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Original Article

Bevacizumab combined with chemotherapy could be superior to chemotherapy alone in relapsed ovarian cancer after PARPi: evidence from a multi-center propensity score-matched analysis

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ABSTRACT

Objective: A retrospective, multi-center propensity score-matched (PMS) analysis was conducted to investigate the efficacy and safety of the treatment strategy that combines bevacizumab and chemotherapy for patients with relapsed epithelial ovarian cancer (EOC) who previously received poly ADP-ribose polymerase inhibitors (PARPis).
Methods: A total of 250 ovarian cancer (OC) patients relapsed after PARPi received chemotherapy with or without bevacizumab at 4 medical centers were enrolled in the study. For both treatments, Kaplan-Meier analysis and Cox regression were used to compare PFS.
Results: In the multivariable analysis of 250 patients, the incorporation of bevacizumab into chemotherapy demonstrated a significant enhancement in PFS (hazard ratio [HR]=0.49; 95% confidence interval [CI]=0.34–0.72; p<0.001). Fifty-five patients were enrolled in Group A (bevacizumab combined with chemotherapy) and 55 were enrolled in Group B (chemotherapy alone regime) after PSM analysis. A statistically significant difference in PFS was observed between the 2 regimens (HR=0.62; 95% CI=0.40–0.97; p=0.036), suggesting that the bevacizumab combined with chemotherapy regimen confers superior clinical benefits. The median PFS was 11 months in Group A and 9 months in Group B. A significant variation was noted in PFS between patients without RCRS (HR=0.50; 95% CI=0.30–0.82) and the platinum-resistant subgroup (HR=0.31; 95% CI=0.14–0.68). Adverse effects of Grade 3–4 were more prevalent in Group A than in Group B. Additionally, instances of severe hypertension and bowel perforation were reported solely within Group A.
Conclusion: In patients diagnosed with EOC relapsed after PARPi, the regime of chemotherapy combined with bevacizumab is associated with better PFS.

Keywords: Ovarian Cancer; PARP Inhibitor; Bevacizumab; Chemotherapy

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Conflict of Interest
No potential conflict of interest relevant to this article was reported.

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Synopsis
For patients experiencing a recurrence of ovarian cancer following treatment with poly ADP-ribose polymerase inhibitors, the concurrent administration of bevacizumab and chemotherapy has shown enhanced progression-free survival compared with chemotherapy alone, accompanied by manageable adverse effects.

INTRODUCTION

Ovarian cancer (OC) ranks as a primary cause of cancer-related deaths in gynecological carcinomas, and it is associated with a poor prognosis [1]. In recent years, chemotherapy has become the primary treatment strategy for OC patients following cytoreductive surgery. Inhibition of the poly ADP-ribose polymerase (PARP) enzyme in BRCA1/2-mutated high-grade serous ovarian carcinoma can lead to synthetic lethality [2], thereby ushering in a new era of precision targeting therapy.

The introduction of PARP inhibitors (PARPis) for maintenance therapy has notably improved both the progression-free survival (PFS) and overall survival (OS) in primary OC [3]. The extensive utilization of PARPi has resulted in the emergence of resistance to PARPi in individuals with recurrent epithelial ovarian cancer (ROC), as well as the formulation of approaches to address PARPi resistance in clinical settings. Some studies have indicated that the platinum-based chemotherapy may be less effective following the administration of PARPi for ROC [4,5]. The post hoc analyses of the SOLO2/ENGOT Ov-21 trial [4] revealed a reduction in the PFS of platinum-based chemotherapy in BRCA-mutated (BRCAm) platinum-sensitive recurrent ovarian cancer (PSOC) patients who had previously received maintenance olaparib, with a median PFS of 7.0 months compared to 14.3 months for those who had not received PARPi (hazard ratio [HR]=2.89; 95% confidence interval [CI]=1.73–4.82). Several retrospective studies have documented the negative impact of PARPi maintenance on post-PARPi chemotherapy. Rose et al.'s study [5] in a single-institution indicated that the median PFS was 2.3 times longer for patients who had not received PARPi (p=0.005) compared to those with BRCAm EOC who had previously received a PARPi. A multi-center retrospective study conducted in Korea revealed that second-line olaparib maintenance therapy is associated with a suboptimal response to subsequent chemotherapy in BRCAm epithelial ovarian cancer (EOC), indicating that resistance to olaparib may contribute to chemotherapy resistance [6]. The partial indication for niraparib and rucaparib maintenance therapy in patients with recurrent ROC lacking germline BRCA (gBRCA) or somatic BRCA mutations has been rescinded by the Food and Drug Administration (FDA) due to the diminished OS outcomes observed in the NOVA [7] and ARIEL3 [8] studies.

The resistance mechanisms to PARPis partially overlap with platinum resistance. Resistance to PARPi in OC involves the restoration of the homologous recombination repair pathway, alterations in non-homologous end-joining repair, the stability of replication forks, increased expression of cellular drug efflux pumps such as ABCB1, among others. Targeting these cross-resistant mechanisms aforementioned may potentially resensitize OC to platinum-based therapies [9]. Platinum sensitivity may serve as a partial predictor of sensitivity to PARPi to some extent [10,11]. Emerging techniques are currently under investigation to overcome resistance to PARPis. This involves the development of novel agents that target the pathways associated with ATR, ATM, CHK1, MEK, WEE1, etc. [12]. However, almost all the

trials related are limited to stages I and II. Currently, there is a scarcity of high-level evidence-based clinical research pertaining to this specific group in clinical settings.

Previous foundational studies have suggested that bevacizumab might have the potential to overcome resistance to PARPis. It is known that the hypoxemic microenvironment associated with a massive tumor burden may also be linked to drug resistance. The anti-angiogenic drug has the potential to "normalize" tumor vasculature and the microenvironment. Besides, preclinical investigations have demonstrated that angiogenesis inhibitors have the potential to replicate the effects of homologous recombination deficiency (HRD) status [13]. Down-regulating the key factors involved in homologous recombination repair (HRR) can enhance the sensitivity of PARPis [12]. Clinical studies have indicated that the combination therapy of PARPis and anti-angiogenics may enhance the objective response rates (ORRs) and PFS of ROC, with a manageable adverse effect profile [13].

Currently, several phase III clinical trials have validated that the combination of bevacizumab with chemotherapy can extend PFS in individuals with ROC [14-16]. This combination has also shown enhancements in the ORR in both platinum-sensitive and platinum-resistant scenarios. The median PFS ranges from 6.7 to 12.4 months in the bevacizumab combined chemotherapy group, compared to 3.4 to 8.4 months in the chemotherapy alone group. Nevertheless, the survival status of patients who had prior treatment with PARPis was not addressed in any of the aforementioned large clinical trials.

Based on our study, it was hypothesized that patients experiencing recurrence of OC after treatment with PARPis, when treated with a combination of bevacizumab and chemotherapy, would exhibit an enhanced PFS compared to those receiving chemotherapy alone. The retrospective evaluation aimed to compare the efficacy and safety of chemotherapy alone vs. the combination of bevacizumab and chemotherapy in OC patients experiencing relapse following PARPi maintenance treatment.

MATERIALS AND METHODS

1. Patients and methods

Patients with relapsed OC, who had previously received maintenance PARPi therapy, were retrospectively analyzed across 4 medical centers from January 2018 to December 2023. To analyze the factors influencing the survival, the study retrospectively analyzed the age of all patients, their International Federation of Gynecology and Obstetrics (FIGO) stage, BRCA gene status, recurrent type related to platinum-free interval (PFI), previous lines of chemotherapy, the type of PARPi, the duration of PARPi administration, the main adverse events (AEs), and the patients' survival outcomes.

Eligible participants met the following criteria: (1) Patients aged 18 years or older, diagnosed with recurrent epithelial ovarian, fallopian tube, or primary peritoneal cancer at FIGO stages I–IV, as confirmed by histological examination, PARPi maintenance was required for all patients. (2) Surgery is required in the initial treatment, whether through primary debulking surgery or interval debulking surgery, and entails achieving a complete response (CR) or partial response (PR) after 4–6 cycles of first-line platinum-based chemotherapy. (3) PARPi maintenance therapy was continued until disease progression or relapse. (4) Absence of

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prior use of vascular targeting drugs, including bevacizumab. (5) Patients had undergone a maximum of 4 previous chemotherapy regimens.

Patients with alternative pathological types, including non-epithelial ovarian malignant tumors, clear cell carcinomas, and borderline ovarian tumors, or those who had received more than 4 prior lines of anticancer regimens were considered ineligible. Patients who commenced the initial chemotherapy with a non-platinum-containing regimen were also excluded. Additional exclusion criteria encompassed severe cardiopulmonary conditions, recent occurrences of moderate to severe bleeding or thrombosis, moderate to severe hypertension or proteinuria, and a history of pelvic or abdominal cavity radiotherapy.

2. Ethic statements

This retrospective study received approval from the Ethics Committee of Chongqing University Cancer Hospital, Chongqing (No. CZLS2023007). The need for informed patient consent was waived because of the retrospective nature of the study.

3. Treatment

Following recurrence, the operable patients underwent a comprehensive evaluation of their physical condition, ascites, as well as computed tomography/magnetic resonance imaging/positron emission tomography-computed tomography imaging, among other assessments. The procedure began with laparoscopic exploration, which was then followed by a comprehensive assessment of the feasibility of achieving optimal tumor reduction. If the probability was substantial, an extra laparotomy was conducted for secondary cytoreduction.

The treatment regimens administered to the patients were determined according to the PFIs. Platinum-sensitive patients (PFI ≥6 months) were administered platinum-based chemotherapy, or the same regimen along with bevacizumab (with one cycle omitted after surgery, at a dosage of 7.5 mg/kg every 3 weeks [Q3W]). The platinum-resistance patients (PFI <6 months) received either single or combination therapies, such as pegylated liposomal doxorubicin, weekly paclitaxel, paclitaxel (albumin binding), gemcitabine, ifosfamide, or topotecan. Some patients also received the same treatment regimen along with bevacizumab. The administration of bevacizumab maintenance was continued until disease progression or the occurrence of intolerable adverse effects. However, the majority of patients declined to undergo bevacizumab maintenance therapy.

4. Follow-up and endpoint

Demographic and clinical data were obtained from hospital databases. Follow-up data were collected from the outpatient clinic of the gynecological centers. The main objective of the study was to assess PFS according to the Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1 [17]. The secondary endpoints encompassed the ORR and safety. The primary endpoint of PFS was specifically defined as the duration from the enrollment of chemotherapy for this treatment regimen to the initial radiologically confirmed disease progression or death, whichever transpires first. The secondary endpoint was ORR defined as the percentage of patients with a best overall response of CR or PR relative to the appropriate analysis set. The treatment effectiveness following chemotherapy was assessed based on the RECIST guideline (version 1.1) [17]. Safety was evaluated in terms of AEs graded according to the Common Terminology Criteria for Adverse Events version 5.0 [18].

5. Statistical analysis

Statistical analysis was conducted using SPSS version 26.0 (IBM Corp., Armonk, NY, USA). A comparison between groups would involve the calculation of the mean, standard deviation, median, and interquartile range to describe quantitative indicators. The indices of the 2 groups were compared using the t-test and rank sum test. Categorical data were analyzed using the χ^2 test, continuity-corrected χ^2 test, or Fisher's exact test. Fisher's exact test was utilized when the χ^2 test was not applicable or when the sample size was less than 40. The Kaplan-Meier was employed for the analysis of survival data, and the log-rank test was utilized to compare the survival curves of the 2 groups. The Cox regression model was employed to examine the influencing factors and to calculate the HR and its corresponding 95% CIs.

RESULTS

1. Patient characteristics

A total of 250 patients diagnosed with relapsed OC after PARPi maintenance were consecutively included in this analysis between January 2018 and December 2023. Fifty-nine patients received treatment with a combination of bevacizumab and chemotherapy doublet (Group A), while 191 patients received chemotherapy alone (Group B) (**Fig. 1**). At the time of analysis, 201 patients exhibited RECIST progression. The median follow-up time for PFS was 15.7 months (range 3–35 months) in Group A and 17.3 months (range 3–43 months) in Group B, respectively. Following propensity score-matched (PMS) analysis, 140 patients were excluded from the study. The parameters, including age, FIGO stage, BRCA gene status, recurrent type related to PFI, previous lines of chemotherapy, the type for PARPi, and the maintenance duration for PARPi, were well balanced.

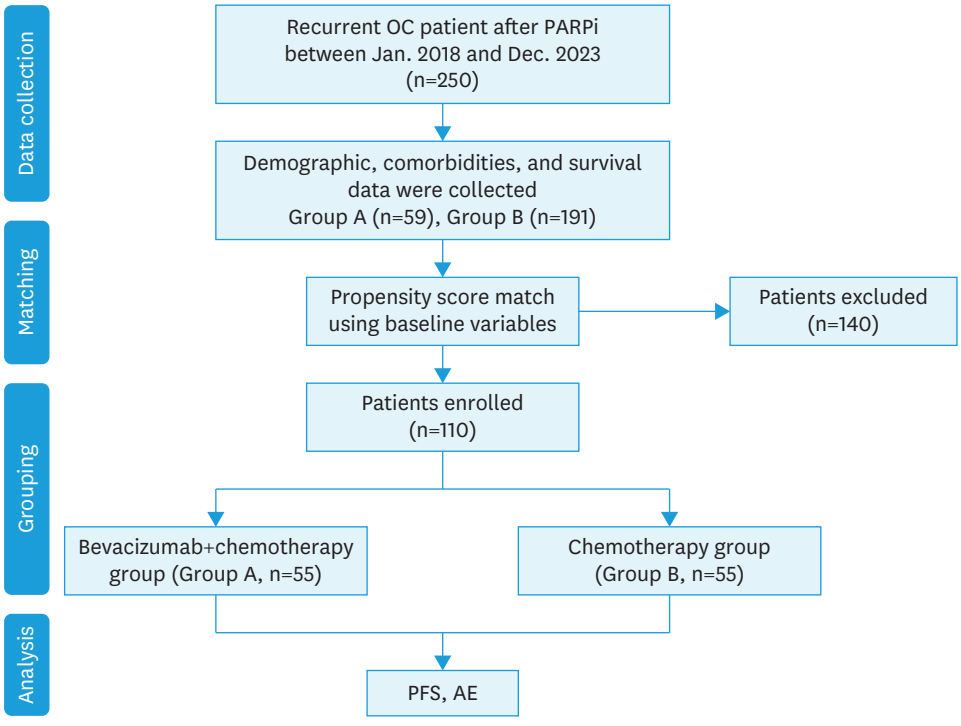

Fig. 1. Study cohort for patients with relapsed OC after PARPi maintenance therapy.
AE, adverse events; OC, ovarian cancer, PARPi, Poly ADP-Ribose Polymerase inhibitors; PFS, progression-free survival.

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For the 250 patients, a univariate analysis identified several factors that may influence PFS. These factors include gBRCA status (HR=1.85; 95% CI=1.36–2.51; p<0.001), PFI (HR=4.09; 95% CI=2.65–6.32; p<0.001), PARPi line: line 3 (HR=2.08; 95% CI=1.38–3.14; p=0.001), line 4 (HR=11.29; 95% CI=3.92–32.51; p<0.001), PARPi duration (HR=0.95; 95% CI=0.93–0.97; p<0.001), recurrent cytoreductive surgery (RCRS) (HR=2.99; 95% CI=1.99–4.49; p<0.001), and bevacizumab (HR=0.68; 95% CI=0.47–0.98; p=0.036). In multivariable analysis, as presented in **Table 1**, after the adjustment for gBRCA status, the PARPi line, PARPi maintenance interval and RCRS, the bevacizumab and chemotherapy doublet were also associated with improved PFS compared to chemotherapy alone (HR=0.49; 95% CI=0.34–0.72; p<0.001).

The patient profiles in terms of age and FIGO stages for both groups were initially unmatched (refer to **Table 2**), prompting the execution of propensity analysis. Ultimately, the average age in both groups was comparable (54.3±8.7 for Group A vs. 53.6±8.1 for Group B, p=0.671). The FIGO stage was also similar between the 2 groups (p=0.775). The mutation rate of BRCA1/2 was 25 (45.5%) for Group A and 26 (47.3%) for Group B, with a p-value of 0.829. The RCRS was performed in 14.5% (8/55) of cases in Group A and 25.5% (14/55) in Group B (p=0.233). The groups based on previous PFIs were also found to be balanced (p=0.849). The distribution of prior PARPi treatment lines was similar in both groups (p=0.875). The majority of patients have previously received no more than 2 lines of chemotherapy, with 80.0% in Group A and 85.4% in Group B.

2. Efficacy outcomes

The PFS were presented in **Fig. 2**. The mean PFS was 11 months for Group A (bevacizumab combined with chemotherapy) and 9 months for Group B (chemotherapy alone). The PFS rates were determined using the Kaplan-Meier method, yielding a HR of 0.67 (95% CI=0.46–0.96; p=0.025). Upon adjusting for clinical backgrounds, Group A exhibited a notably greater benefit in comparison to Group B (HR=0.62; 95% CI=0.40–0.97; p=0.036).

Subgroup analysis revealed that among patients without RCRS, The bevacizumab plus chemotherapy regimen was associated with a reduced risk (HR=0.50; 95% CI=0.30–0.82, as

Table 1. Multivariate analyses of prognostic factors that might influence progression-free survival for recurrent epithelial ovarian cancer after PARPi

Variables	Univariate		Multivariate	
	HR (95% CI)	p-value	HR (95% CI)	p-value
ECOG		0.096		
FIGO stage		0.314		
Age (yr)	1.01 (0.99–1.03)	0.384		
gBRCA	1.85 (1.36–2.51)	<0.001	1.28 (0.91–1.81)	0.294
Platinum sensitivity	4.09 (2.65–6.32)	<0.001	2.11 (1.26–3.53)	0.004
PARPi line				
1		<0.001		0.057
2	1.37 (0.98–1.89)	0.059	1.38 (0.73–2.60)	0.330
3	2.08 (1.38–3.14)	0.001	1.74 (0.72–4.20)	0.220
4	11.29 (3.92–32.51)	<0.001	4.47 (1.46–13.66)	0.009
PARPi type	1.01 (0.74–1.39)	0.959		
PARPi duration	0.95 (0.93–0.97)	<0.001	0.96 (0.93–0.98)	0.001
RCRS	2.99 (1.99–4.49)	<0.001	3.20 (2.07–4.96)	<0.001
Bevacizumab	0.68 (0.47–0.98)	0.036	0.49 (0.34–0.72)	<0.001

CI, confidence interval; ECOG, Eastern Cooperative Oncology Group; FIGO, International Federation of Gynecology and Obstetrics; gBRCA, germline breast cancer susceptibility gene; HR, hazard ratio; PARPi, Poly ADP-Ribose Polymerase inhibitor; RCRS, recurrent cytoreductive surgery.

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Table 2. Demographical characteristics and clinical data of the patients

Variables	Before propensity matching			After propensity matching		
	Group A (n=59)	Group B (n=191)	p-value	Group A (n=55)	Group B (n=55)	p-value
Age (yr)	54.8±8.8	52.1±7.8	0.027	54.3±8.7	53.6±8.1	0.671
FIGO stage			0.031			0.775
1	1 (1.7)	2 (1.0)		1 (1.8)	1 (1.8)	
2	4 (6.8)	3 (1.6)		2 (3.6)	2 (3.6)	
3	44 (74.6)	169 (88.5)		43 (78.2)	47 (85.5)	
4	10 (16.9)	17 (8.9)		9 (16.4)	5 (9.1)	
gBRCA			0.213			0.829
Positive	27 (45.8)	80 (41.9)		25 (45.5)	26 (47.3)	
Negative	24 (40.7)	97 (50.8)		23 (41.8)	24 (43.6)	
Unidentified	8 (13.6)	14 (7.3)		7 (12.7)	5 (9.1)	
Recurrent type			0.702			0.849
Platinum resistance	10 (16.9)	34 (17.8)		8 (14.5)	6 (10.9)	
Platinum partial sensitive	21 (35.6)	57 (29.8)		20 (36.4)	21 (38.2)	
Platinum sensitive	28 (47.5)	100 (52.4)		27 (49.1)	28 (50.9)	
PARPi line			0.991			0.875
1	24 (40.7)	81 (42.4)		22 (40.0)	23 (41.8)	
2	24 (40.7)	75 (39.3)		22 (40.0)	24 (43.6)	
3	10 (16.9)	32 (16.8)		10 (18.2)	8 (14.5)	
4	1 (1.7)	3 (1.6)		1 (1.8)	0 (0.0)	
PARPi type			0.201			1.000
Olaparib	28 (47.5)	94 (49.2)		25 (45.5)	25 (45.5)	
Niraparib	19 (32.2)	75 (39.3)		19 (34.5)	19 (34.5)	
Fluzoparib	12 (20.3)	22 (11.5)		11 (20.0)	11 (20.0)	
PARPi duration	12.7±8.6	14.0±9.0	0.269	13.2±8.8	12.4±7.2	0.919
RCRS			0.489			0.233
Yes	9 (15.3)	39 (20.4)		8 (14.5)	14 (25.5)	
No	50 (84.7)	152 (79.6)		47 (85.5)	41 (74.5)	

Values are presented as number (%) or mean ± standard deviation.
FIGO, International Federation of Gynecology and Obstetrics; gBRCA, germline breast cancer susceptibility gene; PARPi, Poly ADP-Ribose Polymerase inhibitor; RCRS, recurrent cytoreductive surgery.

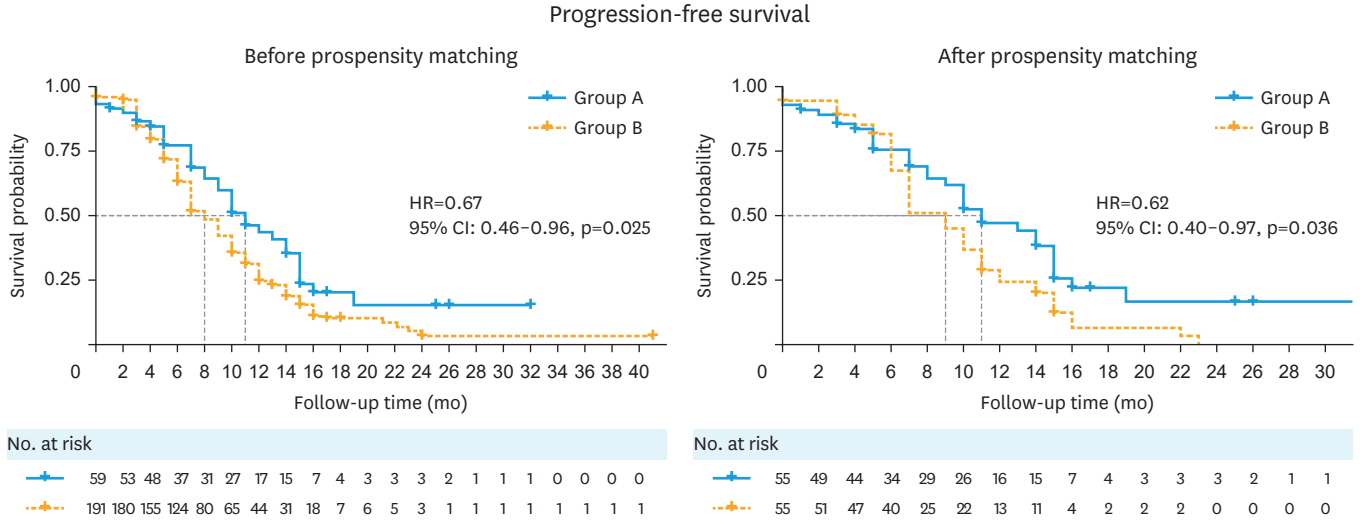

Fig. 2. Kaplan-Meier cumulative event curves of progression-free survival before and after propensity score-matching.
CI, confidence interval; HR, hazard ratio.

shown in **Fig. 3**). In the case of patients with platinum-resistant tumors, the combination of bevacizumab and chemotherapy regimen has been shown to significantly decrease the risk (HR=0.31; 95% CI=0.14–0.68, as depicted in **Fig. 3**). The ORR was 81.36% (48/59) in Group A, compared to 62.83% (120/191) in Group B.

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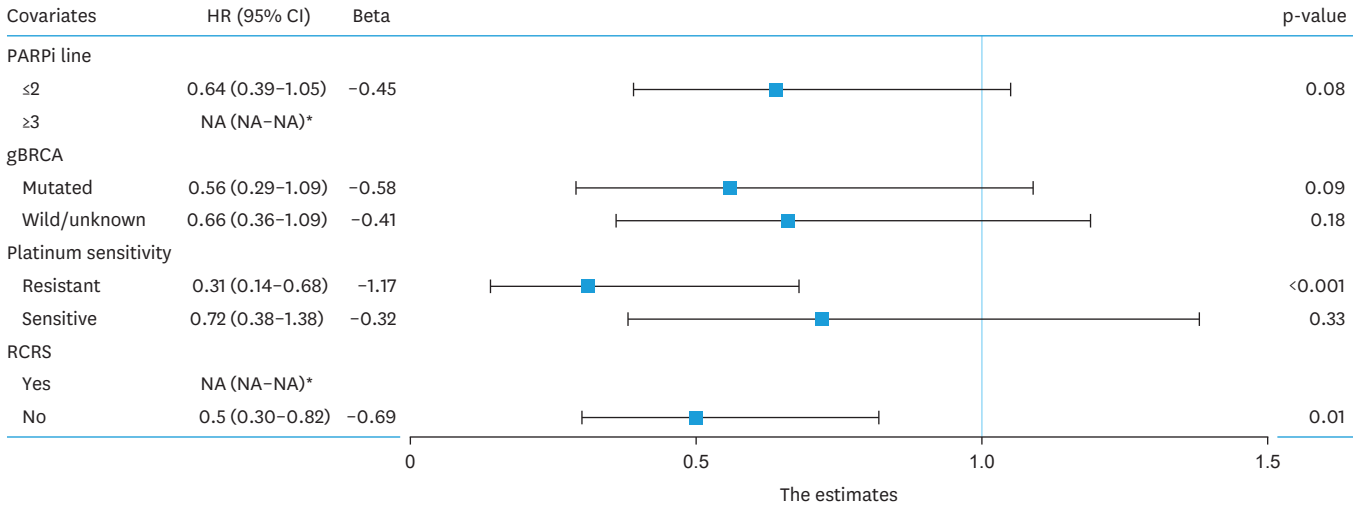

Fig. 3. Subgroup analysis of treatment effect on progression-free survival (forest plot).
CI, confidence interval; gBRCA, germline breast cancer susceptibility gene; HR, hazard ratio; NA, not available; PARPi, Poly ADP-Ribose Polymerase inhibitors; RCRS, recurrent cytoreductive surgery.
*Due to insufficient sample size/events.

3. Toxicity outcomes

The majority of individuals experience mild to moderate general adverse reactions, including nausea, vomiting, fatigue, and anemia. The predominant grades 3–4 adverse effects observed during the course of treatment comprised hematologic toxicity, with a higher incidence in bevacizumab combined with chemotherapy group compared to chemotherapy alone group. Additionally, cardiovascular comorbidities are delineated in **Table 3**. Grades 3–4 neutropenia was observed in 11 (20.0%) of the participants in Group A compared to 3 (5.5%) in Group B. Grades 3–4 leukopenia was observed in 11 (20.0%) of the patients in Group A, compared to 6 (10.9%) in Group B. Grades 3–4 thrombocytopenia was observed in 7 (12.7%) of participants in Group A, compared to 5 (9.1%) in Group B. The bevacizumab-chemotherapy arm showed a higher occurrence of grade ≥2 hypertension and proteinuria. The data of Group A indicated that 5.5% (3 out of 55) of patients who underwent the bevacizumab-chemotherapy regimen experienced severe hypertension. The 1.8% (1/55) experienced bowel perforation, while 3.6% (2/55) developed thrombosis. One instance of internal jugular vein thrombosis, intestinal perforation, deep venous thrombosis in the lower limbs, right external iliac vein, proximal femoral vein, and proximal femoral vein thrombosis, as well as one case of hypertension and left heart failure, were reported in Group A. These conditions showed improvement following drug withdrawal. while there were no cases of grade ≥3 hypertension, thrombosis, bowel perforation, or heart failure in Group B. There were no deaths related to drug use or treatment in either of the groups.

Table 3. Serious AEs for 110 patients treated after Poly ADP-Ribose Polymerase inhibitor

Grade ≥3 AEs	Group A (n=55)	Group B (n=55)
Neutropenia	11 (20.0)	3 (5.5)
Leukopenia	11 (20.0)	6 (10.9)
Thrombocytopenia	7 (12.7)	5 (9.1)
Anemia	5 (9.1)	3 (5.5)
Hypertension	3 (5.5)	0 (0)
Bowel perforation	1 (1.8)	0 (0)
Thrombosis	2 (3.6)	0 (0)
Liver function abnormality	3 (5.5)	0 (0)

Values are presented as number (%).
AE, adverse event.

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DISCUSSION

In this study, we demonstrate that the addition of bevacizumab to chemotherapy can effectively extend PFS in patients with recurrent OC that has relapsed following maintenance PARPis, as compared to treatment with traditional chemotherapy alone. The combined regimen of chemotherapy and bevacizumab was well tolerated by the majority of patients.

Several studies have investigated the clinical efficacies of combining bevacizumab with chemotherapy in patients with ROC. The OCEANS study [16], which examined the efficacy of bevacizumab in combination with GC regime (gemcitabine and carboplatin) followed by bevacizumab as maintenance monotherapy for PSOC, demonstrated a statistically significant extension in PFS for the bevacizumab group compared to the chemotherapy group (12.4 months vs. 8.4 months, p<0.000). The ORR was 78.5% and 57.4% (p<0.000) respectively. The AURELIA [14] trial focused on patients with platinum-resistant, recurrent ovarian cancer and the findings indicated a statistically significant difference in the median PFS between patients receiving bevacizumab plus chemotherapy and those receiving chemotherapy alone (6.7 months vs. 3.4 months, p<0.001). The combined regime demonstrated a significantly higher ORR compared to the chemotherapy-only group (30.9% vs. 12.6%, p<0.001), indicating the superior efficacy of bevacizumab in combination with chemotherapy. Both the GOG0213 and Pfisterer study validated that the incorporation of bevacizumab into conventional chemotherapy regimens (carboplatin-paclitaxel or carboplatin-pegylated liposomal doxorubicin) resulted in enhanced median OS rates among patients diagnosed with PSOC [15,19]. However, none of the aforementioned clinical trials included patients who experienced relapse following PARPi maintenance therapy. This omission may lead to a lack of representativeness in clinical practice, as patients with ROC after PARPi maintenance may exhibit distinct biological characteristics and molecular features. The post-hoc analysis of SOLO2 [4] indicated that resistance to PARPi is probable to have a negative effect on the efficacy of subsequent platinum-based chemotherapy. Despite the trial being questioned due to the imbalance of the baseline, the findings seem plausible considering the cross-drug resistance mechanisms of PARPi and platinum [9,12].

It is challenging to draw a definitive conclusion from the existing data regarding the potential survival benefits of combining bevacizumab with conventional chemotherapy compared to chemotherapy alone in patients with ROC after PARPi treatment. Upon conducting a retrospective analysis in this field, we initially observed that the median PFS was 11 months in the bevacizumab-chemotherapy group, representing an improvement of approximately 2 months compared to the chemotherapy group.

Some participants in our study were monitored post-therapy without receiving bevacizumab maintenance treatment, a factor that may partially account for the slight increase in median PFS of 2 months. Tumor angiogenesis plays a crucial role in cancer metastasis, including OC [20]. Ascites is known to be a predictor of poor prognosis in patients with OC, with approximately 89% of patients in advanced stages presenting with ascites [21]. Patients with multi-line recurrent OC typically exhibit a wide range lesion of large diameter, diffuse distribution, and are prone to complications such as malignant pleural effusion and ascites, particularly among those who have developed platinum-resistance. The improved PFS observed in the subgroup of with platinum-resistance for Group A and Group B is remarkable. The restoration of the balance between pro- and anti-angiogenic factors in tumors has the potential to transiently “normalize” tumor vasculature and the

microenvironment in both preclinical and clinical contexts [22]. Furthermore, bevacizumab has the potential to facilitate the recruitment and infiltration of specific T cells, diminish the infiltration of Treg cells, which are known for their immunosuppressive function, alleviate the immunosuppressive condition, and enhance the effectiveness of immunotherapy [23]. By inhibiting angiogenesis, anti-angiogenic drugs have the potential to induce hypoxia in the tumor microenvironment, leading to the down-regulation of key HRR factors such as BRCA1/2 and RAD51. This, in turn, may result in increased hypoxia-induced HRR defects in tumor cells. Furthermore, the inhibition of VEGFR3 could potentially enable patients with wild-type BRCA or those whose BRCA mutation has reverted to wild-type to derive benefits from PARPis [24]. By inhibiting the platelet-derived growth factor receptor and converging at the transcriptional level with E2F family transcription factors, the downregulation of homology-directed repair (HDR) pathway enzymes at the transcriptional level can be achieved. This suggests that anti-angiogenic therapies have the potential to induce an "HDR deficiency" and enhance sensitivity to PARPis [25]. The EVOLVE study (NCT02681237) initially evaluated the combination therapy of cediranib and PARPi following PARPi treatment. The study revealed a low ORR of 20% in the platinum-resistant group, 0% in PSOC, and 8% in exploratory cohorts among the 34 heavily pretreated patients [26].

In order to optimize the outcome of PARPi rechallenge, certain scholars have recommended the dual approach. Maintenance therapy involving a combination of vascular-targeted agents and PARPis, followed by chemotherapy combined with an anti-angiogenic agent. The Korean Gynecologic Oncology Group (KGOG 3056)/NIRVANA-R trial [27] is examining the effectiveness of niraparib and bevacizumab maintenance therapy in patients with PSOR who have been previously exposed to a PARPi. The ongoing NCT05385068 trial is currently investigating the effectiveness of niraparib rechallenge in combination with anlotinib [28].

Pfisterer et al.'s study [19] indicated that the receipt of previous antiangiogenic treatment did not significantly impact the PFS or the OS. However, an investigation into bevacizumab containing front line chemotherapy [29] revealed that the addition of bevacizumab is linked to a wider array of relapse manifestations, a decreased frequency of complete secondary cytoreductive surgery, and a reduced time to progression for second-line chemotherapy (5 months vs. 8 months; p=0.041). Another study [30] examining the time-dependent risks for progression following bevacizumab-containing therapy revealed that ceasing bevacizumab treatment could elevate the likelihood of subsequent progression in serous OC, irrespective of HRD status. Given the varying opinions regarding the effects of frontline administration of bevacizumab on the future prognosis of OC, our study opted to exclude patients who had previously undergone antiangiogenic therapy.

The FDA suggested dosage of bevacizumab for the management of colorectal cancer was 7.5 mg/kg Q3W. Meta-analyses have investigated the efficacy and safety of various doses of bevacizumab in the management of colorectal cancer [31]. The findings suggest that a dosage of 10 mg may offer superior efficacy in treating colorectal cancer, while 5 mg could be more safer in terms safety. However, there is a scarcity of high-quality evidence regarding the optimal dosage for efficacy in the treatment of OC. The dosage of bevacizumab administered in our study was 7.5 mg/kg Q3W, primarily selected due to the positive outcomes observed in the ICON 7 trial [32], partly influenced by the economic considerations specific to Chinese patients. The incorporation of bevacizumab into the Chinese medical insurance coverage is anticipated to lead to an increased utilization of the FDA-recommended dosage of 15 mg/kg Q3W among patients later.

To offer insights for future research, a subgroup analysis was carried out. The findings indicate a statistically significant difference in patients who did not undergo RCRS (HR=0.5; 95% CI=0.3–0.82; p=0.01) and in patients with platinum resistance (HR=0.31; 95% CI=0.14–0.68; p<0.001). The rate of secondary debulking surgery in this trial was 14.5% in Group A and 25.5% in Group B. These rates were found to be in close alignment with the previous multi-center phase 3 trial [12,15], which documented a secondary debulking surgery rate ranging from 11% to 16% in cases of PSOC. The DESKTOP III study centered on individuals diagnosed with PSOC who were encountering their first recurrence. The results suggested that attaining a satisfactory secondary surgical cytoreduction following chemotherapy could lead to a reduction in tumor burden and an extension of OS compared to receiving chemotherapy alone [33]. Among the 250 patients included in this study, the group with RCRS exhibited a mean PFS of 13.67 months, with the longest PFS reaching 41 months and still ongoing without reaching the endpoint. This is in contrast to the non-RCRS group, which showed a mean PFS of 7.12 months and the longest PFS observed was 25 months. It has been suggested that reducing secondary tumor cells may extend PFS in patients with recurrent OC following treatment with PARPi. However, the subgroup analysis conducted in this study did not reveal any statistically significant variance in PFS within the RCRS subgroup. This lack of significance was attributed to the limited sample size. Additionally, through hypothesis that the removal of resistant clones could partially overcome PARPi resistance, the MITO 35b study [34], a phase III randomized trial conducted in Italy, is enrolling patients who were randomized to receive either olaparib or platinum-based chemotherapy followed by secondary cytoreductive surgery.

In previous large phase 3 trials investigating the combination of bevacizumab and chemotherapy for recurrent OC [15,19], the occurrence of grades 3–4 neutropenia-related AEs ranged from 12% to 22%, whereas in our study, it was reported at 20%. Other AEs related to bevacizumab, such as hypertension, were reported in 12%–28% of the patients, in contrast to 5.5% in the present study. Additionally, AEs related to deep vein thrombosis were observed in 2% to 3% of the patients, compared to 3.6% in this study. In conclusion, the occurrence of myelosuppression and other grades 3–4 serious AEs in this study was comparable to that reported in prior studies, with no identification of novel adverse reactions. The adverse effects of combining bevacizumab with chemotherapy in patients with recurrent OC following PARPi treatment were deemed to be within acceptable limits.

The study was constrained by its retrospective design, a limitation that could potentially be alleviated to some extent through PSM analysis. The presence of a limited sample size may also lead to bias. Our study is grounded in real-world data, where not all patients were willing to continue bevacizumab maintenance after achieving remission from bevacizumab-chemotherapy. Despite its limitations, this investigation aimed to provide insights for the development of future prospective studies. The PFS was found to be extended when bevacizumab was combined with the chemotherapy. Moreover, the AE was tolerable.

In conclusion, for patients with recurrent OC relapsed after treatment with PARPis, the combination of bevacizumab and chemotherapy demonstrates improved PFS, with well-tolerated adverse effects. Prospectively randomized controlled trials are necessary for future research.

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