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Article

Clinical Impact of Olaparib Dose Reduction Compared with Bevacizumab and Standard-Dose Olaparib in Platinum-Sensitive Recurrent Ovarian Cancer

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Simple Summary

In platinum-sensitive recurrent ovarian cancer, bevacizumab (BEV) and Olaparib (OLA) are widely used as maintenance therapies after chemotherapy. However, few studies have compared these two treatments, independent of BRCA mutation or homologous recombination deficiency (HRD) status, and the impact of OLA dose reduction on treatment outcomes remains unclear. In this multicenter retrospective study of 101 patients, we compared three groups: BEV, standard-dose OLA, and dose-reduced OLA. The dose-reduced OLA group showed better progression-free survival than the BEV group and tended to have longer overall survival, without an increase in severe adverse events. These findings suggest that OLA dose reduction may reduce treatment-related toxicity while maintaining clinical effectiveness and improving treatment continuity. Our results indicate that dose-reduced OLA may represent a practical and effective maintenance treatment option in real-world clinical practice, regardless of BRCA mutation or HRD status.

Abstract

Objective: Bevacizumab (BEV) and Olaparib (OLA) have demonstrated clinical efficacy as maintenance therapies for first platinum-sensitive recurrent ovarian cancer. However, direct comparisons between these agents independent of homologous recombination deficiency (HRD) and BRCA status, remain limited and the clinical validity of OLA dose reduction has not yet been confirmed. This study aimed to compare the efficacy and safety of BEV, standard-dose OLA, and dose-reduced OLA as maintenance therapy and to evaluate the clinical utility of OLA dose reduction.

Methods: This retrospective multicenter study included 101 patients with first platinum-sensitive recurrent ovarian, fallopian tube, or primary peritoneal cancer who received maintenance therapy after achieving a response to chemotherapy. Patients were classified into three groups: BEV (n = 34), standard-dose OLA (n = 31), and dose-reduced OLA (n = 36). The primary endpoint was progression-free survival (PFS), and secondary endpoints included overall survival (OS) and adverse events. Survival outcomes were evaluated using Kaplan–Meier analysis and Cox proportional hazards models. **Results:** Median PFS was 16 months in the BEV group, 16 months in the standard-dose OLA group, and 24 months in the dose-reduced OLA group, with significantly longer PFS in the dose-reduced OLA group ($p < 0.001$). In the multivariate Cox analysis, treatment remained an independent prognostic factor for PFS (HR 0.67, 95% CI 0.46–0.96, $p = 0.030$). Median OS was 44, 45, and 64 months, respectively, with no significant differences among groups; PFI ≥ 12 months was the only independent prognostic factor for OS. Grade ≥ 3 hematologic toxicities were more frequent in the OLA groups but

were manageable. **Conclusions:** Dose-reduced OLA was associated with prolonged PFS while maintaining manageable toxicity, supporting its clinical validity as a maintenance option independent of HRD and BRCA status.

Keywords: ovarian cancer; platinum-sensitive recurrence; maintenance therapy; bevacizumab; olaparib

1. Introduction

Ovarian cancer is one of the most lethal gynecologic malignancies and is frequently diagnosed at an advanced stage, with a clinical course characterized by repeated recurrences [1]. The incidence of ovarian cancer is reported to be approximately 1.3 times higher than that reported a decade ago [2]. In 2020, approximately 314,000 new cases of ovarian cancer and 207,000 related deaths were reported worldwide [3]. In the United States, an estimated 19,680 new cases and 12,740 deaths from ovarian cancer were predicted in 2024 with mortality from ovarian cancer exceedings that from cervical and endometrial cancers [4,5]. Despite advances in cytoreductive surgery and chemotherapy, approximately 70–80% of patients with advanced ovarian cancer experience disease recurrence within several years after completion of first-line treatment, highlighting the persistent clinical challenges associated with this disease [6–8].

Paclitaxel plus carboplatin (TC) chemotherapy has been established as the standard first-line treatment for ovarian cancer, based on evidence from pivotal clinical trials including GOG111, OV-10, GOG158, and AGO studies [9–11]. In the recurrent setting, treatment strategies and prognosis are strongly influenced by the platinum-free interval (PFI). Recurrence occurring ≥ 6 months after completion of platinum-based chemotherapy is defined as platinum-sensitive recurrent ovarian cancer (PSROC), for which retreatment with platinum-based regimens is associated with significant clinical benefit [12]. However, prognosis worsens with each recurrence, and cumulative toxicities from repeated chemotherapy remain a major concern [13]. Therefore, the establishment of effective maintenance therapies to prolong remission duration and improve survival outcomes is of critical importance.

For patients with PSROC who achieve a response to chemotherapy, both the National Comprehensive Cancer Network (NCCN) guidelines [14] and the guidelines of the Japan Society of Gynecologic Oncology [15] recommend maintenance therapy with the anti-angiogenic agent Bevacizumab (BEV) or the poly ADP-ribose polymerase (PARP) inhibitor Olaparib (OLA). BEV has demonstrated prolongation of progression-free survival (PFS) and overall survival (OS) in several phase III trials, including GOG213 [16], OCEANS [17], and MITO16B-MaNGO [18], regardless of BRCA mutation or homologous recombination deficiency (HRD) status. In contrast, OLA has shown significant clinical benefit particularly in patients with BRCA variant or HRD-positive tumors, as demonstrated in the SOLO2 [19,20] and Study 19 trials [21].

More recently, the KGOG3052 trial [22] directly compared OLA and BEV as maintenance therapy in patients with BRCA variant-positive PSROC and reported a significantly prolonged PFS in the OLA group. However, evidence directly comparing these two agents regardless of BRCA variant or HRD status remains limited, and optimal treatment selection in real-world clinical practice remains controversial. Furthermore, OLA is frequently associated with adverse events that necessitate dose interruption or reduction. Although dose reduction is commonly implemented to mitigate severe toxicities, evidence regarding the clinical impact of OLA dose reduction on treatment efficacy and survival outcomes remains insufficient.

In this study, we conducted a retrospective multicenter analysis to compare the efficacy and safety of three maintenance strategies—bevacizumab, standard-dose OLA, and dose-reduced OLA—in patients with PSROC, irrespective of BRCA variant and HRD status. The aim of this study was to clarify the comparative clinical outcomes of these maintenance therapies and to evaluate the validity of OLA dose reduction in real-world practice.

2. Materials and Methods

2.1. Patients

A total of 101 patients were included who were newly diagnosed with platinum-sensitive recurrent ovarian, fallopian tube, or primary peritoneal cancer between April 1, 2018, and November 30, 2025, at Iwate Medical University Hospital, Hachinohe Red Cross Hospital, or Iwate Prefectural Central Hospital. All patients received platinum-based chemotherapy at first recurrence, achieved an objective response, and subsequently underwent maintenance therapy.

Patients were classified into three groups according to the maintenance regimen: 34 patients received BEV, 31 received standard-dose OLA, and 36 received dose-reduced OLA.

2.2. Treatments

At first platinum-sensitive recurrence, patients received one of the following platinum-based chemotherapy regimens: paclitaxel plus carboplatin (TC; paclitaxel 175 mg/m² on Day 1 and carboplatin AUC 5 on Day 1, every 3 weeks), paclitaxel plus cisplatin (TP; paclitaxel 175 mg/m² on Day 1 and cisplatin 50 mg/m² on Day 1, every 3 weeks), docetaxel plus carboplatin (DC; docetaxel 60 mg/m² on Day 1 and carboplatin AUC 5 on Day 1, every 3 weeks), gemcitabine plus carboplatin (GC; gemcitabine 800 mg/m² on Days 1 and 8 and carboplatin AUC 5 on Day 1, every 3 weeks), pegylated liposomal doxorubicin plus carboplatin (PLDC; PLD 30 mg/m² on Day 1 and carboplatin AUC 5 on Day 1, every 4 weeks), irinotecan plus cisplatin (CPT-P; irinotecan 60 mg/m² on Days 1, 8, and 15 and cisplatin 60 mg/m² on Day 1, every 4 weeks), or paclitaxel plus nedaplatin (paclitaxel 175 mg/m² and nedaplatin 80 mg/m², every 4 weeks).

When BEV was combined with chemotherapy, it was administered at a dose of 15 mg/kg every 3 weeks according to the institutional bevacizumab administration criteria for ovarian cancer [23]. Bevacizumab maintenance therapy was continued using the same dosing schedule for up to 21 cycles. OLA was initiated at a total daily dose of 600 mg. In cases of treatment-related adverse events, dose reduction to 500 mg/day and subsequently to 400 mg/day was permitted in accordance with the SOLO2 trial protocol. OLA maintenance therapy was continued until documented disease progression.

For patients receiving maintenance therapy for the first time, treatment selection was guided by biomarker status: OLA was preferentially selected for patients with BRCA variants, bevacizumab for homologous recombination-proficient (HRP) tumors, and either agent was permitted for patients with homologous recombination deficiency (HRD) based on clinical considerations. In patients with a history of prior maintenance therapy, treatment selection was based on the ESGO–ESMO guidelines [24], with switching of the maintenance agent recommended. Re-treatment with bevacizumab was allowed in patients who had previously received more than 21 cycles of bevacizumab, and re-treatment with OLA was permitted in patients with BRCA variants who had received OLA for at least 12 months during prior maintenance therapy.

2.3. Endpoints/Variables

The primary endpoint of this study was progression-free survival (PFS). Secondary endpoints included overall survival (OS) and treatment-related adverse events. Tumor response and disease progression were assessed according to the Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1 [25]. Adverse events and treatment-related toxicities were evaluated and graded based on the Common Terminology Criteria for Adverse Events (CTCAE) version 5.0, Japanese Clinical Oncology Group (JCOG) edition [26].

2.4. Statistical Analysis

The data cutoff date was November 30, 2025. The platinum-free interval (PFI) was defined as the time from completion of the previous platinum-based chemotherapy to the diagnosis of recurrence

[27]. PFS and OS were calculated from the initiation of treatment for recurrent disease to the date of second progression, death from any cause, or last follow-up, whichever occurred first.

Survival curves for PFS and OS were generated using the Kaplan–Meier method and compared between groups using the log-rank test. Comparisons of patient characteristics and adverse events among groups were performed using the chi-squared test or the Kruskal-Wallis test, as appropriate.

To evaluate the association between clinical variables and survival outcomes, univariate Cox proportional hazards models were first applied to estimate hazard ratios (HRs) and 95% confidence intervals (CIs). Subsequently, multivariate Cox proportional hazards models were constructed by including clinically relevant variables considered to influence treatment selection or prognosis (stage, PFI, prior maintenance therapy, and tumor response), following us to adjust for potential confounding factors and identify independent prognostic variables.

All statistical analyses were conducted using EZR (Easy R), version 1.54 (Saitama Medical Center, Jichi Medical University), and a two-sided p-value of <0.05 was considered statistically significant [28]

3. Results

3.1. Patient Characteristics

Patient characteristics are summarized in Table 1. The median age was 62 years (range, 33–82) in the BEV group, 59 years (46–74) in the standard-dose OLA group, and 63 years (40–80) in the dose-reduced OLA group. Regarding disease stage-8/26, 8/23, and 4/32 patients were classified as I-II/III-IV, respectively. Serous/endometrioid–clear cell/mucinous/other histological subtypes were classified into proportions of 28/5/1, 27/3/1, and 34/2/0, respectively. The number of HRD-positive cases was found to be 5, 4, and 0, while there were 4, 5, and 2 BRCA mutation–positive cases in the BEV, standard-dose OLA, and dose-reduced OLA groups, respectively. Regarding prior maintenance therapy, BEV had been administered in 6, 15, and 15 patients; OLA in 12, 3, and 3 patients; and BEV plus OLA in 1, 0, and 0 patients, respectively. The median platinum-free interval (PFI) was 17.5 months (range, 6–140), 19 months (6–114), and 21 months (6–96), respectively. Chemotherapy regimens used before maintenance therapy included TC (+BEV) in 27, 22, and 28 patients; TP (+BEV) in 1, 3, and 0 patients; DC (+BEV) in 1 patient in each group; PLDC (+BEV) in 5 patients in each group; and other regimens in 0, 0, and 2 patients, respectively. Tumor response to chemotherapy immediately prior to maintenance therapy consisted of complete response (CR) in 7, 10, and 11 patients, and partial response (PR) in 27, 21, and 25 patients, respectively. No significant difference in response rate was observed among the groups ($p = 0.515$).

Table 1. Patient characteristics.

		BEV (N=34)	Standard-dose OLA (N=31)	Dose-reduced OLA (N=36)	P value
Age	Median, Range	62 (33-82)	59 (46-74)	63(40-80)	0.167**
Diagnosis	Ovarian	20	18	33	0.001*
	Fallopian Tube	5	7	2	
	Peritoneal	9	6	1	
Stage	I~II	8	8	4	0.256*
	III~IV	26	23	32	
Histology	Serous/Endometrioid	28	27	34	0.576*
	Clear/Mucinous	5	3	2	
	Other	1	1	0	
HRD status	Positive	5	4	0	0.119*
	Negative	4	4	2	
	Untested	25	23	34	
BRCA variant	Positive	4	5	2	0.041*

	Negative	12	4	5	
	Untested	18	22	29	
Prior maintenance therapy	BEV	6	15	15	0.014*
	OLA	12	3	3	
	BEV+OLA	1	0	0	
	No treatment	15	13	18	
PFI	Median, Range	17.5(6-140)	19(6-114)	21(6-96)	0.310**
Chemotherapy regimen before maintenance	TC(+BEV)	27	22	28	0.441*
	TP(+BEV)	1	3	0	
	DC(+BEV)	1	1	1	
	PLDC(+BEV)	5	5	5	
	Other		0	2	
Anti-tumor response	CR	7	10	11	0.515*
	PR	27	21	25	

BEV: bevacizumab, OLA: olaparib, HRD: homologous recombination deficiency, PFI: platinum-free interval, TC: paclitaxel + carboplatin, TP: paclitaxel + cisplatin, DC: docetaxel + carboplatin, PLDC: pegylated liposomal doxorubicin + carboplatin, CPT-P: irinotecan + cisplatin, PTX/NDP: paclitaxel + nedaplatin, CR: complete response, PR: partial response, * chi-squared test, **kruskal-wallis-test.

3.2. Survival Analysis

The median follow-up duration was 31 months (range=10–107) in the BEV group and 41 months (7–90) in the overall OLA group. Within the OLA cohort, the median follow-up was 32 months (7–88) in the standard-dose group and 41.5 months (22–90) in the dose-reduced group. Kaplan–Meier survival curves for PFS and OS are shown in Figure 1. The median PFS was 16 months (95% CI= 10–19) in the BEV group and 19 months (95% CI, 15–31) in the OLA group, demonstrating a significant improvement with OLA ($p = 0.002$).

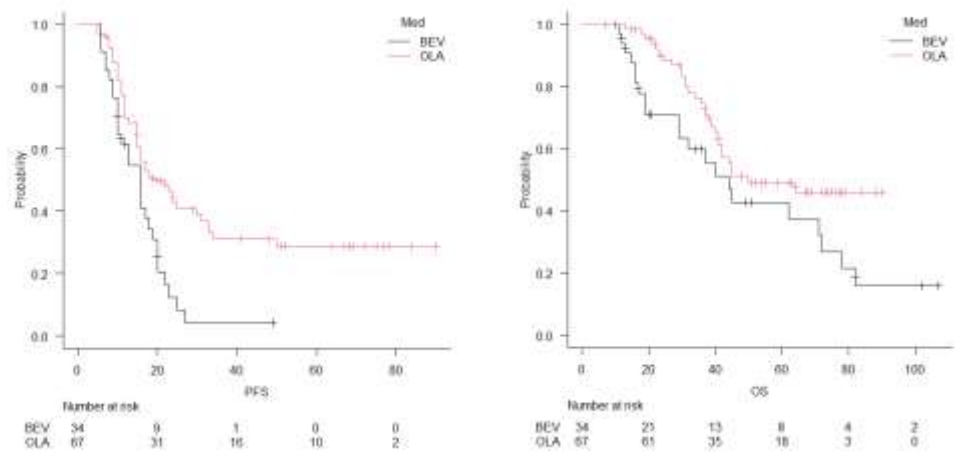


Figure 1. Kaplan–Meier curves for progression-free survival (PFS) and overall survival (OS) among the bevacizumab and olaparib treatment groups. The median PFS was 16 months (95% CI=10–19) in the BEV group and 19 months (95% CI=15–31) in the OLA group. The hazard ratio was 0.48 (95% CI=0.29-0.78; $p = 0.002$). The median OS was 44 months (95% CI=29–72) in the BEV group and 50 months (95% CI=41–not reached) in the OLA group. The hazard ratio was 0.56 (95% CI=0.32-0.99; $p = 0.042$).

Figure 2 presents PFS and OS stratified by OLA dose intensity. The median PFS was 16 months (95% CI=12–31) in the standard-dose OLA group and 24 months (95% CI=15–not reached) in the dose-reduced OLA group. Compared with the BEV group, the dose-reduced OLA group showed a significantly prolonged PFS ($p = 0.0007$). The median OS for the entire cohort was 44 months (95%

CI= 29–72) in the BEV group and 50 months (95% CI, 41–not reached) in the OLA group, with a significant survival benefit observed in the OLA group ($p = 0.042$). In the three-group comparison, the median OS was 45 months (95% CI=32–not reached) in the standard-dose OLA group and 64 months (95% CI=39–not reached) in the dose-reduced OLA group; however, no statistically significant difference was observed.

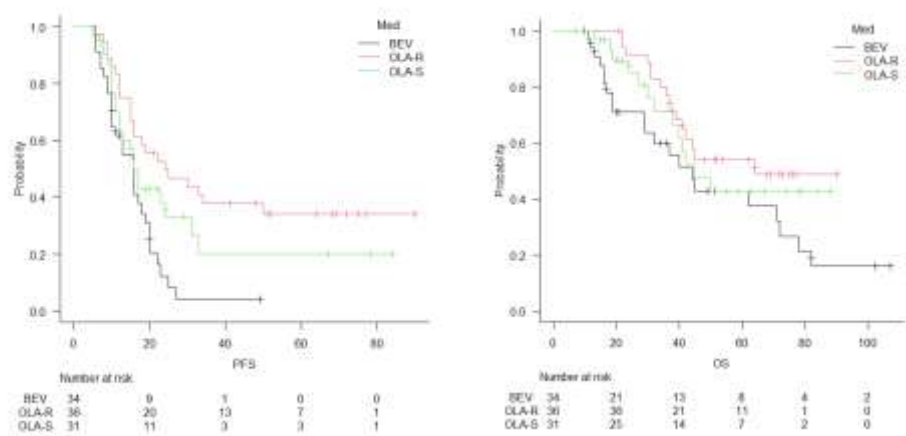


Figure 2. Kaplan–Meier curves for progression-free survival (PFS) and overall survival (OS) among the three treatment groups. Log-rank test was used for group comparisons. The median PFS was 16 months (95% CI=10–19) in the BEV group, 16 months (95% CI=12–31) in the standard-dose OLA (OLA-S) group and 24 months (95% CI=15–not-reached) in the dose-reduced OLA (OLA-R) group. Compared with the BEV group, the hazard ratio was 0.61 (95% CI=0.35–1.07; $p = 0.069$) in the OLA-S and 0.39 (95% CI=0.22–0.70; $p = 0.0007$) in the OLA-R. The median OS was 44 months (95% CI=29–72) in the BEV group, 45 months (95% CI=32–not reached) in the standard-dose OLA (OLA-S) group and 64 months (95% CI=39–NA) in the dose-reduced OLA (OLA-R) group. Compared with the BEV group, the hazard ratio was 0.63 (95% CI=0.31–1.25; $p = 0.184$) in the OLA-S and 0.52 (95% CI=0.27–1.00; $p = 0.060$) in the OLA-R.

We performed univariate and multivariate analyses of PFS and OS for the background factors listed in Table 1. In the univariate analysis, treatment group (BEV, standard-dose OLA, dose-reduced OLA) was significantly associated with PFS, with the OLA groups demonstrating longer PFS compared with the BEV group (HR=0.62, 95% CI=0.47–0.84, $p = 0.002$). A PFI ≥ 12 months was also significantly associated with favorable PFS (HR=0.46, 95% CI=0.27–0.78, $p = 0.003$). Age showed a marginal association with PFS (HR=1.03, $p = 0.028$), whereas stage, histology, prior maintenance therapy, and tumor response were not significantly associated with PFS. In the multivariate Cox analysis, treatment group remained an independent prognostic factor for PFS after adjustment for clinical covariates (HR=0.67, 95% CI=0.46–0.96, $p = 0.030$), confirming the PFS benefit of OLA. A PFI ≥ 12 months showed a trend toward improved PFS (HR=0.58, 95% CI=0.33–1.02, $p = 0.060$). Stage, prior maintenance therapy, and tumor response were not identified as independent prognostic factors (Table 3). Furthermore, In the univariate analysis, treatment group showed a borderline association with OS (HR=0.72, 95% CI=0.51–1.00, $p = 0.050$). A PFI ≥ 12 months was strongly associated with improved OS (HR=0.38, 95% CI=0.21–0.69, $p = 0.001$), whereas age, stage, histology, prior maintenance therapy, and tumor response were not significantly associated with OS. In the multivariate analysis, treatment group did not demonstrate an independent association with OS (HR=0.73, 95% CI=0.49–1.08, $p = 0.114$). A PFI ≥ 12 months remained the only independent prognostic factor for OS (HR=0.43, 95% CI=0.23–0.81, $p = 0.009$). No other variables showed significant associations with OS (Table 4).

Table 3. Univariate and multivariate analyses of PFS for background.

PFS-Cox proportional hazard model (Univariate analysis)				
	Category	HR	95%CI	P value
Treatment	BEV/OLA-S/OLA-R	0.62	0.47-0.84	0.002
Age		1.03	1.00-1.05	0.028
Stage	I • II / III • IV	1.39	0.76-2.53	0.288
Histology	HGSC • EM/CCC • M	1.34	0.67-2.70	0.409
PFI	(<12 / >12 months)	0.46	0.27-0.78	0.003
Prior maintenance	None/BEV/PARP-i/BEV+PARP-i	1.32	0.94-1.85	0.105
Anti-tumor response	CR/PR	1.56	0.97-2.48	0.063
PFS-Cox proportional hazard model (Multivariate analysis)				
	Category	HR	95%CI	P value
Treatment	BEV/OLA-S/OLA-R	0.67	0.46-0.96	0.030
Stage	I • II / III • IV	1.54	0.78-2.99	0.206
PFI	(<12 / >12 months)	0.58	0.33-1.02	0.060
Prior maintenance	None/BEV/PARP-i/BEV+PARP-i	1.06	0.75-1.51	0.732
Anti-tumor response	CR/PR	1.18	0.68-2.05	0.564

PFS; progression-free survival, OS; overall survival, PARP; poly ADP-ribose polymerase, PFI; platinum-free interval, BEV; bevacizumab, OLA-S: standard-dose OLA, OLA-R: dose-reduced OLA, HGSC; high grade serous carcinoma, EM; endometrioid, CCC; clear cell carcinoma, M; mucinous, CR: complete response, PR: partial response, HR; hazard ratio, 95%CI; 95% confidence interval.

Table 4. Univariate and multivariate analyses of OS for background.

OS-Cox proportional hazard model (Univariate analysis)				
	Category	HR	95%CI	P value
Treatment	BEV/OLA-S/OLA-R	0.72	0.51-1.00	0.050
Age		1.02	0.99-1.05	0.191
Stage	I • II / III • IV	1.40	0.68-2.89	0.363
Histology	HGSC • EM/CCC • M	1.35	0.57-3.19	0.499
PFI	(<12 / >12 months)	0.38	0.21-0.69	0.001
Prior maintenance	None/BEV/PARPi/BEV+PARPi	1.45	0.95-2.21	0.085
Anti-tumor response	CR/PR	1.20	0.68-2.11	0.531
OS-Cox proportional hazard model (Multivariate analysis)				
	Category	HR	95%CI	P value
Treatment	BEV/OLA-S/OLA-R	0.73	0.49-1.08	0.114
Age		1.12	0.50-2.51	0.792
Stage	I • II / III • IV	0.43	0.23-0.81	0.009
Histology	HGSC • EM/CCC • M	1.34	0.88-2.04	0.174
PFI	(<12 / >12 months)	0.87	0.46-1.64	0.666
Prior maintenance	None/BEV/PARPi/BEV+PARPi	0.73	0.49-1.08	0.114

PFS; progression-free survival, OS; overall survival, PARP; poly ADP-ribose polymerase, PFI; platinum-free interval, BEV; bevacizumab, OLA-S: standard-dose OLA, OLA-R: dose-reduced OLA, HGSC; high grade serous carcinoma, EM; endometrioid, CCC; clear cell carcinoma, M; mucinous, CR: complete response, PR: partial response, HR; hazard ratio, 95%CI; 95% confidence interval.

3.3. Adverse Events

Major adverse events are summarized in Table 2. Grade ≥3 hematologic toxicities in the BEV, standard-dose OLA, and dose-reduced OLA groups included leukopenia in 8, 4, and 8 patients, neutropenia in 10, 9, and 18 patients, anemia in 4, 3, and 18 patients, and thrombocytopenia in 4, 1, and 2 patients, respectively. A statistically significant difference was observed only for anemia, which

was more frequent in the dose-reduced OLA group ($p=0.010$). Febrile neutropenia occurred in two patients in the BEV group only.

Grade ≥ 3 non-hematologic toxicities included nausea in 2, 2, and 5 patients, peripheral neuropathy in 4, 2, and 1 patients and fatigue in 2 patients in each group. Diarrhea was observed in one patient in the standard-dose OLA group, and anorexia in one patient in the BEV group. Hypertension occurred in 8 patients in the BEV group and 3 patients in the standard-dose OLA group but was not observed in the dose-reduced OLA group, showing a significant intergroup difference ($p = 0.005$). Proteinuria was observed in 4 patients in the BEV group and 2 patients in the standard-dose OLA group. Carboplatin allergy was observed only in the dose-reduced OLA group (2 patients).

Table 2. a. Adverse events (hematologic toxicities) .

	BEV(N=34)		OLA-S(N=31)		OLA-R(N=36)		P value*
	G3	G4	G3	G4	G3	G4	
Leucopenia	7	1	4	0	8	0	0.476
Neutropenia	6	4	8	1	12	6	0.126
Anemia	4	0	3	0	9	4	0.010
Thrombocytopenia	1	3	1	0	2	0	0.315
Febrile neutropenia	1	1	0	0	0	0	0.123

BEV: bevacizumab, OLA: olaparib, OLA-S: standard-dose OLA, OLA-R: dose-reduced OLA, G: grade, * chi-squared test.

Table 2. b. Adverse events (non-hematologic toxicities).

	BEV(N=34)		OLA-S(N=31)		OLA-R(N=36)		P value*
	G3	G4	G3	G4	G3	G4	
Nausea	2	0	2	0	5	0	0.434
Neuropathy	4	0	2	0	1	0	0.307
Diarrhea	0	0	1	0	0	0	0.320
Fatigue	2	0	2	0	2	0	0.983
Appetite Loss	1	0	0	0	0	0	0.353
Hypertension	8	0	3	0	0	0	0.005
Proteinuria	4	0	1	1	0	0	0.101
CBDCA hypersensitivity	0	0	2	0	0	0	0.100

BEV: bevacizumab, CBDCA: carboplatin, OLA-S: standard-dose OLA, OLA-R: dose-reduced OLA, * chi-squared test.

4. Discussion

PARP inhibitors have demonstrated significant efficacy as maintenance therapy for platinum-sensitive recurrent ovarian cancer. In the SOLO2 trial, OLA significantly prolonged median progression-free survival (PFS) to 19.1 months ($p < 0.001$, HR = 0.30), while the Study 19 trial reported median PFS of 8.4 months ($p < 0.001$, HR = 0.35), establishing the clinical benefit of PARP inhibitors in large randomized trials [18–20]. In contrast, the anti-angiogenic agent bevacizumab (BEV) has also shown PFS benefits, with median PFS of 12.4 months in the OCEANS trial ($p < 0.001$, HR = 0.484), 13.8 months in the GOG213 trial ($p < 0.001$, HR = 0.628), and 11.8 months in the MITO16B-MaNGO trial ($p < 0.001$, HR = 0.51). Moreover, the GOG213 trial demonstrated a significant improvement in overall survival (OS), with median OS of 42.2 months ($p = 0.0447$, HR = 0.823) [16–18]. The KGOG3052 trial directly compared OLA and BEV as maintenance therapy in patients with BRCA-mutated platinum-sensitive recurrent ovarian cancer and demonstrated a significantly longer PFS in the OLA group (23.8 months vs. 17.4 months, $p = 0.004$) [22]. However, reports directly comparing these two agents regardless of BRCA mutation or homologous recombination deficiency (HRD) status remain limited.

Furthermore, clear criteria for selecting between these maintenance therapies have not been established, leaving treatment decisions in real-world clinical practice challenging. In addition, OLA frequently requires treatment interruption or dose reduction due to adverse events. Although dose reduction is commonly implemented to avoid severe toxicity, evidence regarding its impact on treatment efficacy and prognosis remains insufficient. In Japan, BRCA testing was approved for insurance coverage in 2018, followed by HRD testing in 2021; however, the high cost of these tests often limits patient consent in routine clinical practice. Although Enomoto et al. analyzed 634 Japanese patients, their study was conducted within a clinical trial framework, and therefore testing costs were not borne by patients [29]. Consequently, establishing effective treatment strategies for patients without biomarker testing is an important unmet clinical need.

Against this background, we conducted a multicenter retrospective study comparing three maintenance strategies—BEV, standard-dose OLA, and dose-reduced OLA—independent of BRCA mutation or HRD status, including patients with negative or untested biomarkers to evaluate both efficacy and safety.

In this study, OLA demonstrated superior PFS (19 months vs. 16 months, $p = 0.002$, HR = 0.478) and OS (50 months vs. 44 months, $p = 0.042$, HR = 0.563) compared with BEV. Furthermore, the median PFS was 16 months (95% CI=12–31) in the standard-dose OLA group and 24 months (95% CI=15–not reached) in the dose-reduced OLA group. The results demonstrated that dose-reduced OLA was associated with significantly longer PFS compared with BEV and full-dose OLA, and this benefit remained significant after adjustment for clinically relevant prognostic factors in the multivariate Cox analysis.

Although the median OS was 45 months (95% CI=32–not reached) in the standard-dose OLA group and 64 months (95% CI=39–not reached) in the dose-reduced OLA group, in the three-group comparison, no statistically significant difference was observed. In contrast to PFS, OS did not differ significantly among the three treatment groups. This may reflect the influence of subsequent therapies, the relatively favorable prognosis of patients with platinum-sensitive disease, and the limited follow-up duration. Importantly, a platinum-free interval (PFI) ≥ 12 months emerged as the only independent prognostic factor for OS, underscoring the strong prognostic significance of platinum sensitivity in recurrent ovarian cancer. This finding is consistent with previous reports demonstrating that PFI is one of the most robust predictors of long-term outcomes in this population.

Regarding safety, anemia occurred significantly more frequently in the dose-reduced OLA group ($p = 0.010$), whereas hypertension was significantly more common in the BEV group ($p = 0.005$). Importantly, no novel safety signals were identified in this study. In the SOLO2 trial, approximately 30% of patients required dose reduction due to adverse events. Francis K.E. et al. reanalyzed the SOLO2 trial according to relative dose intensity (RDI) and reported no significant differences in PFS or OS between groups [30]. Notably, patients with an RDI $< 90\%$ showed a tendency toward prolonged PFS (34.4 months, $p = 0.37$, HR = 1.12) and OS (54.1 months, $p = 0.84$, HR = 0.92), suggesting that OLA efficacy may be maintained despite dose reduction.

Taken together, these findings suggest that early dose adjustment of OLA in response to adverse events may minimize treatment discontinuation, improve treatment continuity, and thereby contribute to prolonged PFS in real-world clinical practice.

In this study, OLA maintenance therapy was effective regardless of BRCA mutation or HRD status. Nakanishi et al. reported that OLA provided superior PFS compared with bevacizumab (27 months vs. 9 months, $p = 0.001$) in 51 Japanese patients with platinum-sensitive recurrent ovarian cancer, irrespective of HRD status [31]. Furthermore, the ENGOT-OV16/NOVA trial [32], which evaluated niraparib—another PARP inhibitor—demonstrated significant PFS prolongation in both BRCA-mutated and non-BRCA-mutated cohorts. These results indicate that PARP inhibitors may represent an effective maintenance strategy independent of biomarker status in platinum-sensitive recurrent ovarian cancer.

Several limitations of this study should be acknowledged. First, this was a small, retrospective multicenter study with a limited sample size and follow-up duration, which may have reduced

statistical power. Second, although general principles guided maintenance therapy selection, the final treatment decision was left to the treating physician, and selection bias cannot be fully excluded. Notably, the distribution of primary tumor sites differed significantly among groups, with a higher proportion of ovarian cancer in the dose-reduced OLA group and more peritoneal cancer in the BEV group. This imbalance may have influenced treatment selection and outcomes. Third, because BRCA mutation and HRD status were not evaluated in all patients, the influence of biomarkers on treatment outcomes could not be fully adjusted. Given the high proportion of patients without HRD testing, treatment decisions were primarily based on clinical factors rather than molecular profiles, reflecting real-world practice limitations.

Fourth, although propensity score-based methods such as inverse probability of treatment weighting (IPTW) or propensity score matching (PSM) are commonly used to reduce selection bias in retrospective studies, these approaches were not applied because the sample size was limited and baseline characteristics were unevenly distributed across the three treatment groups, making stable weighting or adequate matching difficult. Therefore, multivariate Cox regression was used as the primary adjustment method.

5. Conclusions

In conclusion, this retrospective multicenter study compared BEV, standard-dose OLA, and dose-reduced OLA as maintenance therapy for platinum-sensitive recurrent ovarian cancer. The dose-reduced OLA group demonstrated a significant improvement in PFS and a favorable trend toward prolonged OS. This benefit remained significant after adjustment for clinical covariates in the multivariate Cox analysis. Dose reduction of OLA may enhance treatment continuity while avoiding severe adverse events, representing a clinically meaningful strategy in real-world practice. These findings support the feasibility of biomarker-independent treatment selection and provide evidence for the clinical validity of OLA dose reduction as a maintenance therapy option. The dose-reduced OLA group demonstrated a significant improvement in PFS and a favorable trend toward prolonged

OS. Dose reduction of OLA may enhance treatment continuity while avoiding severe adverse events, representing a clinically meaningful strategy in real-world practice. These findings support the feasibility of biomarker-independent treatment selection and provide evidence for the clinical validity of OLA dose reduction as a maintenance therapy option.

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