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ORIGINAL RESEARCH

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Salvage chemotherapy and maintenance therapy with poly adenosine diphosphate-ribose polymerase inhibitors for bevacizumab-resistant relapse of epithelial ovarian cancer

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Abstract

Adjuvant chemotherapy combined with bevacizumab, an angiogenesis inhibitor, can improve the survival of advanced epithelial ovarian cancer (EOC), but relapse during bevacizumab maintenance therapy may occur. Despite poly adenosine ribose-polymerase (PARP) inhibitors were shown to achieve remission in the relapsed patients upon salvage chemotherapy and long-term maintenance, there is little evidence on their efficacy or criteria for selecting bevacizumab-resistant recurrent EOC patients who would benefit from PARP inhibitors. In this single-center, retrospective, case-series study, we evaluated the efficacy, safety and selection criteria for salvage chemotherapy followed by PARP inhibitors in bevacizumab-resistant EOC patients who recurred during bevacizumab maintenance. The primary endpoint was post-progression survival (PPS), and the secondary endpoints were progression-free survival (PFS) and safety. In all, the data of 49 EOC patients, most of whom were graded as stage III (91.8%) with high-grade serous histology (81.6%), were assessed. They were classified into three groups based on platinum-free interval (PFI) and response to salvage chemotherapy: platinum-based chemotherapy followed by PARP inhibitors, platinum-based chemotherapy followed by non-PARP inhibitors, and non-platinum-based chemotherapy. Survival analysis showed the median PFS and median PPS for the platinum-based chemotherapy followed by PARP inhibitors group were 326 and 771 days, which were significantly longer than the other groups. The highly platinum-sensitive relapse (PSR) group (PFI $>$12 months) achieved prolonged PPS, while there was no relationship between the clinical status on salvage chemotherapy and response to PARP inhibitors. Adverse events during PARP inhibitor led to withdrawal and dose reduction in $>$40% of patients; however, no patients discontinued the drugs. Altogether, the study results showed that maintenance therapy using PARP inhibitor was effective and feasible for patients selected based on platinum sensitivity from bevacizumab-resistant relapsed EOC. PFI after adjuvant chemotherapy could predict bevacizumab-resistant EOC patients' response to PARP inhibitors, which might be effective despite therapeutically insufficient salvage chemotherapy.

Keywords

Bevacizumab; Poly adenosine-diphosphate ribose polymerase inhibitor; Niraparib; Olaparib; Ovarian cancer; Platinum sensitivity

1. Introduction

Adjuvant chemotherapy after surgical cytoreduction is an effective treatment that improves the survival of patients with advanced epithelial ovarian cancer (EOC) [1]. Bevacizumab, an angiogenesis inhibitor, has been used in combination with adjuvant chemotherapy or as subsequent maintenance therapy, especially in advanced EOC [2, 3], to control large-volume ascites and pleural effusion [3, 4]. In addition, bevacizumab maintenance was shown to effectively prolong their progression-free survival (PFS). However, relapse during bevacizumab maintenance is quite common. The GOG-0218 study examined the impact of combination and maintenance therapy with bevacizumab on the PFS of patients with stage III/IV EOC. The investigators observed that bevacizumab could prolong the patients' PFS by approximately 3–4 months despite the final overall survival (OS) did not significantly differ between patients with and without bevacizumab [3]. Therefore, treatment strategies for relapsed patients during bevacizumab maintenance have become one of the main

issues in managing advanced EOC.

The realistic goal and treatment for relapsed cases are to achieve remission by salvage chemotherapy and long-term maintenance therapy. For patients with platinum-sensitive relapsed EOC who were partially or highly responsive to platinum-based chemotherapy, the U.S. Food and Drug Administration approved the use of poly adenosine ribose-polymerase (PARP) inhibitors such as niraparib and olaparib for maintenance therapy [5, 6]. In addition, PARP inhibitor re-challenge has been investigated as an attempt to prolong the total PFS while maintaining treatment safety [7, 8].

PARP inhibitors were shown to provide significant PFS prolongation to responders. Despite case selection by platinum sensitivity or genomic status is required, there is currently little evidence on the efficacy of this approach or criteria for the proper selection of bevacizumab-resistant recurrent EOC patients who would potentially respond to PARP inhibitors. The Nova study reported that prior bevacizumab therapy did not affect the PFS of patients who were later treated with niraparib [9]. However, no analysis of PARP inhibitor use for bevacizumab-resistant patients has yet been conducted. For olaparib use in patients with recurrent EOC, both the Study 19 and SOLO-2 clinical trials did not adequately consider the impact of prior bevacizumab use [10, 11]. Based on these, we raised the following questions: (1) Is maintenance therapy with PARP inhibitors really effective and feasible for bevacizumab-resistant relapsed EOC patients selected based on platinum sensitivity? (2) Are there other indicators that could predict response to PARP inhibitors for bevacizumab-resistant relapsed EOC patients?

Herein, we evaluated the efficacy and safety of PARP inhibitors in the maintenance therapy of bevacizumab-resistant EOC recurrent patients based on their platinum sensitivity and treatment efficacy after salvage chemotherapy.

2. Materials and methods

2.1 Patient population

In this single-center, observational, case-series study, we retrospectively analyzed the medical records of 131 patients with advanced EOC treated with bevacizumab and platinum-based chemotherapy between June 2015 and 2021. These patients received primary induction therapy consisting of systemic chemotherapy, in some instances, in addition to neoadjuvant chemotherapy (NAC) and primary cytoreductive surgery. NAC was administered to minimize residual tumor volume for achieving R0 resection.

All patients received adjuvant chemotherapy: carboplatin Area Under the Curve 5 (Calvert's formula) and paclitaxel (180 mg/m^2) every 3 weeks (6 courses total, including NAC), followed by bevacizumab maintenance: bevacizumab (15 mg/kg) every 3 weeks (up to 21 courses total, including NAC).

The study consisted of 49 patients whose cancer had recurred despite salvage chemotherapy and bevacizumab maintenance therapy. Seventy-five patients whose cancer did not recur and seven patients who did not undergo salvage chemotherapy for cancer recurrence were excluded. The salvage chemotherapy regimen was selected based on the algorithm in Fig. 1, and in some instances, patients were subsequently switched to PARP inhibitor maintenance. This algorithm had two selection criteria, namely, platinum sensitivity and treatment efficacy after salvage chemotherapy, and was based on the following hypotheses: (1) Platinum sensitivity as a predictor of PARP inhibitor efficacy might be applicable in bevacizumab-resistant recurrent EOC [9, 11], and (2) A greater tumor reduction effect with salvage chemotherapy was more likely the improve treatment outcomes [12].

Based on this algorithm, we selected patients with bevacizumab-resistant recurrent EOC who might respond adequately treated with PARP inhibitor maintenance therapy, which was continued until disease progression.

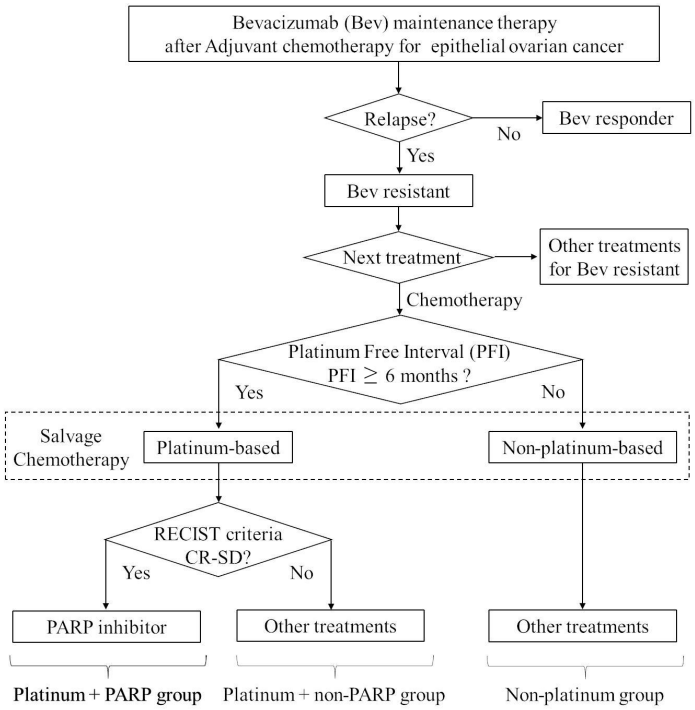

FIGURE 1. Treatment algorithm for PARP inhibitor selection. One hundred and thirty-one patients with epithelial ovarian cancer (EOC) who underwent adjuvant chemotherapy with platinum-based chemotherapy followed by maintenance therapy with bevacizumab were included. Of the 56 patients who relapsed, 49 were eligible for this study, as seven patients treated with non-chemotherapy modalities were excluded. If the response to platinum-based chemotherapy was CR-SD (Complete Response-Stable Disease; identified using the response evaluation criteria in solid tumors; RECIST criteria 1.1), the patients were switched to maintenance with a poly adenosine diphosphate-ribose (PARP) inhibitor. Twenty-nine of the 49 patients were indicated for PARP inhibitor maintenance therapy after salvage chemotherapy.

2.2 Evaluation endpoints

The primary evaluation endpoint was post-progression survival (PPS). The secondary endpoints were PFS and adverse events. PPS and PFS were defined as the time from the diag-

nosis of recurrence to the confirmation of disease progression or death, respectively. As a variable for survival comparison, platinum-free survival (PFI), defined as the time from the last use of platinum-based chemotherapy to the diagnosis of recurrence, was used as an indicator of platinum sensitivity.

Genomic profiling data, such as homologous recombination deficiency (HRD) status, germline breast cancer gene (*BRCA)* testing, and microsatellite instability testing, were also recorded for patients if performed. Disease staging was determined based on pre-treatment imaging examinations. The histologic diagnosis was determined by debulking surgery or biopsy of metastases (for example, axillary lymph node biopsy in inoperable patients). Treatment response was determined using the Response Evaluation Criteria in Solid Tumors (RECIST criteria 1.1), and adverse events were graded according to the common terminology criteria for adverse events 4.0.

2.3 Statistical analysis

Comparisons between groups were performed using chi-square, Wilcoxon rank sum, and Kruskal-Wallis tests. p value < 0.05 was considered statistically significant. Kaplan-Meier methods were used to generate survival curves. All statistical analyses were performed using the R software (version 3.5.2, R Core Team, Vienna, Austria).

3. Results

3.1 Baseline patient characteristics

Forty-nine EOC patients who relapsed during bevacizumab maintenance therapy were enrolled and classified into three groups: Platinum + PARP (N = 29), Platinum + non-PARP (N = 9), and non-Platinum (N = 11). The characteristics of all three groups are shown in Table 1. Most patients were classified as FIGO (The International Federation of Gynecology and Obstetrics) stage III (91.8%) and had high-grade serous histology (81.6%).

Although *BRCA* and HRD genomic data were unavailable in more than 80% of the patients, it was evenly distributed among the three groups. We found no significant differences in the completion of primary debulking surgery or rate of preoperative neoadjuvant chemotherapy. All relapses occurred during bevacizumab maintenance or within 3 months after its completion, although approximately 10% of the patients were unable to continue therapy due to adverse events. Following the Fig. 1 algorithm, 29 of 49 patients were selected for PARP inhibitor maintenance therapy after salvage chemotherapy**.**

3.2 Survival analysis

Survival analysis showed that the median PFS and median PPS for the platinum-based chemotherapy followed by PARP inhibitors group were 326 and 771 days, respectively, which were significantly longer than the other treatment groups.

Kaplan-Meier curves also show significant survival benefits in the platinum-based chemotherapy followed by PARP inhibitor group (Fig. 2) (PPS, OS, and PFS $p < 0.001$). The survival interval for each of these PARP inhibitors, olaparib or niraparib, is shown in Table 2.

Subgroup analyses were performed to assess the algorithm for selecting PARP inhibitors for maintenance therapy. First, the maintenance group was classified according to PFI. A PFI from 6 to 12 months was defined as partially platinum-sensitive relapse (PSR), while PFI >12 months was defined as highly PSR. Survival analysis showed no significant difference in either PPS or PFS for patients who underwent platinum-based chemotherapy followed by PARP inhibitors based on platinum sensitivity (Fig. 3).

Next, we compared the survival of the platinum-based chemotherapy followed by PARP inhibitor group with the salvage chemotherapy according to treatment response. The results showed that the treatment response of the patients to salvage chemotherapy was 76.7% for partial response (PR), 13.3% for complete response (CR), and 10% for stable disease. The PR group was subdivided as follows: high-PR, defined as $\geq$70% reduction of the largest recurrent lesions; poor-PR, defined as $<$40% reduction, and; others as moderate-PR. The treatment responses in the platinum-based chemotherapy followed by PARP inhibitor group were classified into the following three groups: high-PR or higher, moderate PR, and poor PR or lower. The survival analysis showed no significant differences in PPS and PFS for treatment responses to salvage chemotherapy (Fig. 4).

3.3 Platinum sensitivity and treatment response to salvage chemotherapy

The treatment response to salvage chemotherapy was compared between patients with high and partial platinum sensitivity. The results showed that patients' response in the CR-high PR group was significant in the highly platinum-sensitive group (Pearson's Chi-squared test $p = 0.01$).

3.4 Adverse events of PARP inhibitors

PARP inhibitors olaparib and niraparib were used in 82.8% and 17.2% of the patients. The duration of administration and adverse events for each drug are shown in Table 3. Adverse events during the PARP inhibitor maintenance phase included withdrawal and dose reduction in more than 40% of patients. However, no patients discontinued the drug due to adverse events.

4. Discussion

The study evaluated the efficacy and safety of salvage chemotherapy followed by PARP inhibitors in bevacizumab-resistant EOC recurrent patients and examined potential selection criteria for patients who would benefit from this treatment.

Relapse while on bevacizumab maintenance is not clinically uncommon. Comparatively, our bevacizumab-resistant cohort demonstrated a poorer prognosis, even when treated by PARP inhibitors: the median PFS of patients with *BRCA* gene mutations or HRD was 15.3 months in our study, compared to 19.2 months in the SOLO-2 trial [11]. To our knowledge, no previous studies have examined the criteria for platinum-based chemotherapy followed by maintenance therapy with PARP inhibitors for bevacizumab-resistant relapsed EOC.

TABLE 1. Baseline patient characteristics.

Variables	Platinum + PARP (N = 29)	Platinum + non-PARP (N = 9)	Non-Platinum (N = 11)	*p* value
Median age (range)	59.4 (47.0–69.2)	56.2 (54.1–60.6)	58.7 (49.5–66.0)	0.91
Histology (N (%))				
HGSC	25 (86.2%)	6 (66.7%)	9 (81.8%)	0.42
Others	4 (13.8%)	3 (33.3%)	2 (18.2%)	
FIGO stage (N (%))				
IIB	0 (0.0%)	1 (11.1%)	0 (0.0%)	
IIIA	2 (6.9%)	0 (0.0%)	1 (9.1%)	
IIIB	4 (13.8%)	2 (22.2%)	1 (9.1%)	0.90
IIIC	21 (72.4%)	6 (66.7%)	8 (72.7%)	
IV	2 (6.9%)	0 (0.0%)	1 (9.1%)	
Genomic status (N)				
BRCA m+/wt/NA	2/4/23	0/1/8	0/3/8	0.62
HRD/HRP/NA	3/1/25	1/1/7	0/1/10	0.71
Neoadjuvant chemotherapy (N (%))	16 (55.2%)	6 (66.7%)	6 (54.5%)	0.81
Completion of debulking surgery (N (%))				
Optimal	19 (65.5%)	5 (55.6%)	7 (63.6%)	0.77
Suboptimal	7 (24.1%)	3 (33.3%)	4 (36.4%)	

Three groups of patients are described. They were classified according to the use of non-platinum-based chemotherapy, use of platinum-based chemotherapy as salvage chemotherapy, and use of PARP inhibitors following platinum-based chemotherapy.
HGSC, high-grade serous carcinoma; FIGO, International Federation of Gynecology and Obstetrics; BRCA m+, mutation+; wt, wild type; NA, Not Available; HRD, Homologous Recombination Deficiency; HRP, Homologous Recombination Proficient; Optimal, Defined as ≤1 cm residual tumor; Suboptimal, Defined as >1 cm residual tumor; PARP, poly adenosine ribose-polymerase.

TABLE 2. Survival interval for the two PARP inhibitors.

Survival type	Olaparib (N = 24)	Niraparib (N = 5)
PFS (days)	316 (228–654) (*BRCA* m+/HRD 459 (377–562))	333 (136–368)
PPS (days)	839 (605–1150) (*BRCA* m+/HRD 588 (576–684))	409 (349–466)

Survival is expressed using PFS and PPS, and for the PARP inhibitors group, survival based on the type of drug used is shown. For patients in the olaparib group with known HRD status, the median PFS and PPS were 459 and 588 days, respectively.
Data are presented as medians and interquartile range. PFS, progression-free survival; PPS, post-progression survival. HRD: homologous recombination deficiency. BRCA m+: breast cancer gene mutation positive.

We selected patients with bevacizumab-resistant recurrent EOC based on their platinum sensitivity and treatment response after salvage chemotherapy and classified them into three groups. Survival analysis showed that patients who underwent salvage chemotherapy with platinum-based chemotherapy and then switched to PARP inhibitor maintenance had a significant improvement in survival. Drug withdrawal or dose reduction was required for patients who experienced adverse events during the PARP inhibitor treatment period; however, no patients discontinued the drugs due to adverse events. PARP inhibitor maintenance was continued until disease progression, and survival was prolonged in proportion to the duration of maintenance therapy. Known adverse events of PARP inhibitors include bone marrow suppression, anemia, nausea and renal dysfunction. We also observed that the frequency of adverse events in this present study did not exceed those of previously reported studies [9, 11].

The PFI length following adjuvant chemotherapy could predict response to PARP inhibitor in bevacizumab-resistant relapsed EOC. A significant trend toward improved survival was observed in patients with PFI >12 months compared to those with PFI ≤12 months. As indicated by the time between platinum-based chemotherapy and relapse, platinum sensitiv-

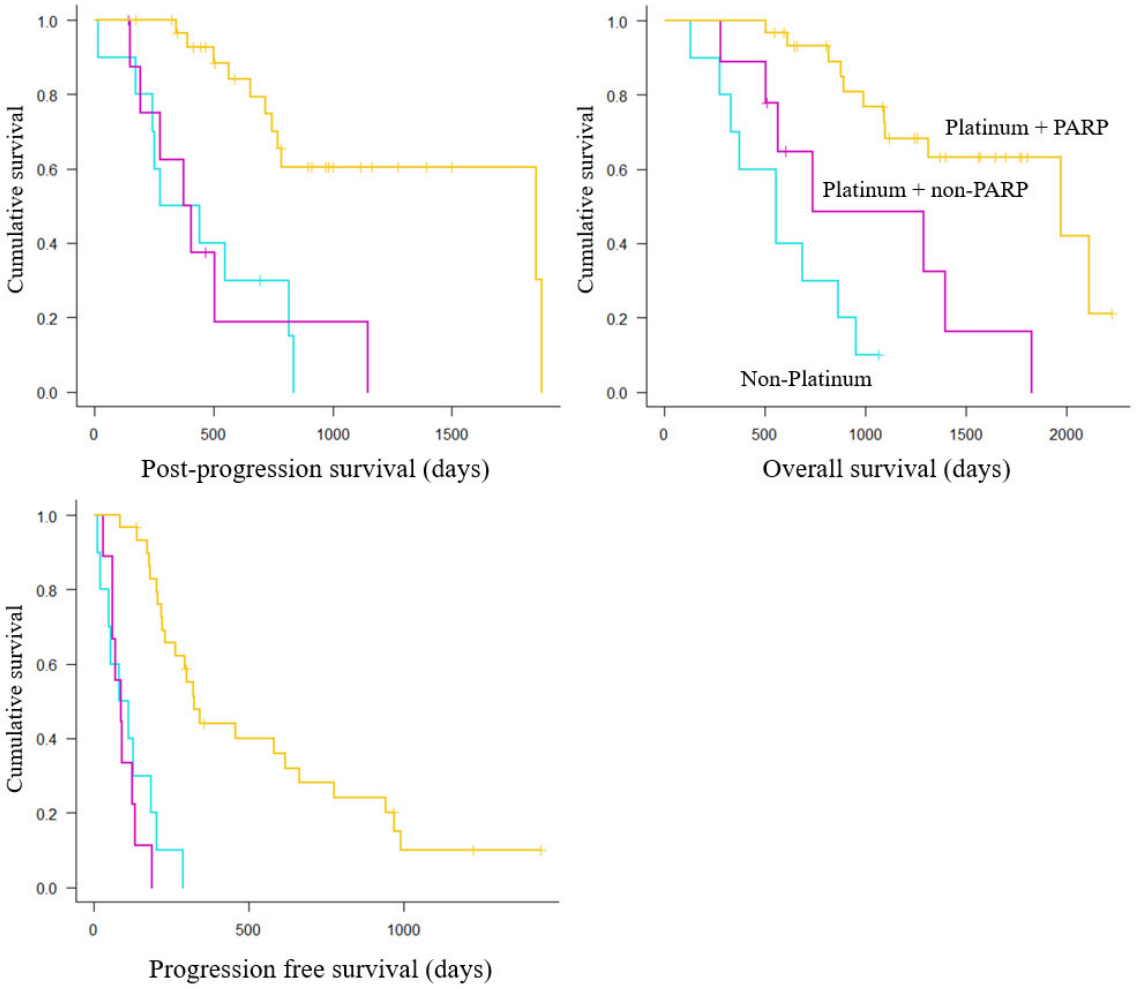

FIGURE 2. Kaplan-Meier curves for the platinum-based chemotherapy, platinum-based chemotherapy followed by PARP inhibitors, and non-platinum-based chemotherapy groups of patients with bevacizumab-resistant recurrence of epithelial ovarian cancer. Post-progression survival (PPS), Overall survival (OS), and progression-free survival (PFS) were compared. The platinum-based chemotherapy followed by PARP inhibitors group showed significantly longer PFS, OS, and PPS ($p < 0.001$). PARP, poly adenosine ribose-polymerase.

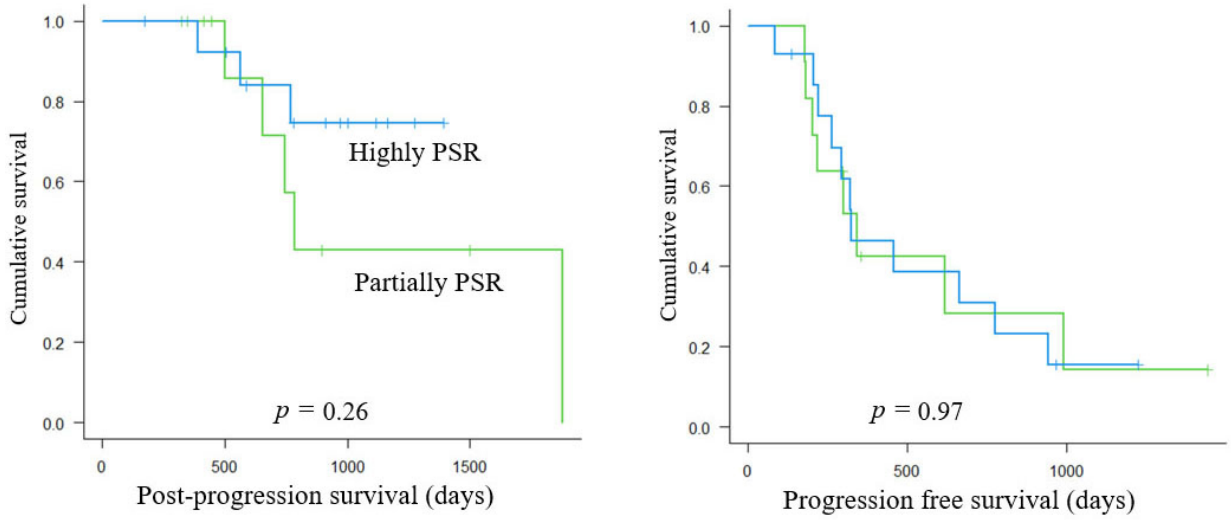

FIGURE 3. Kaplan-Meier curves for patients with platinum-based chemotherapy followed by PARP inhibitors, according to platinum sensitivity. The platinum-based chemotherapy followed by PARP inhibitor maintenance group, including platinum-sensitive relapse (PSR), was classified by platinum-free interval (PFI) and compared for survival. PFI from 6 to 12 months, partially PSR; PFI >12 months, highly PSR.

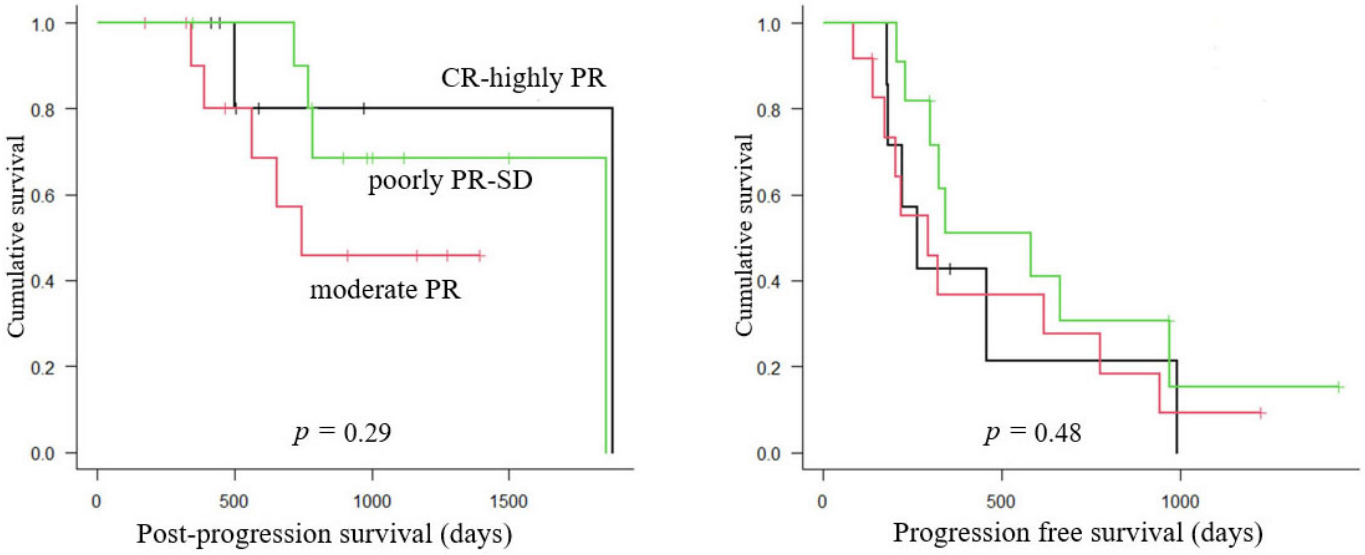

FIGURE 4. Kaplan-Meier curves for patients with platinum-based chemotherapy followed by PARP inhibitors, according to treatment response to salvage chemotherapy. Survival was compared for RECIST classification of treatment response to salvage chemotherapy after further subdividing the partial response (PR) group as follows: high-PR, ≥70% reduction of the largest recurrent lesions; poor-PR, <40% reduction; and moderate-PR for all others.
CR: Complete Response. SD: Stable Disease.

TABLE 3. Adverse events during PARP inhibitor maintenance therapy.

Features	Olaparib (N = 24)	Niraparib (N = 5)
Treatment interval (days)	258 (150–529)	175 (105–245)
Adverse events CTCAE any grade (N (%))		
	tiredness 1 (4%)	
	nausea 1 (4%)	anemia 1 (20%)
	anemia 2 (8%)	hypertension 1 (20%)
CTCAE grade ≥3 (N (%))		
	anemia 6 (25%)	neutropenia 2 (40%)
	thrombocytopenia 4 (17%)	thrombocytopenia 2 (40%)
Required dose reduction or withdrawal (N (%))		
	10 (42%)	4 (80%)
Required termination of drug (N (%))		
Due to adverse events	0 (0%)	0 (0%)
Due to disease progression	19 (79%)	5 (100%)

CTCAE, Common Terminology Criteria for Adverse Events.

ity is a known predictor of response to salvage chemotherapy and PARP inhibitor maintenance therapy [13, 14]. Patients with longer PFI and preserved platinum sensitivity are expected to respond to salvage chemotherapy [12, 13]. This characteristic observed in primary EOC is lost at each relapse, with the duration of response to relapse therapy rarely exceeding the PFS of primary chemotherapy [15] and decreasing response rate as the number of chemotherapy lines increases [16–19]. The classic behavior of relapsed ovarian cancer is that the longer the duration of remission after adjuvant chemotherapy, the better the response to salvage chemotherapy [20]. Therefore, PFI is also considered a predictor of treatment response for PARP inhibitor maintenance [14]. This platinum sensitivity/resistance mechanism was described by a previous study [12]. After platinum-based chemotherapy, platinum-resistant/low-sensitive tumor clones are selected. Therefore, the time to recurrence and the platinum sensitivity at recurrence depend on the amount of residual tumor and the growth rate of resistant clones [12], suggesting that prolonged PFI by adjuvant chemotherapy preserves the effect of platinum chemotherapy in the event of recurrence, and PARP inhibitor maintenance therapy is effective for the residual tumor after platinum chemotherapy [21].

In this present study, we found that PARP inhibitors were effective for bevacizumab-resistant relapsed EOC even if the therapeutic effect of salvage chemotherapy was

insufficient. Considering that most therapeutic responses to salvage chemotherapy were PRs and there was a wide range of differences in treatment efficacy, we subdivided the PR patients and included PR patients close to stable disease. Survival analysis showed no significant differences in PSS and PFS among the three groups classified according to these treatment responses.

Literature on the relationship between the clinical status of patients on salvage chemotherapy and treatment response to PARP inhibitors is limited. Previous studies found that 87.6% to 100% of the patients had PR or better response [11, 22], and there is insufficient evidence to predict the treatment response of PARP inhibitors for patients with poor PR and stable disease. Matteis *et al*. [19] reported that treatment with pre-PARP inhibitor and clinical status were not determinants of PARP inhibitor responses and adverse events. Even if the therapeutic effects of salvage chemotherapy were insufficient, the indications for PARP inhibitor maintenance could be expanded.

The limitation of this study was its retrospective nature with a small number of patients at a single institution. A larger number of patients must be accumulated for multivariate analysis.

5. Conclusions

This study showed that maintenance therapy with PARP inhibitor might be effective and feasible for bevacizumab-resistant EOC relapsed patients if selected based on their sensitivity to platinum. The length of PFI after adjuvant chemotherapy could also be a predictor of PARP inhibitor response. Additionally, PARP inhibitors may also be effective even if the therapeutic effect of salvage chemotherapy is insufficient.

ABBREVIATIONS

EOC, epithelial ovarian cancer; PPS, post-progression survival; PFS, progression-free survival; PFI, platinum-free interval; CR, complete response; PR, partial response; CTCAE, Common Terminology Criteria for Adverse Events.

AUTHOR CONTRIBUTIONS

TY—collected the data from medical records, searched the literature, and wrote the manuscript. MK and HO—contributed to the conception of the study. All authors contributed to editorial changes in the manuscript. All authors read and approved the final manuscript. All authors performed the clinical practice and documented the patients' medical records.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

All patients provided written informed consent. The study received ethical approval from the institutional review board of the local ethics committee of Kansai Medical University (#2021392).

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

REFERENCES

[1] DeVita VT, Lawrence TS, Rosenberg SA. DeVita, Hellman, and Rosenberg's cancer: principles & practice of oncology. 11th ed. Wolters Kluwer: Philadelphia, PA. 2018.

[2] Perren TJ, Swart AM, Pfisterer J, Ledermann JA, Pujade-Lauraine E, Kristensen G, *et al*. A phase 3 trial of bevacizumab in ovarian cancer. The New England Journal of Medicine. 2011; 365: 2484–2496.

[3] Tewari KS, Burger RA, Enserro D, Norquist BM, Swisher EM, Brady MF, *et al*. Final overall survival of a randomized trial of bevacizumab for primary treatment of ovarian cancer. Journal of Clinical Oncology. 2019; 37: 2317–2328.

[4] Sjoquist KM, Espinoza D, Mileshkin L, Ananda S, Shannon C, Yip S, *et al*. REZOLVE (ANZGOG-1101): a phase 2 trial of intraperitoneal bevacizumab to treat symptomatic ascites in patients with chemotherapy-resistant, epithelial ovarian cancer. Gynecologic Oncology. 2021; 161: 374–381.

[5] United States National Library of Medicine. Niraparib capsules, for oral use. United states prescribing information. 2017. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2017/208447lbl.pdf (Accessed: 12 June 2022).

[6] United States National Library of Medicine. Olaparib tablets, for oral use. United states prescribing information. 2014. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2017/208558s000lbl.pdf (Accessed: 12 June 2022).

[7] Pujade-Lauraine E, Colombo N, Glasspool R, Asselain B, Huzarski T, Korach J, *et al*. OReO/ENGOT Ov-38: a phase IIIb trial of olaparib maintenance retreatment in patients with epithelial ovarian cancer. Annals of Oncology. 2017; 28: V351–V352.

[8] Moubarak M, Harter P, Ataseven B, Traut A, Welz J, Baert T, *et al*. Re-treatment with PARPi in patients with recurrent epithelial ovarian cancer: a single institutional experience. Gynecologic Oncology Reports. 2022; 40: 100939.

[9] Mirza MR, Monk BJ, Herrstedt J, Oza AM, Mahner S, Redondo A, *et al*. Niraparib maintenance therapy in platinum-sensitive, recurrent ovarian cancer. The New England Journal of Medicine. 2016; 375: 2154–2164.

[10] Ledermann J, Harter P, Gourley C, Friedlander M, Vergote I, Rustin G, *et al.* Olaparib maintenance therapy in patients with platinum-sensitive relapsed serous ovarian cancer: a preplanned retrospective analysis of outcomes by *BRCA* status in a randomised phase 2 trial. The Lancet. Oncology. 2014; 15: 852–861.

[11] Pujade-Lauraine E, Ledermann JA, Selle F, Gebski V, Penson RT, Oza AM, *et al*. Olaparib tablets as maintenance therapy in patients with platinum-sensitive, relapsed ovarian cancer and a *BRCA*1/2 mutation (SOLO2/ENGOT-Ov21): a double-blind, randomised, placebo-controlled, phase 3 trial. The Lancet. Oncology. 2017; 18: 1274–1284.

[12] Tomao F, D'Incalci M, Biagioli E, Peccatori FA, Colombo N. Restoring platinum sensitivity in recurrent ovarian cancer by extending the platinum-free interval: myth or reality? Cancer. 2017; 123: 3450–3459.

[13] Chuang YT, Chang CL. Extending platinum-free interval in partially platinum-sensitive recurrent ovarian cancer by a non-platinum regimen: its possible clinical significance. Taiwanese Journal of Obstetrics & Gynecology. 2012; 51: 336–341.

[14] Cortez AJ, Tudrej P, Kujawa KA, Lisowska KM. Advances in ovarian cancer therapy. Cancer Chemotherapy and Pharmacology. 2018; 81: 17–38.
[15] Markman M, Markman J, Webster K, Zanotti K, Kulp B, Peterson G, *et al*. Duration of response to second-line, platinum-based chemotherapy for ovarian cancer: implications for patient management and clinical trial design. Journal of Clinical Oncology. 2004; 22: 3120–3125.
[16] Herzog TJ, Monk BJ. Bringing new medicines to women with epithelial ovarian cancer: what is the unmet medical need? Gynecologic Oncology Research and Practice. 2017; 4: 13.
[17] Bruchim I, Jarchowsky-Dolberg O, Fishman A. Advanced (>second) line chemotherapy in the treatment of patients with recurrent epithelial ovarian cancer. European Journal of Obstetrics, Gynecology, and Reproductive Biology. 2013; 166: 94–98.
[18] Sisay M, Edessa D. PARP inhibitors as potential therapeutic agents for various cancers: focus on niraparib and its first global approval for maintenance therapy of gynecologic cancers. Gynecologic Oncology Research and Practice. 2017; 4: 18.
[19] Matteis ED, Cormio G, Naglieri E, Scavelli C, Loizzi V, Cito P, *et al*. ReOL-Olaparib in the real world. A retrospective observational study to evaluate the impact of olaparib on the real-world treatment of *BRCA* carrier patients with recurrent ovarian cancer. European Journal of Gynaecological Oncology. 2019; 40: 759–764.
[20] Letendre L, Kiely JM, Hoagland HC. Reinduction chemotherapy for acute nonlymphocytic leukemia. Mayo Clinic Proceedings. 1984; 59: 618–621.
[21] Beltrame L, Di Marino M, Fruscio R, Calura E, Chapman B, Clivio L, *et al*. Profiling cancer gene mutations in longitudinal epithelial ovarian cancer biopsies by targeted next-generation sequencing: a retrospective study. Annals of Oncology. 2015; 26: 1363–1371.
[22] Cecere SC, Giannone G, Salutari V, Arenare L, Lorusso D, Ronzino G, *et al*. Olaparib as maintenance therapy in patients with *BRCA* 1–2 mutated recurrent platinum sensitive ovarian cancer: real world data and post progression outcome. Gynecologic Oncology. 2020; 156: 38–44.

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