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Clinically Relevant Response to Treatment with Olaparib in a Patient with Refractory Multidrug-Resistant Ovarian Cancer and Central Nervous System Involvement: A Case Report

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Statistical Analysis C
Data Interpretation D
Manuscript Preparation E
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Patient: Female, 52-year-old
Final Diagnosis: Epithelial ovarian cancer with central nervous system involvement
Symptoms: Abdominal pain • convulsions • dyspnea • weigh loss
Medication: —
Clinical Procedure: —
Specialty: Oncology

Objective: Unusual or unexpected effect of treatment

Background: Despite advances in diagnosis and treatment, epithelial ovarian cancer (EOC) continues to be highly lethal. Undoubtedly, the introduction of poly(adenosine diphosphate-ribose) polymerase inhibitors such as olaparib will alter this clinical picture. Phase III studies have already documented clinically relevant outcomes, particularly among patients with *BRCA* mutations and homologous recombination deficiency.

Case Report: Here we present a case report that documents the evolution of refractory multidrug-resistant, *BRCA1*-mutated EOC in a patient who had advanced clinical deterioration, carcinomatosis, and central nervous system (CNS) involvement that responded favorably to olaparib, resulting in a tripling of her progression-free survival.

Conclusions: Olaparib proved to be a safe and effective option for the treatment of a patient with multidrug-resistant, *BRCA1*-mutated EOC with CNS metastases. This suggests that early initiation of the drug in similar cases can be very useful.

MeSH Keywords: Genes, BRCA1 • Neoplasm Metastasis • Ovarian Neoplasms • Poly(ADP-ribose) Polymerases

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Background

Epithelial ovarian cancer (EOC), which is characterized by persistent recurrences and lethality, is the third leading cause of death in women aged 40 to 59 years [1,2]. Poly(adenosine diphosphate-ribose) polymerase (PARP) inhibitors are effective in controlling the disease and increasing progression-free survival (PFS) [3]. Olaparib, a PARP inhibitor that induces death in *BRCA1/2*-deficient cell lines, has significant activity in patients with *BRCA*-mutated, platinum-resistant ovarian cancer (31% response rate and 40% rate of disease stabilization for >8 weeks) [4]. It has been proposed as maintenance monotherapy in patients with platinum-sensitive recurrences [5]. We report the case of a 52-year-old woman with high-grade serous papillary EOC and central nervous system (CNS) metastases who received multiple treatments, including radiation therapy, and responded very favorably to olaparib, with a tripling of PFS (Figure 1).

Case Report

The patient was a 52-year-old Mexican woman with a 6-month history of abdominal pain, increased abdominal circumference, dyspnea, pleuritic pain, and weight loss (6 kg in 2 months), with no relevant medical history. A computed tomography (CT) scan of her abdomen and thorax revealed a cystic tumor in the pelvic cavity that involved both ovaries, with peritoneal carcinomatosis (Figure 2A), as well as an accumulation of ascitic fluid and pleural effusion (Figure 2B).

The woman's cancer antigen 125 (CA-125) level was 5923 UI/mL, a biopsy showed a high-grade serous papillary tumor, and cytologic testing of the pleural effusion confirmed a diagnosis of stage IVA EOC. After she received genetic counseling and provided informed consent for testing, a pathogenic mutation in exon 11 of *BRCA1* was documented.

The patient was deemed not to be a candidate for surgical resection because of the extent of the carcinomatosis and the presence of pleural effusion. Therefore, she was treated with 6 cycles of first-line chemotherapy with carboplatin plus paclitaxel, but her EOC responded poorly and she had persistent elevation of CA-125 (240 UI/mL at the lowest point). Lacking surgery to reduce tumor burden, second-line chemotherapy was started with tamoxifen plus thalidomide as palliation in the absence of bevacizumab. After 6 months of treatment, the patient's CA-125 level was undetectable and no tumor activity was seen on CT scan.

Eleven months later, a CT scan showed new tumor activity and her CA-125 level had risen to 1097 UI/mL. She was then started on third-line chemotherapy with trabectedin plus liposomal doxorubicin. After 6 cycles, a positron emission tomography CT (PET-CT) scan showed a complete metabolic response.

Five months later, the patient had a new recurrence and surgical tumor debulking was attempted but was unsuccessful. She then began experiencing episodes of convulsive crisis, whereupon fourth-line chemotherapy was started with gemcitabine plus carboplatin. After an 8-mm lesion in the right frontal lobe and a second lesion in the left cerebellar hemisphere were seen on CNS CT and the findings were corroborated with magnetic resonance imaging (Figure 3), the patient received whole-brain radiation therapy.

Five months later, she received 4 cycles of liposomal adriamycin (5th-line treatment), and PET-CT showed an increase in tumor activity. Etoposide therapy was begun and after 2 cycles, the patient's CA-125 level was 860 UI/mL, PET-CT showed stable disease, and her clinical condition deteriorated. Therefore, weekly paclitaxel was started, without good results, and compassionate use of letrozole was begun. After 3 months, the patient's clinical condition continued to worsen, with increased

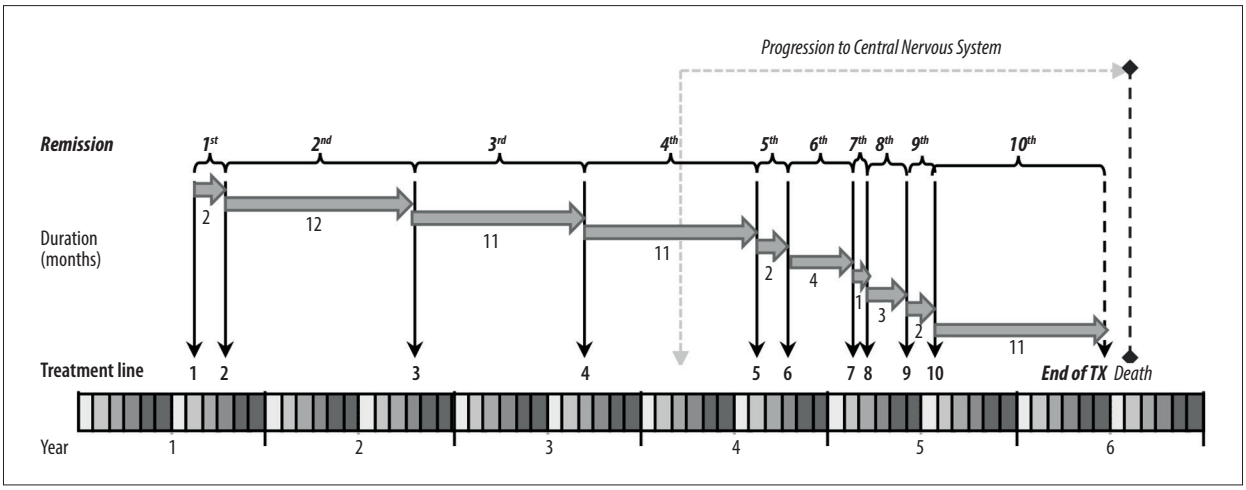

Figure 1. Timeline from first visit to death.

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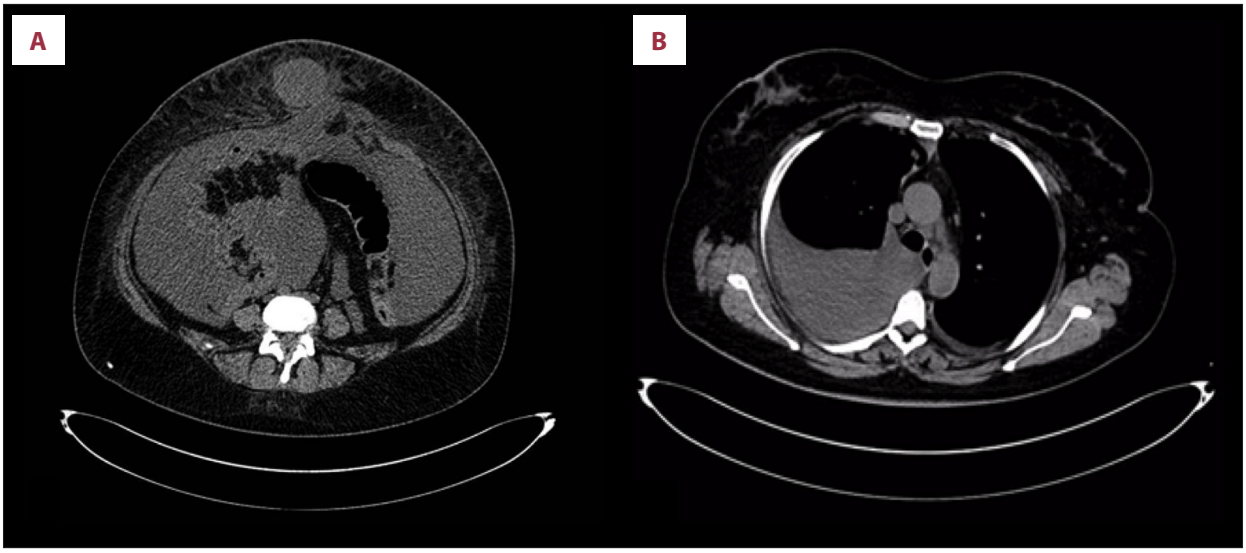

Figure 2. Computed tomography (CT) scans at the start of treatment. (**A**) Abdominal CT scan showing carcinomatosis. (**B**) Thoracic CT scan showing pleural effusion.

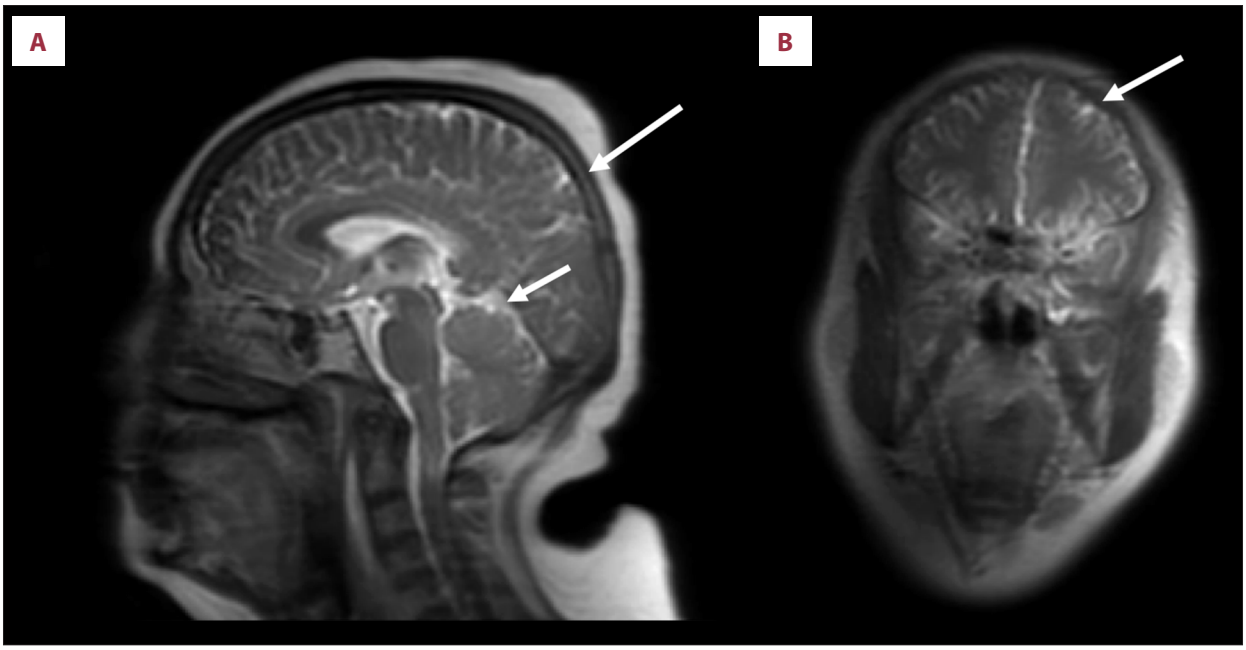

Figure 3. Magnetic resonance imaging of the head 23 months after the first visit (**A:** Midline plane; **B:** Coronal plane). The arrows point to metastatic lesions.

dyspnea, neurological deterioration, and an elevated CA-125 level (2334 UI/mL). Ninth-line therapy then was started with gemcitabine, but her CA-125 level remained unchanged (2525 UI/mL) and she had continued neurological worsening, characterized by poor response to stimuli and inability to walk, and she was confined to bed most of the day.

Given that the patient's tumor was *BRCA1*-mutated, olaparib was begun at 400 mg twice daily. Seven days after initiation of therapy, the patient had significant neurologic improvement (alert, oriented, and able to walk again), and her abdominal pain and dyspnea diminished considerably.

At the start of treatment with olaparib, the patient only had grade 1 nausea, fatigue, and dizziness. By Week 4, all her symptoms of toxicity had disappeared, except for vertigo, which was adequately controlled with diphenidol. After 8 weeks of treatment, the patient presented with anemia, neutropenia, and an increased CA-125 level (313 UI/mL), which prompted treatment interruption. One month later, when a PET-CT scan and CA-125

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level (431 UI/mL) indicated activity in the remaining tumor, olaparib was restarted at a lower dose (300 mg twice daily).

For 8 more months, the patient continued to improve while she was being treated with olaparib and her disease was biochemically stable. She had only very low toxicity: Grade 1 anemia and no thrombocytopenia or changes on tests of renal or hepatic function.

Nine months after olaparib therapy was begun, disease progression was document again, with an increase in CA-125 level (1816 UI/mL), evidence on CT of peritoneal and lymph node progression, and peripheral edema in the left leg due to superficial and deep vein thrombosis. Those findings prompted the definitive suspension of olaparib. Disease progression continued and she died 2 months later.

Discussion

The most relevant characteristic of this case is the excellent clinical response to treatment with olaparib that was seen even after prior disease progression and multidrug resistance. The patient recovered from near total incapacity and deep neurological deterioration. Olaparib treatment kept her disease at bay for nearly a year with neurological recovery, something seldom seen after a lack of response to whole-brain radiation therapy.

The patient's EOC failed to respond to any treatment in a sustained fashion, and olaparib was the tenth-line treatment. In 2016, the drug was not available in México and had to be imported specifically for this patient, and its use was not as widespread then as it is today.

Previous cases have been documented in the literature of successful olaparib monotherapy in patients with *BRCA2*-mutated EOC and leptomeningeal disease [6], and in patients with primary peritoneal *BRCA1*-mutated cancer with persistently elevated CA-125 levels [7].

Mutations in *BRCA1* and *BRCA2*, which have been reported in 5.8% to 24.8% of all cases, are a major risk factor in EOC [8]. They are associated with earlier presentation, greater susceptibility to chemotherapy, and overall better prognosis. *BRCA1* and *BRCA2* are suppressor genes whose function is to maintain genomic stability and regulate cell growth. Mutations in the genes are seen in 90% of cases of hereditary breast-ovarian cancer syndrome. The average age of patients at presentation of EOC with *BRCA1* mutation is 45 years *vs.* 57 years for *BRCA2* mutation [9].

In general with EOC, recurrences happen locally; however, the literature suggests that *BRCA* mutation carriers may have an increased rate of distant metastases [10]. *BRCA* screening is recommended for patients recently diagnosed with EOC because a mutation has implications for prognosis, prevention, and treatment.

PARP is crucial for DNA repair through base excision. Thus, inhibition of PARP leads to breaks in double-stranded DNA that cannot be adequately repaired in tumors with homologous recombination deficiency because of the aberrant activation of low-fidelity repair mechanisms mediated by non-homologous end unions, a process known as synthetic lethality [5,11].

Olaparib is a PARP inhibitor that induces synthetic lethality in *BRCA1/2*-deficient cell lines [12]. Currently, olaparib is used as monotherapy in patients with platinum-sensitive disease (defined as an objective response to platinum-based therapy for >6 months) that has recurred. A dosage of 400 mg twice daily has been shown to significantly improve PFS compared with placebo [13]. Since 2014, the average PFS for the drug has increased (11.2 months with olaparib *vs.* 4.3 months with placebo, P=0.0001) [14]. Because olaparib has significant activity in *BRCA*-mutated, platinum-resistant ovarian cancer, it has been suggested as fourth-line treatment in that setting [4].

Our patient had received multiple treatments and her disease had responded poorly to most of them, whereas monotherapy with olaparib resulted in very meaningful benefits. Her PFS was nearly triple that reported for best responses to treatment, and her evident and clear clinical improvement lends credence to earlier documentation in the literature. Nevertheless, caution is warranted regarding the outcomes described here because ours is only a case report, in which the patient's response and PFS were evaluated clinically. More evidence must be gathered about olaparib monotherapy for EOC. Pharmacokinetic studies of the drug have demonstrated that it is able to penetrate the blood-brain barrier, and research in animal models has shown that it has intracerebral antitumor activity [15].

Clinical reports exist about the antimetastatic activity of olaparib within the CNS. Experimental models have shown that the drug increases the sensitivity of certain tumors to chemotherapy and radiation therapy [16]. Our case report is not useful in determining whether olaparib has an effect on overall survival in patients with EOC and clinical studies should be performed to investigate whether the drug is useful as a last-recourse rescue therapy.

Conclusions

Our study underscores the usefulness of *BRCA* testing in all patients with EOC and suggests that olaparib has antitumor activity against *BRCA*-mutated EOC metastases within the CNS,

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even after the failure of 10 lines of treatment, radiation therapy, and advanced clinical deterioration in a patient. Starting olaparib early could be very beneficial in cases like ours.

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Conflicts of interest

AztraZeneca México provided medical writing assistance with the manuscript but was not involved in the analysis of the data or the final content.

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