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CASE REPORT

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Successful management of metastatic ovarian carcinosarcoma with olaparib plus bevacizumab: a case report

Takuya Yokoe[1,*], Masato Kita[1], Gen-ichiro Sumi[1], Hiroshi Shiraga[1], Hidetaka Okada[1]

[1]Department of Obstetrics and Gynecology, Kansai Medical University, 573-1191 Hirakata, Osaka, Japan

***Correspondence**
yokoetk@hirakata.kmu.ac.jp
(Takuya Yokoe)

Abstract

Background: Ovarian carcinosarcoma (OCS) is a rare, highly aggressive, and treatment-resistant tumor. Some important advances in chemotherapy have been reported, including an anti-vascular endothelial growth factor antibody, bevacizumab (Bev)-containing regimen, and a poly-ADP ribose polymerase (PARP) inhibitor, olaparib. Olaparib is specifically a treatment option for OCSs with breast cancer gene (*BRCA*) mutations, and the clinical study on the combination of olaparib and Bev was reported for homologous recombination deficient epithelial ovarian cancer. However, there are no reports on treating advanced OCS with *BRCA* mutations by olaparib plus Bev effectively. In this study, to the best of our knowledge, we report the first case of successful management of multiple liver and para-aortic metastases of OCS with a *BRCA* mutation using olaparib plus Bev. **Case**: A 75-year-old woman presented to the hospital with complaints of abdominal distension. A staging laparotomy and histological analysis revealed a primary OCS. She received platinum doublet regimens as adjuvant chemotherapy. As myChoice® CDx test of the surgical specimen revealed a *BRCA*2 mutation, the combination regimen of olaparib (400 mg daily) plus Bev (15 mg/kg every three weeks) was chosen as the maintenance therapy. After four months of this chemotherapy, a computed tomography scan revealed significant shrinkage of both the liver metastases and para-aortic lymph nodes. Progression-free survival has been noted for over 14 months. **Conclusions**: The combination therapy of olaparib plus Bev could be a potential therapeutic option for advanced OCS.

Keywords

Ovarian carcinosarcoma; PARP inhibitor; Olaparib; Bevacizumab

1. Introduction

Ovarian carcinosarcoma (OCS) is rare, accounting for less than 1–2% of all ovarian cancers [1, 2], and is considered a highly aggressive tumor. In addition, there is no effective chemotherapy regimen [3], unlike that for normal epithelial ovarian cancers. Platinum-based chemotherapy regimens are generally recommended as the primary treatment for OCS; however, OCS recurs in most patients, leading to a 5-year survival rate of less than 10% [4]. Recently, some important advances in the treatment of OCS have been reported. First, a case report showed the effectiveness of bevacizumab (Bev)-containing regimens (an anti-vascular endothelial growth factor (VEGF) antibody) for the treatment of OCS [5]. Second, OCSs with breast cancer gene (*BRCA*) mutations have been reported [6] and treated successfully with the poly-ADP ribose polymerase (PARP) inhibitor, olaparib [7, 8]. Olaparib and Bev are targeted therapy agents, and the clinical study on the combination of olaparib and Bev for homologous recombination deficient (HRD) epithelial ovarian cancer reported a significant increase in substantial progression-free survival and safety [9]. However, there is no enough evidence for treating advanced OCS with *BRCA* mutations by olaparib plus Bev effectively. In this study, to the best of our knowledge, we report the first case of successful management of multiple liver and para-aortic metastases of OCS with a *BRCA* mutation.

2. Case report

2.1 Clinical picture

A 75-year-old woman visited our hospital complaining of abdominal distension. Preoperative imaging revealed a pelvic mass and multiple liver and para-aortic lymph node metastases (Fig. 1). She had a clinical history of pelvic organ prolapse at the age of 65 and had undergone a tension-free vaginal mesh surgery. She was diagnosed with breast cancer at the age of 67 years and had continued to use oral aromatase inhibitors following breast cancer surgery. The germline *BRCA* mutations, in consideration of hereditary breast cancer, were not tested. She had a family history of prostate cancer with bone

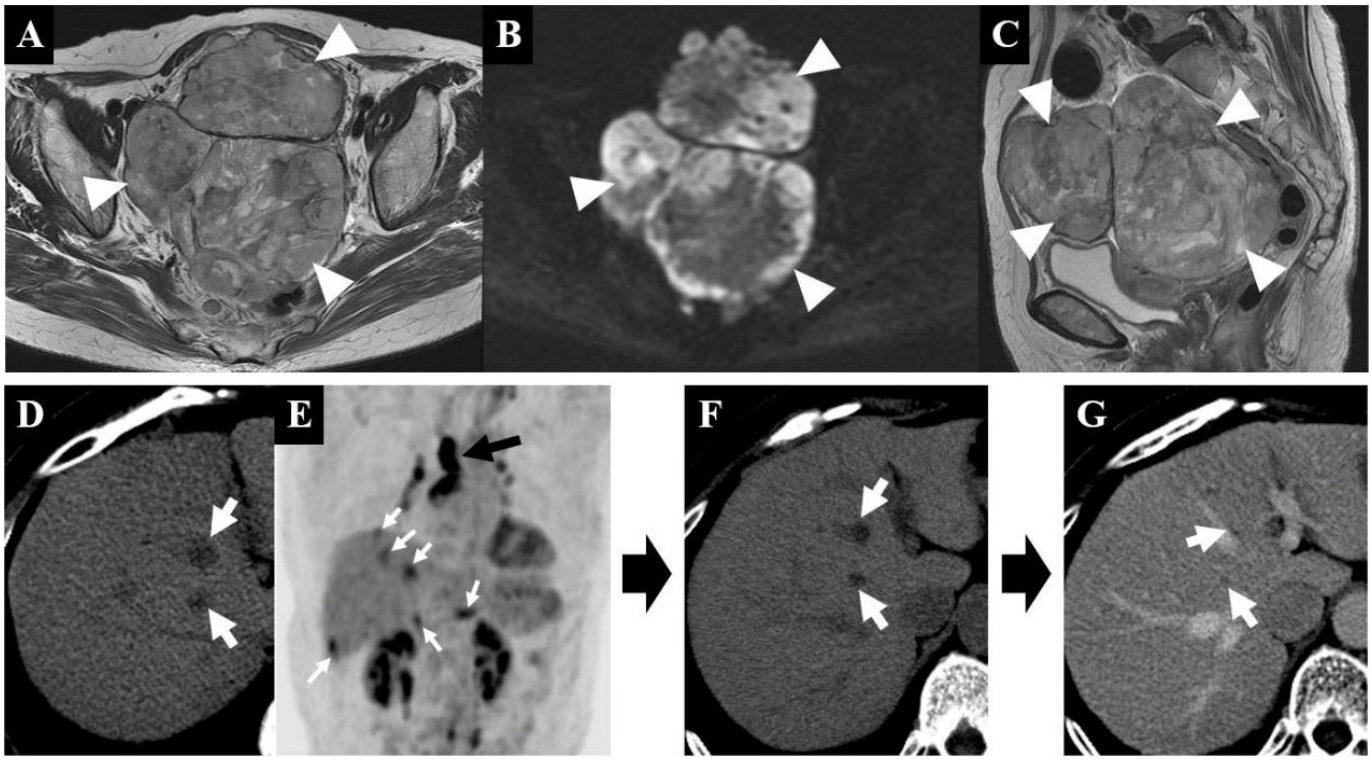

FIGURE 1. MRI, PET, and CT of liver and para-aortic lymph nodes metastases. (A–E) The preoperative images. (A–C) Magnetic resonance imaging (MRI) images showing a pelvic mass (White arrows) (A: T2WI axial; B: DWI axial; C: T2WI sagittal). (D–E) Fluorodeoxyglucose (FDG)-positron emission tomography (PET)/Computerized tomography (CT) images show hepatic metastases (white arrows) and para-aortic lymph node swelling (black arrow). (F–G) CT image of the course of treatment. The liver metastases are shrinking with treatment progression (F: Plain CT; G: Contrast-enhanced CT).

metastasis in an older brother; however, there was no history of breast or ovarian cancer in the family.

2.2 Initial treatment

She underwent staging laparotomy comprising hysterectomy, bilateral adnexectomy, and omentectomy. Due to severe postoperative adhesions after pelvic organ prolapse, a supracervical hysterectomy was performed instead of a total hysterectomy. Histological analysis revealed a primary OCS (Fig. 2).

2.3 Adjuvant chemotherapy

She received one cycle of carboplatin (5 AUC) and paclitaxel (180 mg/m^2) and 5 cycles of carboplatin (5 AUC) and docetaxel (70 mg/m^2) plus Bev (15 mg/kg) every three weeks. In the first chemotherapy after surgery, Bev was not administered because it began within 4 weeks post-surgery. Since she developed hypersensitivity to the alcohol in the paclitaxel given as the first round of chemotherapy, docetaxel was chosen instead for subsequent chemotherapy. After completion of chemotherapy, the cancer antigen 125 (CA125) levels decreased and remained in the normal range (Fig. 3); however, swelling of the small residual lymph nodes was revealed by a computed tomography (CT) scan, and the clinical response was diagnosed as partial response using the response evaluation criteria in solid tumors (RECIST) (Fig. 1, Fig. 3).

After staging laparotomy, adjuvant chemotherapy was administered: one cycle of TC (combination of paclitaxel [180 mg/m^2] and carboplatin [5 AUC]) and 5 cycles of DC+Bev

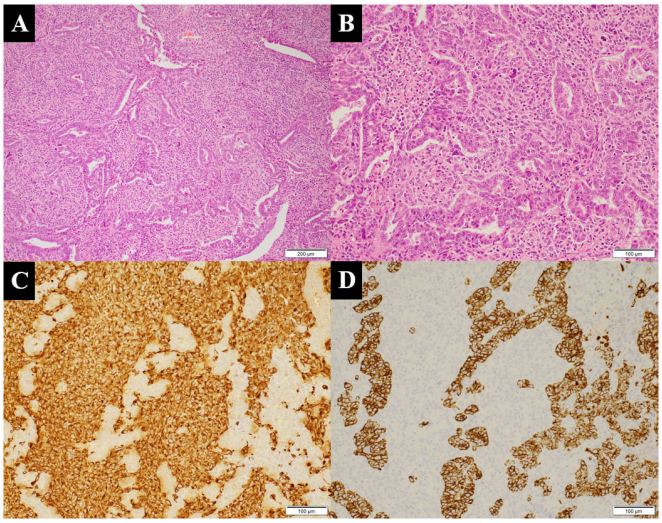

FIGURE 2. Histopathology of the ovarian tumor. Immunohistochemical staining results are shown. Keratin was positive in the adenocarcinoma component and negative in the sarcomatoid component, and Vimentin was negative in the adenocarcinoma component and positive in the sarcomatoid component. Therefore, ovarian carcinosarcoma was diagnosed. (A: HE ×100; B: HE ×200; C: vimentin ×200; D: keratin ×200).

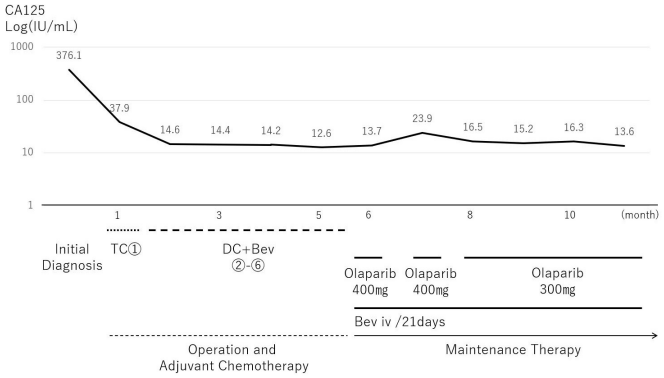

FIGURE 3. CA125 trend and interventions.

(DC, combination of docetaxel [70 mg/m^2] and carboplatin [5 AUC]; Bev, bevacizumab [15 mg/kg]) every three weeks. After two rounds of chemotherapy, the tumor marker became negative. Then, olaparib (400 mg daily) plus Bev (15 mg/kg every three weeks) was started as maintenance therapy, and the tumor markers still remained negative.

2.4 HRD test and maintenance therapy

At our institution, genetic testing using surgical specimens is actively performed, especially for persistent ovarian cancers such as carcinosarcoma; it was therefore performed for this case as well. The myChoice® CDx test (Myriad Genetics, Salt Lake City, UT, USA) result of the surgical specimen revealed a *BRCA*2 mutation; hence, the combination regimen of olaparib (400 mg daily) plus Bev (15 mg/kg every three weeks) was chosen as the maintenance therapy. Four months after olaparib plus Bev maintenance therapy, a CT scan revealed significant shrinkage of both liver metastases and para-aortic lymph nodes. The clinical response for liver metastases was considered as complete response (CR) according to the RECIST criteria (Fig. 1, Fig. 4); progression-free survival (PFS) has been maintained for over 14 months. With respect to adverse effects, temporary myelosuppression occurred; no other adverse effects were observed.

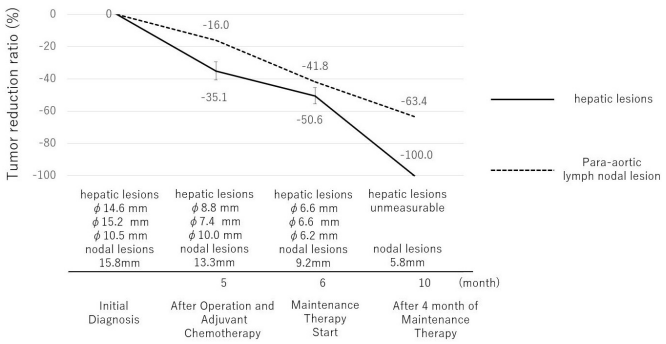

FIGURE 4. Tumor reduction ratio after operation and adjuvant/maintenance therapy.

The tumor marker CA125 was negative after initial surgery. A platinum-containing regimen of six cycles of postoperative chemotherapy was used (TC, combination of paclitaxel and carboplatin, CBDCA+PTX; DC, combination of docetaxel and carboplatin, CBDCA+DTX). Maintenance therapy with olaparib and bevacizumab was then initiated. Tumor markers remained negative.

Three hepatic metastases and one para-aortic lymph node were followed up; CT images were used to compare the total horizontal and vertical diameters for hepatic metastases and the short diameters for lymph nodes. The clinical response to platinum-containing postoperative adjuvant chemotherapy was CR for liver metastases. However, the reduction of metastatic lymph nodes was slower than that of liver metastases. After the initiation of maintenance therapy, both liver metastases and enlarged lymph nodes markedly reduced in size.

3. Discussion

In this study, we reported a rare case of successfully controlled multiple metastases of OCS with chemotherapy. OCS is a rare, highly aggressive, and treatment-resistant tumor. Approximately half the patients have lymph nodes metastasis and carcinomatous peritonitis, and most are in International Federation of Gynecology and Obstetrics stage 3–4 at the time of diagnosis [10]. Platinum doublets is the predominant chemotherapy regimen used for OCS empirically; however, there is no consensus on an effective chemotherapy regimen unlike that for epithelial ovarian cancer. This rapid tumor progression is thought to result from the growth of sarcomatoid elements within the OCS [3]. It has been reported that OCS may originate from monoclonal stem cells and is less likely to respond markedly to drugs than epithelial ovarian cancer [11, 12]. Hence, many other regimens including trabectedin, pegylated liposomal doxorubicin, pemetrexed, and immune checkpoint inhibitors have been used on a trial basis; however, cases showing long-term survival are still rare [3].

To our knowledge, this is the first report of a metastatic OCS treated with olaparib plus Bev. For the usage of Bev, there have been some useful case reports on the combination chemotherapy for OCS [5]. In the report by Koyanagi *et al* [5], the regimen of platinum-doublet chemotherapy and Bev was adopted for OCS, based on the guidelines for epithelial ovarian cancer. However, in the phase III trial of chemotherapy with Bev for ovarian cancer, which was reported at the same time as this case report, there was no mention of OCS in the patient population [13]. In addition, for olaparib, there have been case reports on the treatment of non-high-grade serous ovarian carcinoma (HGSOC) histological types, including OCS [6–8, 14] (Table 1, Ref. [5, 7, 8]).

This table shows the details of cases with advanced-stage ovarian carcinosarcoma that were successfully managed with olaparib and/or bevacizumab. Olaparib was chosen as maintenance therapy in case 1 and as primary chemotherapy in case 2, and the clinical response was better than partial response (PR) according to the RECIST criteria. In case 3, a Bev-containing regimen was chosen as the primary medication, with reference to the guidelines for epithelial ovarian cancer, and the treatment response was CR. Case 4, which is the current case, was diagnosed with ovarian carcinosarcoma with distant metastasis and enlarged lymph nodes. The response to primary adjuvant therapy was PR, and the response to maintenance therapy with the combination of olaparib and Bev

TABLE 1. Literature review of cases that showed successful management of ovarian carcinosarcoma.

Case		#1 [7]	#2 [8]	#3 [5]	#4 (our case)
Age		62	61	73	75
Primary Surgery	Perfection	Nonoptimal	Optimal	Optimal	Suboptimal
	Histology	Carcinosarcoma			
	Peritoneal Implant	Yes	Yes	No	Yes
	cT	3c	3a	1x	3c
	cN	x	x	X	1 (PeN)
	cM	0	0	1 (Virchow Lym)	1 (Liver & PAN)
1st medication	Regimen	CBDCA + DTX	None (Refused)	CBDCA + PTX + Bev	CBDCA + PTX/DTX + Bev
	Response Evaluation	PR	SD (Spleen meta after 6M)	CR	PR
2nd medication	Regimen	olaparib	olaparib	-	olaparib + Bev
	Response Evaluation	PR	CR	-	CR
Recurrence	yes/no	No	No	No	No
	Region	-	-	-	-
	Progression-free interval	— (>7M)	unknown	unknown	— (>14M)

was CR. At present, the patient has been recurrence-free for more than 14 months.

Olaparib traps PARP on the DNA at the site of a single-strand break and prevents the repair of this break; this leads to tumor apoptosis due to the generation of double-strand breaks that are not repaired correctly in tumors with HRD, including *BRCA* mutations [9]. The non-HGSOC histological types have also been reported to have *BRCA* mutations comparable to those seen in HGSOC [6, 14].

Recently, the combination of olaparib plus Bev was reported in the Platine, Avastin and olaparib in 1st Line (PAOLA-1) trial for epithelial ovarian carcinoma [9]. The PAOLA-1 trial reported a significant improvement in PFS when patients with HRD ovarian cancer, including *BRCA* mutations, and advanced ovarian cancer received olaparib plus Bev. However, this clinical trial excluded cases of OCS from the patient population, and the therapeutic effect of olaparib plus Bev on OCS remains unknown. Our report suggests that this regimen may be effective in OCS with *BRCA* mutations, although it is a single case report. In addition, even if the *BRCA* mutation is unknown, some reports suggest that if the patient is highly sensitive to platinum-containing regimens, a response to olaparib can be expected [8]. This means that high-platinum sensitivity in primary chemotherapy for OCS may act as a biomarker to predict response to olaparib. Further, for other PARP inhibitors for ovarian carcinosarcoma, clinical studies using niraparib, immune checkpoint inhibitors, and dostarlimab began in July 2020 but are not yet complete [4]. The results of this clinical study may help to clarify which of the two targeted therapy agents used in our case contributed more to the effectiveness of the treatment.

The advantages of Bev and PARP inhibitors are that they have few serious side effects and can be used as maintenance therapy to suppress cancer growth over a long period of time [8]. Hence, a maintenance therapy including Bev and PARP inhibitors could be an option for aggressive malignancies such as OCS.

4. Conclusions

We reported a case of successful management of a metastatic OCS with chemotherapy followed by olaparib and Bev. This maintenance therapy could be a potential therapeutic option for advanced OCS.

ABBREVIATIONS

OCS, ovarian carcinosarcoma; VEGF, vascular endothelial growth factor; Bev, bevacizumab; *BRCA*, breast cancer gene; PARP, poly-ADP ribose polymerase; HRD, homologous recombination deficient; MRI, magnetic resonance imaging; FDG, fluorodeoxyglucose; PET, positron emission tomography; CT, computerized tomography; GATA3, GATA binding protein 3; PAX8, paired-box gene 8; RECIST, response evaluation criteria in solid tumors; HGSOC, high-grade serous ovarian carcinoma; PAOLA-1, Platine, Avastin and olaparib in 1st line; PFS, progression-free survival; CBDCA, carboplatin; PTX, paclitaxel; DTX, docetaxel.

AUTHOR CONTRIBUTIONS

GS, HS, and MK performed the primary debulking surgery. GS, HS, and TY managed the hospitalization for the first round of chemotherapy. HO and MK reviewed the treatment plan and decided to use the regimen of Olaparib+Bev for this patient. TY handled the pharmaceutical follow-up, performed the literature search, and wrote the manuscript. MK and HO supported the preparation of the final manuscript. All authors

contributed to editorial changes in the manuscript. All authors read and approved the final manuscript.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

Ethics approval is not applicable, and consent to participate has been taken from the patient.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

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