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Case Report
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Successful Neoadjuvant and Adjuvant Treatment of High-Grade Serous Carcinoma of the Ovary with BRCA1 Somatic Mutation: A Case Report

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Abstract

High-grade serous carcinoma (HGSC) is the most common ovarian cancer, linked to BRCA1 mutations. Though initial response to treatment is good, relapse is common within a few years. We present the case of a 55-year-old woman diagnosed with advanced-stage HGSC who had a somatic BRCA1 mutation. She was on neoadjuvant chemotherapy with Polymeric Micelle Formulation of Paclitaxel, carboplatin, bevacizumab, and atezolizumab. Unfortunately, atezolizumab had to be discontinued after three doses due to immune-related side effects. Subsequently, the patient underwent cytoreductive surgery. A comprehensive pathological evaluation confirmed the presence of residual disease with no evidence of metastasis. After six chemotherapy cycles, her CA-125 levels dropped significantly, from 2350 IU/ml to less than 5.5 IU/ml and reached normal levels on further treatment, showing tremendous response. Maintenance therapy was done with olaparib. In view of the possibility of recurrences and other side effects, her case was further reviewed. As she had cytoreductive surgery with margin positivity near the ureter, she was advised to continue Olaparib beyond 3 years with close monitoring. Over the due course of months, the patient showed no signs of disease. With a thorough MDT discussion, olaparib therapy was extended beyond the standard two-year duration. Regular follow-ups revealed a further drop in CA-125 levels. This case highlights the treatment approach combining chemotherapy, surgery, and adept surveillance. It also supports the use of olaparib in high-risk patients and emphasizes the need for long-term monitoring.

Keywords: Olaparib, Carcinoma, Serous, Somatic mutation, BRCA1 Gene, CA-125 antigen

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Introduction

High-grade serous carcinoma (HGSC) is the most common and aggressive histological subtype of ovarian cancer. BRCA1 mutations which can be both germline and somatic variants are significant in HGSC [1]. A study analyzing 71 HGSC patients found that 25.4% had loss-of-function germline variants, and 9.9% had somatic variants in DNA recombination repair pathway genes, including BRCA1 [1]. High-grade serous ovarian carcinoma (HGSC) is known for its high recurrence rates, with approximately 75% of patients experiencing relapse within the first three years of initial treatment [2]. BRCA1 somatic mutations are frequently detected in HGSC and can influence treatment outcomes [(1)]. The integration of surgery with adjuvant maintenance therapy using olaparib and bevacizumab has demonstrated significant improvements in survival outcomes for patients with advanced ovarian cancer [3]. Here, we describe the successful treatment of a patient with HGSC carrying a BRCA1 somatic mutation using a combination of neoadjuvant chemotherapy of bevacizumab and atezolizumab, followed by surgery, and initiation of adjuvant olaparib and bevacizumab.

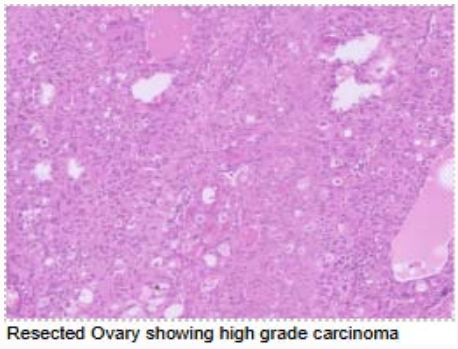


Figure 1: Resected Ovary showing high grade carcinoma.

Case Presentation

We present the case of a 55-year-old female with previous history of chondrosarcoma of left lower limb, operated and on observation, evaluated for loose stools, low abdominal pain and burning sensation. An external MRI of the abdomen revealed an ovarian mass with ascites, following which the patient presented to our institution for further evaluation.

Histopathology and PET CT (as shown in Figure 1) confirmed a high-grade serous carcinoma of the ovary 21 × 16 × 15 cm FIGO stage III C. Baseline CA-125 was 2350 U/ml. Comprehensive genomic profiling revealed the presence of a BRCA1 somatic mutation. The patient was initially managed with neoadjuvant chemotherapy, with polymeric micelle formulation of paclitaxel 120 mg, and carboplatin 150 mg for 24 weeks along with bevacizumab 500 mg (16 cycles) and atezolizumab. Post two weekly cycles, her CA-125 was 2250 U/ml, and bevacizumab was added along with chemotherapy.

Based on the tumor board decision, treatment with atezolizumab was discontinued after 3 doses in view of an immune-related adverse event as the patient developed grade 4 fatigue. Prior to the third neoadjuvant chemotherapy, her CA-125 dropped to 900 ng/mL. Neoadjuvant chemotherapy was given for 6 cycles with CA-125 monitoring, unlike the frequent practice of administering 3-4 cycles without serial monitoring. At this point, the CA-125 was near normal, and radiographic imaging demonstrated a significant reduction in tumor size, indicating a favorable response.

Subsequently, the patient underwent cytoreductive surgery (R0 resection of mass), and a comprehensive pathological evaluation confirmed the presence of residual disease with no evidence of metastasis. Adjuvant treatment was initiated with olaparib, a poly (ADP-ribose) polymerase (PARP) inhibitor in view of somatic BRCA1 positivity (as shown in Figure 4) and bevacizumab was continued. Regular follow-up evaluations revealed a sustained response, with CA-125 dropping to a minimum of 7U/ml during the last evaluation with no evidence of disease recurrence or progression during the adjuvant therapy phase. Follow-up PET CT in February 2024 (as shown in Figure 2) showed no new findings and CA-125 levels less than 5.5 (as shown in Figure 3). Subsequent PET CT follow-up in August 2024 showed no new findings. Upon completing 18 months of maintenance Olaparib, repeat PET CT scan did not reveal any major findings, and she continued to remain on PARP inhibitor without any major adverse events. The multidisciplinary team decided to continue olaparib beyond the routine practice of stopping it at the end of two years as there was no residual disease.

We monitored her treatment using circulating tumor cells (CTCs), which remained undetectable throughout and at the completion of two years of maintenance therapy. Further continuation of olaparib required literature review, as the recommended duration of first-line Olaparib therapy in this setting is two years. The results of this study established maintenance of olaparib as a new standard of care for patients with newly diagnosed advanced ovarian cancer harboring a BRCA1 or BRCA2 mutation. The possibility of stopping the therapy and possible risk of recurrences v/s continuation of the therapy with possible development of certain side effects with bone marrow suppression, myelodysplastic syndrome was explained to the family. Her case was further reviewed at MDT and recommended that in a patient with cytoreductive surgery and margin positivity near the ureter, olaparib continuation was advised beyond 2 years or at least 3

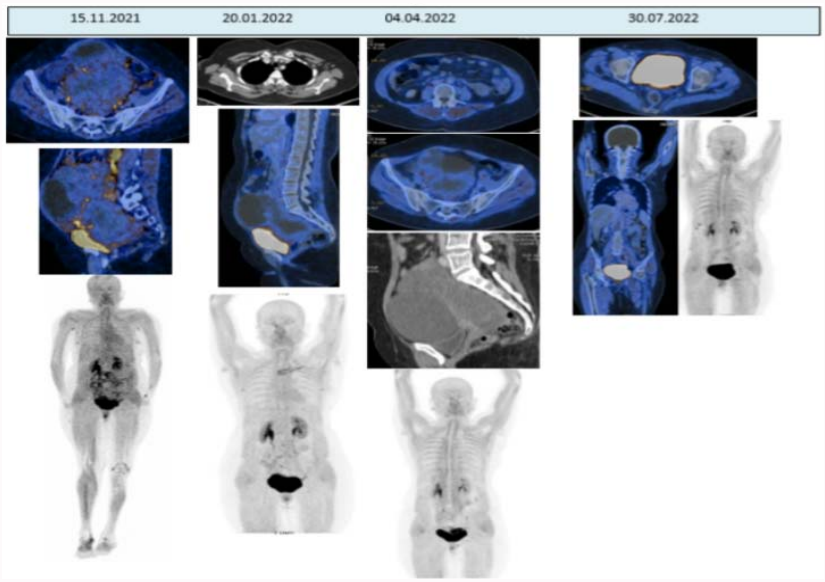
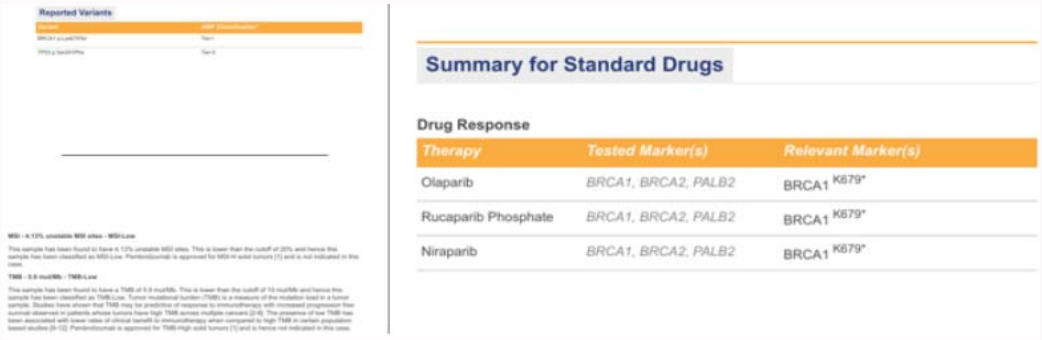


Figure 2: ^{1}F-FDG -FDG PET Scan Showing Metabolically Active Lesions in High-Grade Serous Ovarian Carcinoma



Reported Variants

Summary for Standard Drugs

Drug Response

Therapy	Tested Marker(s)	Relevant Marker(s)
Olaparib	BRCA1, BRCA2, PALB2	BRCA1 K679*
Rucaparib Phosphate	BRCA1, BRCA2, PALB2	BRCA1 K679*
Niraparib	BRCA1, BRCA2, PALB2	BRCA1 K679*

Figure 3: Genetic report.

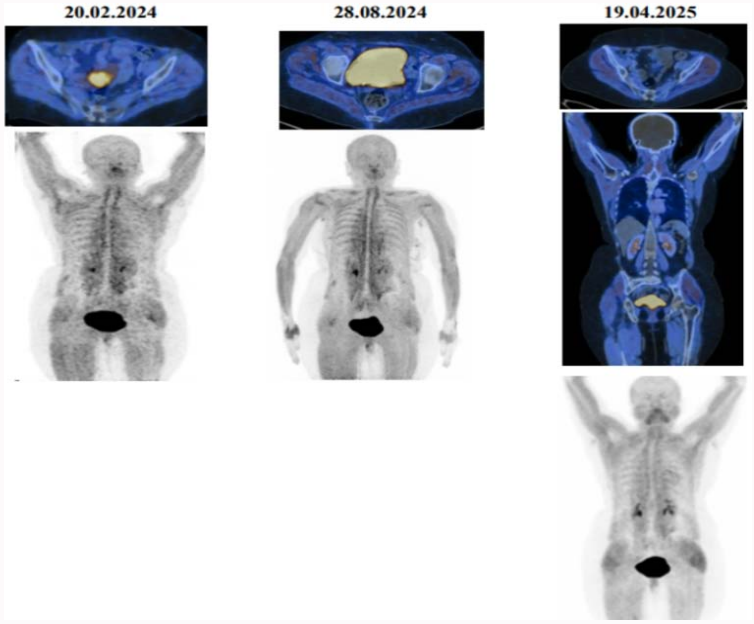


Figure 4: Follow-up ^{18}F-FDG -FDG PET/CT performed in February 2024 demonstrated no new metabolically active lesions, indicating absence of disease progression.

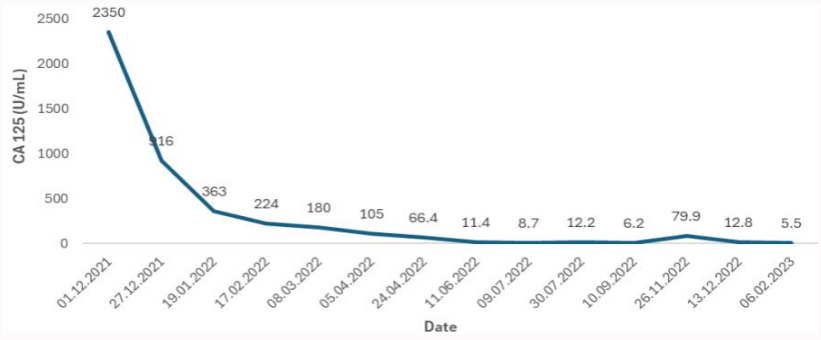


Figure 5: Trend of serum CA-125 levels showing a decline from 2,350 U/mL to less than 5.5 U/mL during treatment.

years along with close monitoring.

By demonstrating a substantial and clinically meaningful prolongation of progression-free survival, with a 70% reduction in the risk of disease progression or death compared to placebo, the trial highlighted the importance of incorporating PARP inhibition early in the treatment course. The median progression-free survival (PFS) was 56 months with olaparib *vs* 13.8 months with placebo. Duration of use was up to 2 years or until progression or unacceptable toxicity.

These findings support routine BRCA testing at diagnosis to identify patients who may benefit from targeted maintenance therapy. Although olaparib was associated with higher rates of anemia and fatigue, the overall safety profile was manageable, and most adverse events were mild to moderate [5]. After 7 months of another review, the patient was advised to continue olaparib for 4-7 years. She was

advised to follow up once in 3 months with CBC CA-125 reports. Though the patient had completed 2 years of olaparib, she had no chemo tolerance issues.

Discussion

This case highlights the potential efficacy of neoadjuvant chemotherapy in combination with targeted therapies for patients with HGSC of the ovary harboring BRCA1 somatic mutations. The addition of bevacizumab, a vascular endothelial growth factor (VEGF) inhibitor, and atezolizumab, an immune checkpoint inhibitor, to the chemotherapy regimen may have contributed to the favorable treatment response observed in this patient. Furthermore, the subsequent administration of adjuvant olaparib and bevacizumab has likely played a crucial role in maintaining the patient's disease-free status. olaparib tablets have been evaluated as maintenance therapy in patients with platinum-sensitive, relapsed ovarian cancer harboring a BRCA1 or BRCA2 mutation. Treatment is administered continuously until either disease progression or unacceptable toxicity occurs, with no pre-specified maximum duration. In clinical practice, many patients can remain on therapy for 2 to 3 years or longer if the drug is well tolerated.

Notably, treatment with olaparib has demonstrated a substantial improvement in median progression-free survival, reaching 19.1 months compared to 5.5 months with placebo [4]. Although olaparib was associated with higher rates of anemia and fatigue, the overall safety profile was manageable, and most adverse events were mild to moderate [5]. The combination of a PARP inhibitor and VEGF inhibitor in the adjuvant setting has shown promising results in clinical trials and represents a novel treatment strategy for patients with ovarian cancer. The OPINION trial was a non-randomized, open-label, phase III b study designed to reflect daily practice by enrolling patients with BRCA1/2 mutations and platinum-sensitive relapsed ovarian cancer. Median progression-free survival reached approximately 14 months, and the safety profile mirrored earlier randomized trials. This study reinforced that olaparib is effective in a broader, more heterogeneous patient population outside strictly controlled clinical settings [6].

She has completed 2 years of maintenance therapy with olaparib and there is paucity of literature on further continuation of drug beyond two years. A U.S.-based retrospective study assessed real-world outcomes of olaparib maintenance monotherapy in approximately 300 patients with platinum-sensitive relapsed ovarian cancer. The median time on therapy was 8.1 months, which was slightly shorter than in clinical trials, mainly due to treatment, discontinuation from fatigue or gastrointestinal side effects. Overall, disease control and tolerability were comparable to pivotal studies, supporting olaparib as a viable option in routine practice, even among older and more comorbid patients [7]. In an Italian multicenter cohort, researchers evaluated real-world experience with olaparib maintenance in high-grade serous ovarian cancer. Median treatment duration was approximately 12 months, and nearly one-third of patients required dose reductions due to adverse events like fatigue and anemia. Nevertheless, the real-world progression-free survival remained comparable to clinical trial data, demonstrating the effectiveness and feasibility of olaparib in routine oncology practice [8]. A retrospective analysis focused on elderly patients over 65 years receiving olaparib maintenance therapy for platinum-sensitive recurrent ovarian cancer. Outcomes demonstrated that older patients achieved meaningful disease control, with manageable toxicities primarily requiring dose adjustments rather than discontinuation. The findings confirm that age alone should not preclude the use of olaparib, provided careful monitoring is in place [9]. A Canadian observational study explored the real-world use of olaparib in combination with bevacizumab for newly diagnosed advanced ovarian cancer, reflecting the PAOLA-1 regimen. Patients with homologous recombination deficiency (HRD) derived from the most benefit, consistent with trial findings. The study confirmed the practicality of integrating this combination into standard care, underscoring the importance of HRD testing to guide treatment selection [10].

PARP inhibitors and anti-angiogenic agents, such as bevacizumab, have more recently changed upfront therapy. Unfortunately, other targeted therapies, including immunotherapy, have not seen the same success. Emerging therapeutic targets and modalities such as small molecule tyrosine kinase inhibitors, lipid metabolism targeting agents, gene therapy, ribosome targeted drugs as well as several other therapeutic classes have been and are currently under investigation [11]. The first PARP inhibitor olaparib was approved by the United States Food and Drug Administration (FDA) in 2016 as a maintenance treatment for *BRCA*-mutated recurrent HGSC following ≥3 lines of chemotherapy and extended to treatment following first-line chemotherapy in 2018. Tumor *BRCA* testing and PARP inhibitor monotherapy for the maintenance of adult patients with *BRCA*-mutated platinum-sensitive relapsed (PSR) HGSC was first approved by Health Canada in April 2016. Currently, tumor *BRCA* testing is performed reflexively for newly diagnosed HGSC patients in Ontario in several referral centers [12]. Despite the importance of identifying BRCA1 mutations in the clinical setting for the management of HGSC, our understanding of the molecular phenotypes associated with BRCA1 mutations remains poor. A deeper characterization of these tumors could allow the identification of new therapeutic targets beyond PARP inhibitor therapy aimed at optimizing patient care [13]. To bridge the gap between research discoveries and tangible improvements in patient outcomes, it is imperative to revisit scientific findings and identify dependable biomarkers for prognosis and therapy decisions [14]. BRCA testing might be a reliable tool to personalize treatment in patients with high-grade serous ovarian cancer [15].

In our institution, a total of 80 cases had undergone full genomic panel testing, among which eight cases demonstrated somatic mutations identified by comprehensive genomic profiling. The patient described in this report had a prior history of chondrosarcoma of the leg, extensive disease in the sigmoid colon, and fallopian tube. A recent liquid biopsy panel performed in this case did not reveal any detectable mutations. The SOLO1/GOG-3004 phase 3 trial evaluated long-term use of Olaparib, with patients receiving therapy for up to 7 years [16]. In that study, the median duration of Olaparib treatment was 24.6 months, and the authors noted that the potential for achieving cure might be enhanced with prolonged maintenance therapy. Importantly, no new safety signals emerged during extended follow-up.

The PAOLA-1/ENGOT-ov25 trial demonstrated that adding olaparib to bevacizumab maintenance therapy significantly improved progression-free survival in patients with advanced ovarian cancer. The PAOLA-1/ENGOT-ov25 trial highlighted that this combination significantly enhances progression-free survival, with favorable trends observed in overall survival as well. Such therapeutic strategies underscore the potential of combining targeted agents with standard

care to achieve better tumor response and improved long-term disease outcomes. The final overall survival results from this trial indicated a positive trend in survival outcomes for patients receiving combination therapy.

However, considering the balance of risk and benefit, it remains essential to monitor patients for signs and symptoms suggestive of myelodysplastic syndrome (MDS). The incidence of new primary malignancies in the trial included six cases (2.3%) among patients receiving olaparib and three cases (2.3%) among those receiving placebo. Notably, an increased incidence of MDS and acute myeloid leukemia (AML) has been reported in trials of PARP inhibitor maintenance therapy in relapsed ovarian cancer.

The risk of developing MDS or AML in this context should be interpreted considering potential baseline factors, such as prior exposure to DNA damaging chemotherapy, as well as the typically long latency period associated with these hematologic malignancies.

The multidisciplinary team is currently evaluating the long-term use of PARP inhibitors and the importance of close monitoring of disease status/recurrence of CTCs in patients with improved survival outcomes. There have been encouraging safety signals as observed in The SOLO1/GOG 3004 Trial, where the incidence of MDS/AML was 1.5% at 7-year follow up, of note none in those who are currently receiving olaparib at 7-year follow up at the time of publication [16]. We plan to closely monitor her for any signs of olaparib induced Myelodysplastic Syndrome.

Conclusion

This case report describes a patient with high-grade serous ovarian carcinoma harboring a somatic BRCA1 mutation, who achieved a significant response to neoadjuvant chemotherapy with bevacizumab and atezolizumab, followed by surgery and adjuvant olaparib with bevacizumab. Despite normal CA125 levels, adjuvant therapy was extended due to the risk of microscopic residual disease. Since recurrences typically occur within 2–3 years, long-term maintenance and MRD monitoring were planned. The PAOLA-1/ENGOT-ov25 trial demonstrated that adding olaparib to bevacizumab maintenance significantly improved progression-free and overall survival, supporting multimodal, precision-based approaches in BRCA1-mutated ovarian cancer to enhance therapeutic response and survival outcomes.

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