

Original Article

Olaparib combined with bevacizumab as first-line maintenance therapy for ovarian cancer

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Abstract: Objective: To evaluate short-term and long-term survival outcomes as well as the safety profile of olaparib combined with bevacizumab as first-line maintenance treatment for patients with ovarian cancer. Methods: We retrospectively analyzed the clinical data of 136 ovarian cancer patients treated at Affiliated Xingtai People Hospital of Hebei Medical University between December 2021 to December 2022. Patients were divided into a control group (n = 45) and an olaparib group (n = 91) according to the order of admission. All patients received bevacizumab maintenance therapy, while the olaparib group additionally received olaparib. Treatment was administered in 28-day cycles for a total of 15 cycles. Serum levels of tumor markers were measured before and after treatment. In addition, angiogenic factor levels were measured. Peripheral blood T-lymphocyte subsets were analyzed by flow cytometry. Adverse events during treatment were recorded, and progression-free survival (PFS) and overall survival (OS) were calculated. Results: After treatment, serum tumor markers, angiogenic factors, and apoptotic factors decreased in both groups, with significantly greater reductions occurring in the olaparib group than in the control group ($P < 0.05$). Meanwhile, the proportions of peripheral blood CD3+ and CD4+ T cells and the CD4+/CD8+ ratio increased more markedly in the olaparib group ($P < 0.05$). There was no significant difference in the incidence of treatment-related adverse events between the two groups ($P > 0.05$). The 3-year OS rate (58.24% vs. 46.67%) and PFS rate (48.35% vs. 24.44%) were significantly higher in the olaparib group than in the control group ($P < 0.05$), with more pronounced benefits in HRD-positive and BRCA-mutant patients. Patients with homologous recombination deficiency (HRD)-positive status and BRCA mutations also achieved significantly improved OS and PFS ($P < 0.05$). Conclusion: Olaparib combined with bevacizumab as first-line maintenance therapy effectively reduces tumor markers, inhibits angiogenesis, promotes apoptosis, and enhances immune function, thereby significantly improving long-term survival without increasing major adverse reactions, with particularly notable benefits in HRD-positive and BRCA-mutant patients.

Keywords: Ovarian cancer, first-line maintenance therapy, olaparib, bevacizumab, progression-free survival, overall survival

Introduction

Ovarian cancer remains one of the most common gynecological malignancies and is the leading cause of gynecological cancer-related death among women worldwide [1]. Due to the lack of early specific symptoms, approximately 70% of patients are diagnosed at Federation of Gynecology and Obstetrics (FIGO) Stage III-IV [2]. Although maximal cytoreductive surgery combined with platinum-based chemotherapy remains the standard first-line treatment, long-term outcomes are still poor, with relapse rate as high as 60-80% [3, 4]. Many advanced ovarian cancer patients exhibit reduced platinum

sensitivity and thus have a poorer prognosis and shorter life expectancy [5]. Therefore, strategies to delay disease progression, reduce recurrence risk, and prolong survival after first-line chemotherapy have become a major focus of clinical research in ovarian cancer.

Maintenance therapy aims to extend remission by continuously controlling residual micro-metastases and suppressing tumor growth after surgery [6]. Anti-angiogenic drugs have been widely used in ovarian cancer management. Bevacizumab is a recombinant humanized monoclonal antibody that targets VEGF. It blocks the interaction between vascular endo-

thelial growth factor (VEGF) and its receptors, reduces tumor angiogenesis, decreases nutrient supply to the tumor, and thus inhibits tumor growth and metastasis [7]. Clinical trials have demonstrated that bevacizumab-based regimens, whether used as extended therapy after initial chemotherapy or in combined regimens, significantly prolong time to disease progression [8-10]. However, anti-angiogenic monotherapy provides only modest survival benefits, suggesting that the combination therapies with different molecular mechanisms are needed to achieve optimal long-term outcomes. In recent years, significant advances have been made in ovarian cancer maintenance therapy with poly (ADP-ribose) polymerase (PARP) inhibitors [11]. Olaparib was the first approved PARP inhibitor for ovarian cancer treatment. By inhibiting PARP enzyme activity, it disrupts single-strand DNA repair, leading to accumulation of DNA damage and preventing homologous recombination repair of double-strand breaks, thereby inducing synthetic lethality effect in tumor cells [12]. Early preclinical and clinical investigations suggested a potential synergistic interaction between PARP inhibitors and anti-angiogenic therapies [13, 14]. The phase III PAOLA-1/ENGOT-ov25 trial demonstrated that olaparib combined with bevacizumab significantly improved progression-free survival (PFS) in patients who achieved remission after chemotherapy and bevacizumab induction [15], with particularly pronounced benefits in patients with homologous recombination deficiency (HRD)-positive tumors [16]. This synergistic effect is supported by a solid biological rationale and has shown significant PFS benefits in clinical practice. Therefore, the combined use of olaparib and bevacizumab as first-line maintenance therapy has strong biological rationale and considerable clinical potential.

Although large-scale international trials have confirmed the superior efficacy of this combination, long-term survival data, real-world safety profiles, and mechanistic evidence in the Chinese population remain limited. Building on the established efficacy of olaparib-bevacizumab combination in first-line maintenance therapy for newly diagnosed advanced ovarian cancer, this retrospective study compared the clinical efficacy and safety of bevacizumab monotherapy versus bevacizumab in combination with olaparib in patients who received bev-

acizumab-based maintenance therapy at our institution. This study not only validated the survival benefit and safety of this combination regimen in real-world clinical practice, but also systematically analyzed dynamic changes in serum tumor markers, angiogenesis- and apoptosis-related parameters, and peripheral blood T-lymphocyte subsets. By exploring the long-term therapeutic efficacy and potential mechanisms of this combination regimen from multiple dimensions, including real-time efficacy monitoring, mechanisms of action, and tumor microenvironment immune modulation, this study provides new insights and empirical evidence to optimize its individualized clinical application.

Materials and methods

General data

This retrospective study included 136 patients diagnosed with ovarian cancer who were treated at Affiliated Xingtai People Hospital of Hebei Medical University between December 2021 and December 2022.

Inclusion criteria: ① Histologically confirmed ovarian cancer [17]; ② Achievement of complete remission (CR) or partial remission (PR) after first-line systemic therapy; ③ Use of bevacizumab as maintenance therapy after first-line chemotherapy; ④ Karnofsky performance status [18] score > 60; ⑤ Expected survival time longer than 6 months.

Exclusion criteria: ① Presence of other concurrent malignancies; ② Concurrent systemic infection or inflammatory disease; ③ Concurrent immunodeficiency or hematological diseases; ④ Evidence of hepatic or renal impairment; ⑤ Severe adverse reactions or hypersensitivity to study drugs; ⑥ Impaired consciousness, cognitive impairment, or psychiatric disorders; ⑦ Pregnancy or lactation; ⑧ Incomplete clinical data.

This study was approved by the Ethics Committee of Affiliated Xingtai People Hospital of Hebei Medical University. Given the retrospective and anonymous nature of the data analysis, which entails no additional risks, and because all data were de-identified before analysis, the requirement for individual informed consent was waived.

Grouping and treatment regimens

A total of 136 ovarian cancer patients were allocated to the control group (n = 45) and the olaparib group (n = 91). Group allocation reflected the evolution of clinical practice during this period: before July 2022, bevacizumab monotherapy was the standard maintenance regimen (control group, n = 45); after July 2022, following the publication of PAOLA-1 trial results and changes in reimbursement policies, the olaparib-bevacizumab combination became the recommended first-line maintenance therapy, and all subsequently enrolled patients received this combination regimen (olaparib group, n = 91). The difference in sample sizes between the two groups objectively reflects this shift in clinical practice.

All patients received bevacizumab (Roche, Switzerland; S20120069; 400 mg/vial) at a standard dosage of 7.5 mg/kg once every three weeks during the whole treatment course. Patients in the olaparib group additionally received olaparib capsules (AbbVie Deutschland GmbH & Co. KG, USA; H20180049: 150 mg/tablet) at a total daily dose of 300 mg, divided into two doses during the first 10 days of each cycle. The dose was modified according to the severity of adverse events. Patients in the control group received no other medications. Both groups received 15 treatment cycles, each lasting 28 days.

Observation indicators

No additional blood draws or tests were performed. All data analyzed were historical data generated and archived during patients' routine clinical follow-up visits while receiving maintenance therapy. Data were independently extracted from the electronic medical record system by two researchers and cross-verified. The retrospectively extracted data included: ① Biomarker testing: Serum tumor markers [carbohydrate antigen 125 (CA125), carbohydrate antigen 19-9 (CA19-9), carcinoembryonic antigen (CEA), human epididymis protein 4 (HE4), and alpha-fetoprotein (AFP)], angiogenic mediators [matrix metalloproteinase-9 (MMP-9), angiopoietin-2 (Ang-2), and stromal cell-derived factor-1 alpha (SDF-1 α)], and apoptosis-related markers [soluble Fas (sFas), soluble Fas ligand (sFasL), and B-cell lymphoma-2 (Bcl-2)] were measured in serum/plasma samples collected

during routine clinical care. All tests were performed by the hospital clinical laboratory/central laboratory using enzyme-linked immunosorbent assay (ELISA) according to standard operating procedures. The raw data of each marker test should be compiled into [Supplementary Table 1](#). ② Circulating tumor cells (CTCs) testing: CTCs were isolated from blood samples using immunoaffinity-based positive enrichment. ③ Quantification of T-cell populations: Proportions of CD3+, CD4+, CD8+ T cells and the CD4+/CD8+ ratio were measured as part of routine immune function monitoring using a LSRFortessa™ X-20 flow cytometer (BD Biosciences, USA), with standardized CD3 antibody (BD Biosciences, USA), CD4 antibody (BioLegend, USA), and CD8 antibody (Thermo Fisher Scientific, USA) reagent kits according to the manufacturer's instructions. ④ Adverse reactions: Treatment-related adverse events, including nausea, vomiting, rash, myelosuppression, thrombocytopenia, leukopenia, hypertension, fatigue, and hepatic/renal impairment, were retrospectively extracted from electronic medical records. ⑤ Follow-up and survival data: Patient follow-up records, including dates of disease progression, recurrence, and all-cause mortality events, were retrospectively extracted from the electronic medical record system and the hospital death registry. Follow-up was censored in December 2025. PFS was defined as the time from treatment initiation to the first radiologically or clinically confirmed disease progression or death from any cause [19]. Overall survival (OS) was defined as the time from treatment initiation to death from any cause; patients without death events were censored at the last follow-up date [20].

Statistical methods

Statistical analyses were performed using SPSS 26.0 (IBM Corp., Armonk, NY, USA). Normality of all quantitative variables was assessed using the Shapiro-Wilk test. Normally distributed data were expressed as mean $\pm$ standard deviation (mean $\pm$ SD) and compared using the independent-samples t-test. Non-normally distributed data were expressed as median (interquartile range), and compared using the Mann-Whitney U test. For multiple comparisons of serum tumor markers and angiogenesis/apoptosis-related factors before and after treatment, the false discovery rate (FDR) correction (Benjamini-Hochberg procedure)

Table 1. Comparison of baseline demographic and clinical characteristics between the groups

Variable	Control group	Olaparib group	χ^2/t value	P value
N	45	91	-	-
Age (years)	63.17±5.50	62.09±6.73	0.323	0.718
BMI (kg/m ²)	21.53±2.21	21.70±2.42	0.569	0.505
Disease course (years)	4.49±1.03	4.56±1.11	0.182	0.941
Time from chemotherapy to maintenance (months)	1.32±0.13	1.28±0.10	0.384	0.556
Pathological type [n (%)]			0.116	0.342
Serous	38 (84.44)	78 (85.71)		
Endometrioid	7 (15.56)	13 (14.29)		
ECOG performance [n (%)]			0.368	0.543
0	32 (71.11)	64 (70.33)		
1	13 (28.89)	27 (29.67)		
FIGO stage [n (%)]			0.450	0.519
III	33 (73.33)	68 (74.73)		
IV	12 (26.67)	23 (25.27)		
Response to first-line chemotherapy [n (%)]			0.141	0.776
CR	24 (53.33)	50 (54.95)		
PR	21 (46.67)	41 (45.05)		
HRD status [n (%)]			0.653	0.132
Positive	28 (62.22)	55 (60.44)		
Negative	17 (37.78)	36 (39.56)		
BRCA mutation [n (%)]			0.729	0.125
Yes	18 (40.00)	40 (43.96)		
No	27 (60.00)	51 (56.04)		

Note: ECOG, Eastern Cooperative Oncology Group; FIGO, International Federation of Gynecology and Obstetrics; HRD, homologous recombination deficiency; BRCA, breast cancer susceptibility gene; BMI, body mass index; CR, complete remission; PR, partial remission.

ture) was applied to control the type I error rate. Categorical variables were presented as counts and percentages and compared using the χ^2 test or Fisher's exact test. Survival curves for PFS and OS were plotted using the Kaplan-Meier method, and differences between subgroups were examined using the log-rank test. Multivariable Cox proportional hazards regression was used to evaluate the independent effects of various clinicopathological factors, including treatment group, HRD status, BRCA mutation, FIGO stage, platinum response, ECOG performance status, age, and BMI, on PFS and OS. Results were expressed as hazard ratios (HRs) with 95% confidence intervals (CIs). All tests were two-sided, and a *P*-value < 0.05 was considered statistically significant.

Results

Baseline characteristics

There were no significant differences in age, BMI, disease course, Karnofsky score, interval

from first-line chemotherapy to maintenance treatment, histological type, ECOG performance status, FIGO stage, response to first-line chemotherapy, HRD status, or BRCA mutation frequency between the two groups (all *P* > 0.05, **Table 1**).

Serum tumor marker levels

Post-treatment levels of CA125, CA19-9, CEA, CTC, HE4, and AFP were significantly reduced in both groups compared with baseline values (*P* < 0.05). In addition, post-treatment levels of these markers in the olaparib group were markedly lower than those in the control group (*P* < 0.05; **Figure 1**).

Serum angiogenic factor levels

In both groups, post-treatment serum levels of MMP-9, Ang-2, and SDF-1 α were significantly decreased compared with baseline (*P* < 0.05). Furthermore, post-treatment levels of MMP-9, Ang-2 and SDF-1 α in the olaparib group were

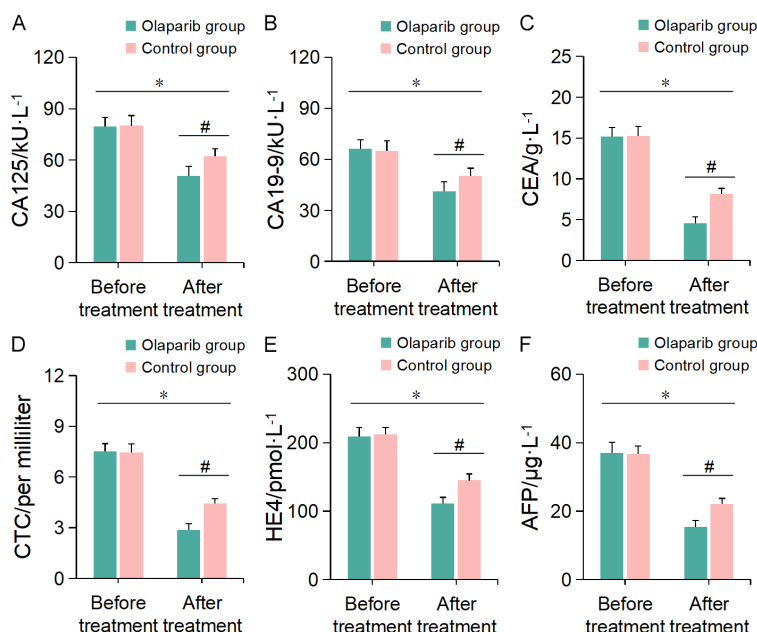


Figure 1. Comparison of serum tumor marker levels between the two groups before and after treatment. A. CA125; B. CA19-9; C. CEA; D. CTC; E. HE4; F. AFP. Notes: CA, carbohydrate antigen; CEA, carcinoembryonic antigen; CTC, circulating tumor cells; HE4, human epididymis protein 4; AFT, alpha-feto-protein. * $P < 0.05$, compared with baseline value within the same group; # $P < 0.05$, compared with the control group.

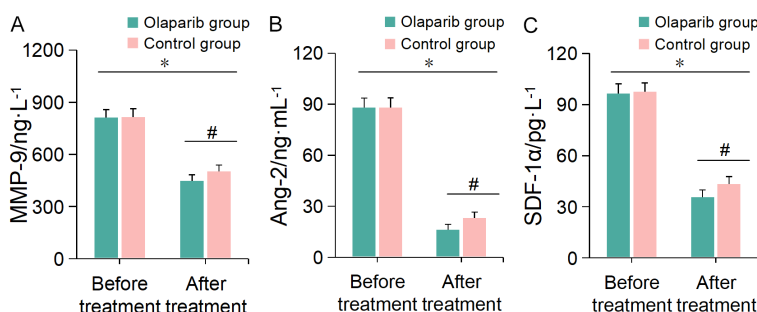


Figure 2. Comparison of peripheral blood angiogenic factor levels before and after treatment between the two groups. A. MMP-9; B. Ang-2; C. SDF-1α. Notes: MMP, matrix metalloproteinase-9; Ang-2, angiotensin-2; SDF-1α, stromal cell-derived factor-1α. * $P < 0.05$, compared with baseline value within the same group; # $P < 0.05$, compared with the control group.

significantly lower than the control group ($P < 0.05$) (Figure 2).

Serum apoptotic factor levels

In both groups, post-treatment serum levels of sFas, sFasL, and Bcl-2 were significantly decreased compared with baseline ($P < 0.05$). Moreover, post-treatment levels of these markers in the olaparib group were significantly lower than those in the control group ($P < 0.05$) (Figure 3).

Peripheral blood T-lymphocyte subset

Post-treatment proportions of CD3+ and CD4+ T cells and the CD4+/CD8+ ratio were significantly increased in both groups compared with baseline (all $P < 0.05$). Additionally, post-intervention proportions of CD3+ and CD4+ T cells and the CD4+/CD8+ ratio in the olaparib groups were significantly higher than those in the control group ($P < 0.05$) (Figure 4).

Adverse events

No significant differences were observed between the two groups in the incidence of nausea, vomiting, rash, myelosuppression, thrombocytopenia, leukopenia, hypertension, fatigue, hepatic dysfunction, or renal dysfunction ($P > 0.05$; Figure 5).

Survival outcomes

The median follow-up duration was 20.25 months for the control group and 36.04 months for the olaparib group. The 3-year OS rates were 46.67% and 58.24%, and the 3-year PFS rates were 24.44% and 48.35%, respectively. The 3-year OS and PFS rates in the olaparib group were significantly higher than those in the control group (both $P < 0.05$). The median PFS and OS in the control group were 31.52 months and 23.56 months, respectively; in the olaparib group, median PFS was not reached and median OS was 35.43 months. Compared with the control group, the olaparib group demonstrated significantly prolonged median PFS (HR = 0.52, 95% CI: 0.34-0.79, $P < 0.001$), representing a 48% reduction in the risk of disease progression. Median OS showed a trend toward improvement (HR = 0.68, 95% CI: 0.45-1.03, $P = 0.068$), although this did not reach statistical significance. The results are shown in Figure 6.

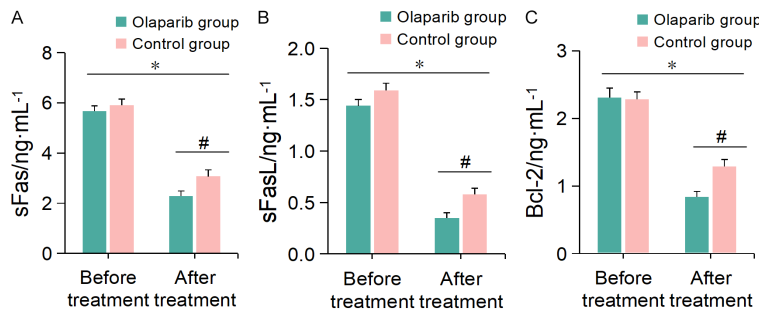


Figure 3. Comparison of serum apoptotic factor levels before and after treatment between the two groups. A. sFas; B. sFasL; C. Bcl-2. Notes: sFas, soluble factor-associated suicide; sFasL, soluble factor-associated suicide ligand; Bcl-2, B-cell lymphoma-2. * $P < 0.05$, compared with baseline value within the same group; # $P < 0.05$, compared with the control group.

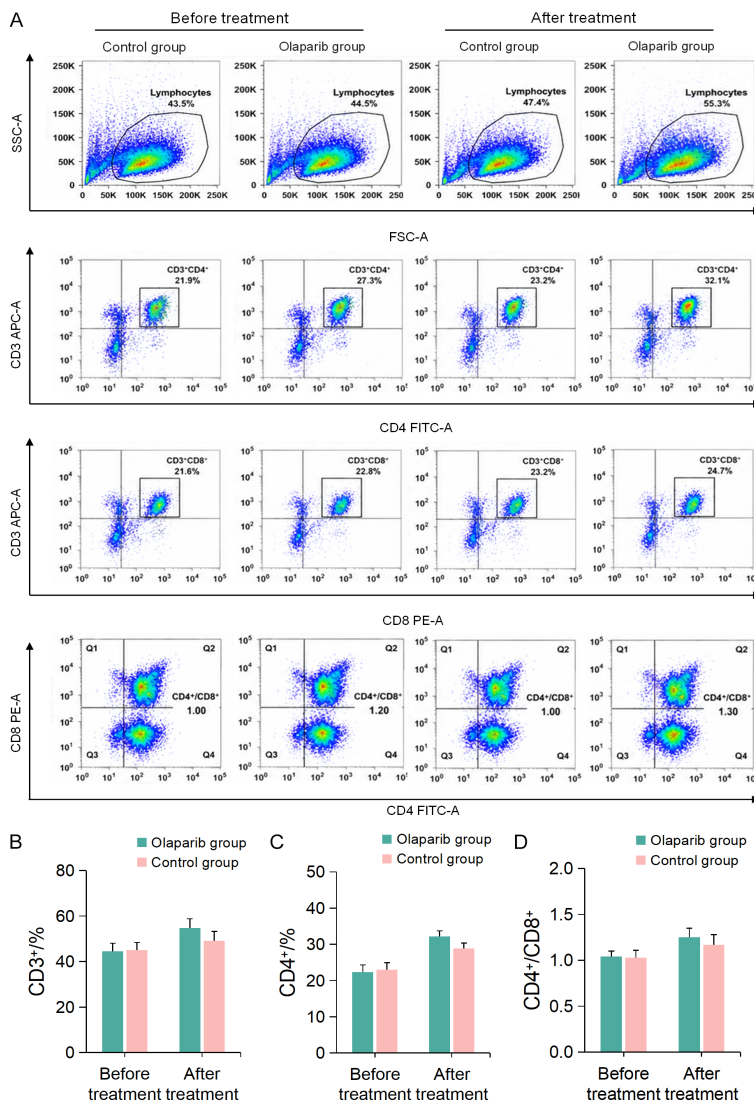


Figure 4. Comparison of serum T-lymphocyte subsets before and after treatment between the two groups. A. Flow cytometry scatter plot; B. Percentage of CD3⁺ cells; C. Percentage of CD4⁺ cells; D. CD4⁺/CD8⁺ ratio. Notes: $P < 0.05$, compared with baseline value within the same group; # $P < 0.05$, compared with the control group.

In the HRD-positive subgroup, the median follow-up duration was 25.44 months in the control group and 40.09 months in the olaparib group. The 3-year OS rates were 57.14% in the control group and 76.36% in the olaparib group, and the 3-year PFS rates were 39.29% and 56.36%, respectively. All 3-year survival endpoints were significantly higher in the olaparib group than in the control cohort (both $P < 0.05$). In the HRD-positive subgroup, the median PFS and OS in the control group were 41.87 months and 21.38 months, respectively; in the olaparib group, median PFS was not reached and median OS was 39.05 months. The PFS benefit in the olaparib group was more pronounced (HR = 0.48, 95% CI: 0.28-0.82, $P = 0.007$), corresponding to a 52% reduction in disease progression risk; the OS benefit was also significant (HR = 0.55, 95% CI: 0.31-0.98, $P = 0.041$). Detailed outcomes are presented in Figure 7.

In the BRCA-mutated subgroup, the median follow-up duration was 26.81 months in the control group and 42.20 months in the olaparib group. The 3-year OS rates were 66.67% in the control group and 80.00% in the olaparib group, and the 3-year PFS rates were 50.00% and 70.00%, respectively. All 3-year survival endpoints were significantly higher in the olaparib group than in the control group (all $P < 0.05$). Median PFS was not reached in either group, and median OS was 33.29 months in the control group versus not reached in the olaparib group. The olaparib group demonstrated the greatest PFS benefit (HR = 0.42, 95% CI: 0.21-0.84, $P = 0.013$), with a

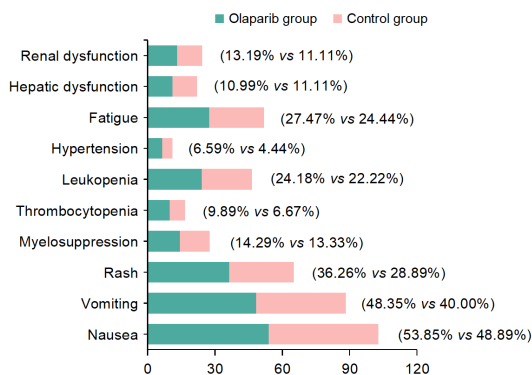


Figure 5. Comparison of the incidence of adverse events between the two groups.

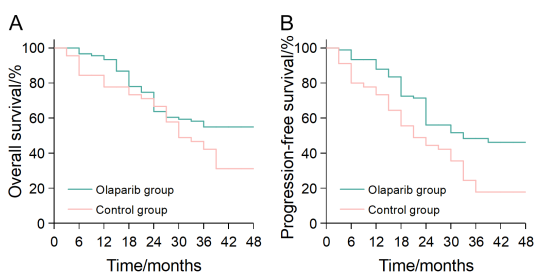


Figure 6. Kaplan-Meier survival curves for both groups. A. Overall survival; B. Progression-free survival.

marginally significant OS benefit (HR = 0.58, 95% CI: 0.29-1.16, $P = 0.123$). The results are shown in **Figure 8**.

Multivariate Cox proportional hazards regression analysis

In the PFS analysis (**Table 2**), patients receiving olaparib combined with bevacizumab had a significantly lower risk of disease progression or death compared with the bevacizumab monotherapy group (HR = 0.52, 95% CI: 0.31-0.87, $P = 0.013$). In addition, HRD-positive status (HR = 0.45, $P = 0.001$) and BRCA mutation (HR = 0.38, $P < 0.001$) were strong favorable prognostic factors, whereas FIGO stage IV was a significant unfavorable prognostic factor (HR = 1.68, $P = 0.042$). Platinum response, ECOG score, age, and BMI were not independently associated with PFS in this model.

In the OS analysis (**Table 3**), the treatment effect showed a favorable trend but did not reach statistical significance (HR = 0.61, 95% CI: 0.36-1.04, $P = 0.068$). FIGO stage IV (HR = 1.89, $P = 0.017$), HRD-positive status (HR =

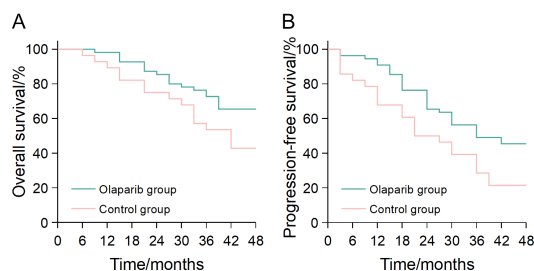


Figure 7. Kaplan-Meier survival curves for HRD-positive patients in both groups. A. Overall survival; B. Progression-free survival. Note: HRD, homologous recombination deficiency.

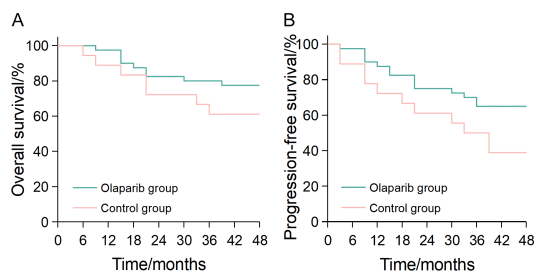


Figure 8. Kaplan-Meier survival curves for BRCA-mutant patients in both groups. A. Overall survival; B. Progression-free survival. Note: BRCA, breast cancer susceptibility gene.

0.52, $P = 0.013$), BRCA mutation (HR = 0.41, $P = 0.003$), and age (HR = 1.03, $P = 0.045$) were identified as independent predictors of OS.

Discussion

Even after achieving complete or partial response following maximal cytoreductive surgery and platinum-based chemotherapy, a substantial proportion of patients experience disease recurrence within 3 years [21]. After recurrence, platinum sensitivity decreased, treatment options became limited, and long-term survival rates decreased significantly [22, 23]. The core goal of maintenance therapy is to inhibit residual microscopic lesions, delay drug resistance, and improve the tumor microenvironment, thereby achieving long-term disease control [24]. Bevacizumab, as an anti-angiogenic agent, has been shown to prolong PFS, but its OS benefit is limited [25]. The PARP inhibitor olaparib exerts potent antitumor activity by inhibiting DNA repair pathways [26]. To assess the clinical value of olaparib plus bevacizumab as first-line maintenance treatment for ovarian cancer, this study assessed the influence of the combined regimen on short-term response

Table 2. Multivariable Cox regression analysis for PFS

Variable	HR	95% CI	P value
Treatment group (combination vs monotherapy)	0.52	0.31-0.87	0.013
FIGO stage (IV vs III)	1.68	1.02-2.76	0.042
HRD status (positive vs negative)	0.45	0.28-0.73	0.001
BRCA mutation (mutant vs wild-type)	0.38	0.22-0.66	< 0.001
Platinum response (CR vs PR)	0.71	0.45-1.12	0.143
ECOG score (2 vs 0-1)	1.45	0.89-2.36	0.136
Age (per 1-year increase)	1.02	0.99-1.05	0.234
BMI (per 1 kg/m ² increase)	0.98	0.94-1.02	0.345

Note: PFS, progression-free survival; ECOG, Eastern Cooperative Oncology Group; FIGO, International Federation of Gynecology and Obstetrics; HRD, homologous recombination deficiency; BRCA, breast cancer susceptibility gene.

Table 3. Multivariable Cox regression analysis for OS

Variable	HR	95% CI	P value
Treatment group (combination vs monotherapy)	0.61	0.36-1.04	0.068
FIGO stage (IV vs III)	1.89	1.12-3.19	0.017
HRD status (positive vs negative)	0.52	0.31-0.87	0.013
BRCA mutation (mutant vs wild-type)	0.41	0.23-0.74	0.003
Platinum response (CR vs PR)	0.65	0.40-1.06	0.085
ECOG score (2 vs 0-1)	1.62	0.95-2.76	0.077
Age (per 1-year increase)	1.03	1.00-1.06	0.045

Note: OS, overall survival; ECOG, Eastern Cooperative Oncology Group; FIGO, International Federation of Gynecology and Obstetrics; HRD, homologous recombination deficiency; BRCA, breast cancer susceptibility gene.

markers and long-term survival outcomes, aiming to provide real-world evidence to optimize maintenance treatment strategies.

Serum tumor markers are widely used as indicators of disease progression and treatment response in ovarian cancer. CA125 remains the primary biomarker, and its levels correlate with tumor burden [27]. HE4 provides complementary value by improving specificity [28]. CTCs represent circulating tumor cells and are closely associated with micrometastasis and recurrence risk [29]. Although CEA, CA19-9, and AFP are not specific biomarkers, they may reflect tumor biological aggressiveness in some patients [30-32]. Our data confirmed that serum levels of CA125, CA19-9, CEA, CTC, HE4, and AFP decreased significantly after treatment in both groups, with more pronounced reductions in the olaparib group. Bevacizumab inhibits the VEGF signaling pathway, reduces neovascularization, limits tumor nutrient supply, and subsequently suppresses tumor growth [33]. Olaparib inhibits PARP enzymatic activity, disrupting single-strand DNA break repair and leading to the accumulation of DNA double-strand breaks

during tumor cell replication, which markedly accelerates apoptosis and reduces tumor marker levels [34]. After combination treatment, anti-angiogenic therapy induces tumor hypoxia, which may further impair homologous recombination repair capacity, rendering tumor cells more sensitive to PARP inhibition and ultimately producing a synergistic anti-tumor effect [35]. The sustained reduction in tumor markers indicates long-term inhibition of tumor cell activity, laying a foundation for long-term survival benefits. Furthermore, we found that patients in the olaparib combination group had higher proportions of CD3+ and CD4+ T cells and a higher CD4+/CD8+ ratio in peripheral blood. This suggests that combination regimen contributes to immune function restoration, which is of great significance for prolonging PFS.

Angiogenesis provides oxygen and nutrients essential for tumor growth, invasion, and metastasis and is a key factor in ovarian cancer progression and poor prognosis [36]. Extensive angiogenesis is frequently observed in chemoresistant tumors, suggesting that inhibition of

angiogenesis may improve chemotherapy efficacy [37]. MMP-9 a matrix-degrading enzyme that cleaves extracellular matrix and basement membrane components; upon release, it binds to VEGF, thereby promoting endothelial cell migration and angiogenesis [38]. Ang-2 is a key driver of vascular remodeling. Together with VEGF, it induces vascular basement membrane detachment and enhances endothelial cell plasticity to facilitate neovascularization [39]. SDF-1 α binds to C-X-C chemokine receptor type 4 (CXCR4) on endothelial cell membranes, chemotactically recruiting endothelial progenitor cells to hypoxic regions where they secrete pro-angiogenic factors, and also directly activates angiogenic signaling pathways [40]. Our data demonstrated that serum levels of MMP-9, Ang-2, and SDF-1 α decreased significantly after treatment in both groups, with more pronounced reduction in the olaparib combination group. Therefore, olaparib may significantly reduce angiogenic factor production and secretion, inhibit endothelial cell migration, and thus suppress angiogenesis. In addition to angiogenesis, apoptosis is closely related to tumor occurrence and progression. sFas neutralizes membrane FasL and competitively blocks death receptor-mediated apoptotic signaling, enabling malignant cells to evade immune surveillance and accelerate disease progression [41]. Soluble FasL (sFasL) is a soluble form of Fas that may reflect tumor malignancy, distant metastasis, and unfavorable clinical outcomes [42]. Bcl-2 is an anti-apoptotic protein, and its overexpression enhances chemoresistance and promotes tumor survival [43]. Our analysis revealed that serum levels of sFas, sFasL and Bcl-2 decreased after treatment in both groups, with more pronounced reductions in the olaparib combination group. This suggests that olaparib exerts a pro-apoptotic effect on tumor cells by regulating the activity of key molecules.

Safety is a key factor determining the feasibility of long-term maintenance therapy [44]. Our data demonstrated that incorporation of olaparib into bevacizumab maintenance treatment did not significantly increase the incidence of adverse events, including nausea, vomiting, rash, myelosuppression, thrombocytopenia, leukopenia, hypertension, fatigue, or hepatic and renal dysfunction. This may be attributable to the oral formulation of olaparib and the abil-

ity to individualize dosing according to patient tolerance. Furthermore, during the maintenance therapy phase, overall tumor burden was lower and patient's physical condition was more stable than during chemotherapy, contributing to better drug tolerance. Second, our data demonstrated that patients receiving bevacizumab plus olaparib had significantly higher 3-year OS and PFS rates than those receiving bevacizumab alone. Subgroup stratification analysis indicated that the survival benefit of the combination strategy was substantially more pronounced in HRD-positive and BRCA-mutant patients. HRD or BRCA mutations resulted in defective DNA homologous recombination repair, rendering tumor cells highly cells highly susceptible to PARP inhibitor cytotoxicity [45, 46]. The hypoxic state induced by anti-angiogenic therapy further exacerbates the DNA repair defect, potentiates the synthetic lethality effect, and thereby significantly prolongs PFS and OS [47]. Therefore, HRD status and BRCA mutations may serve as key biomarkers for identifying patients most likely to benefit from this combination regimen. The combined maintenance therapy demonstrated a stronger therapeutic advantage in this patient subgroup underscoring the importance of precise stratified treatment.

Although our data demonstrated a pronounced survival advantage associated with first-line olaparib plus bevacizumab regimen, several limitations should be acknowledged: ① This was a single-institution retrospective study, with inherent risks of selection and information bias; ② Unequal sample sizes between the two groups may have compromised the robustness of statistical comparisons; ③ There was a significant difference in median follow-up time between the two groups (20.25 months vs. 36.04 months), indicating the distinct enrollment periods. This resulted in insufficient follow-up maturity in the control group at the data cutoff, reducing the reliability of long-term (e.g., 3-year) survival estimates and compromising cross-group comparisons of long-term efficacy; ④ No multivariate Cox regression modeling was implemented to identify independent predictors of clinical outcomes; ⑤ Although follow-up extended to 3 years, the prolonged recurrence pattern typical of ovarian cancer necessitates longer observation; ⑥ Immunological analysis was limited to flow cytometric pheno-

typing of peripheral blood T-lymphocyte subsets and lacked assessment of T-cell function, such as antigen-specific proliferation, cytotoxicity, or cytokine secretion. Therefore, the direct functional link between changes in T-cell subsets and antitumor immune efficacy has not yet been established; ⑦ Given the limited sample size, this study was underpowered to detect rare serious adverse events (incidence < 5%); ⑧ We did not directly measure changes in hypoxia markers or dynamic HRD status before and after treatment; thus, the proposed synergistic mechanism requires validation in future prospective studies with serial assessment of hypoxia markers (e.g., HIF-1 α CAIX) and HRD scores. Therefore, multi-institutional, large-scale, prospective studies are needed to comprehensively validate the sustained therapeutic benefits and long-term safety of this combination maintenance regimen. At the same time, individualized long-term management strategies should be formulated according to molecular classification and serial HRD assessment. In addition, the potential synergistic effects of triple regimens combining PARP inhibitors, anti-angiogenic agents, and immunotherapeutic agents warrant systematic investigation to further improve survival outcomes in advanced ovarian cancer.

Conclusion

Olaparib combined with bevacizumab as first-line maintenance therapy for ovarian cancer significantly reduces serum tumor marker and angiogenic factor levels, promotes apoptosis and immune function restoration, and prolongs PFS and OS. Moreover, the combination regimen does not significantly increase adverse events, with particularly pronounced benefits in HRD-positive and BRCA-mutant patients. These findings provide robust evidence to support clinical maintenance treatment strategies.

Disclosure of conflict of interest

None.

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