patients. Additionally, the number of utilized regimens did not significantly affect OS.

Funding/support statement

R. Konno received research funding from Yakult Pharmaceutical Industry Co (Tokyo, Japan) and Chugai Pharmaceutical (Tokyo, Japan), as well as lecture honoraria from Japan Vaccine Co (Tokyo, Japan), MSD Japan (Tokyo, Japan), and Chugai Pharmaceutical Co (Tokyo, Japan). The funding received from these organizations did not play a role in study design or the outcomes.

Conflicts of interest statement

The remaining authors have no conflict of interest to declare.

Acknowledgments

We would like to thank Editage (www.editage.com) for English language editing and Publication Support.

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