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Case Report

Recurrent ovarian cancer with BRCA reversion: a case study and comprehensive literature review

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ABSTRACT

Herein, this report presents the case of a 48-year-old female with a history of breast cancer (2013) and subsequent high-grade epithelial ovarian cancer (2020), illustrating the complex evolution of therapeutic resistance in BRCA1-mutated malignancies. Following initial response to paclitaxel-carboplatin chemotherapy and complete surgical debulking, the patient experienced multiple disease relapses transitioning from platinum-sensitive to platinum-resistant states. Comprehensive molecular profiling via Tempus xF+ next-generation sequencing revealed a pathogenic BRCA1 mutation alongside a secondary BRCA1 reversion mutation, conferring partial restoration of homologous recombination repair and resistance to both platinum-based chemotherapy and PARP inhibitors. Subsequent therapies, including pemetrexed and liposomal irinotecan, were employed with limited success. This case underscores the dynamic molecular evolution of recurrent ovarian cancer under therapeutic pressure and highlights the critical role of serial genomic profiling in guiding personalized treatment strategies. Emerging approaches targeting alternative DNA repair mechanisms and novel antibody–drug conjugates may hold promise for overcoming resistance in BRCA-mutated, therapy-refractory ovarian cancer.

Keywords: BRCA reversion, Carcinoma ovary, Platinum resistance, Liquid biopsy, Parp inhibitors resistance

INTRODUCTION

Epithelial ovarian cancer (EOC) remains one of the most lethal gynecologic malignancies, largely due to its late-stage diagnosis, high recurrence rates, and eventual development of chemoresistance.[1] Among its molecular subtypes, tumors harboring BRCA1 or BRCA2 mutations represent a distinct group characterized by defective homologous recombination (HR) DNA repair, leading to initial hypersensitivity to platinum-based chemotherapy and poly (ADP-ribose) polymerase (PARP) inhibitors.[2,3]

Despite promising responses to these agents, the majority of BRCA-mutated ovarian cancers eventually relapse and develop resistance, representing a major clinical challenge.[4] Resistance to platinum agents and PARP inhibitors arises through several mechanisms, including secondary (reversion) mutations in BRCA1/2 that restore HR function, increased drug efflux via upregulated P-glycoprotein transporters, stabilization of replication forks, and activation of alternative DNA repair pathways.[5-7]

The emergence of BRCA reversion mutations is particularly significant, as they reinstate partial protein function and consequently confer cross-resistance to both PARP inhibitors and platinum compounds.[8] Continuous molecular evolution under therapeutic pressure

underscores the importance of serial genomic profiling to guide treatment decisions and identify new therapeutic vulnerabilities.[9] Advances in next-generation sequencing (NGS) and circulating tumor DNA (ctDNA) analysis have enabled real-time assessment of tumor heterogeneity and resistance mechanisms, providing opportunities for precision oncology approaches in recurrent ovarian cancer.[10]

This case report describes a patient with recurrent, BRCA1-mutated high-grade epithelial ovarian cancer who developed a secondary BRCA1 reversion mutation, leading to resistance against platinum-based chemotherapy and PARP inhibition. This case highlights the dynamic molecular landscape of BRCA-associated ovarian cancer and the critical role of repeated molecular testing in optimizing individualized therapy.

CASE REPORT

A 48-year-old female with a prior history of breast cancer, diagnosed in December 2013, was successfully managed with surgery, adjuvant chemotherapy (Paclitaxel and Doxorubicin), and partial breast radiation therapy. Her breast cancer remained in remission until June 2020, when she was diagnosed with high-grade epithelial ovarian cancer.

Initial management included neoadjuvant chemotherapy with paclitaxel (175 mg/m^2 IV weekly for 3 doses) and carboplatin, followed by interval laparoscopic debulking surgery achieving complete resection (R0). Post-operative continuation of the paclitaxel-carboplatin regimen resulted in symptomatic relief and normalization of CA-125 levels. Treatment cascade is shown in Figure 1.

First relapse (platinum-sensitive, 2021)

Within one year, the patient experienced disease relapse, marked by rising CA-125 and symptoms recurrence. Classified as platinum-sensitive, the patient received carboplatin and gemcitabine chemotherapy. Post-therapy maintenance involved oral cyclophosphamide and etoposide targeting angiogenesis but was discontinued due to disease progression.

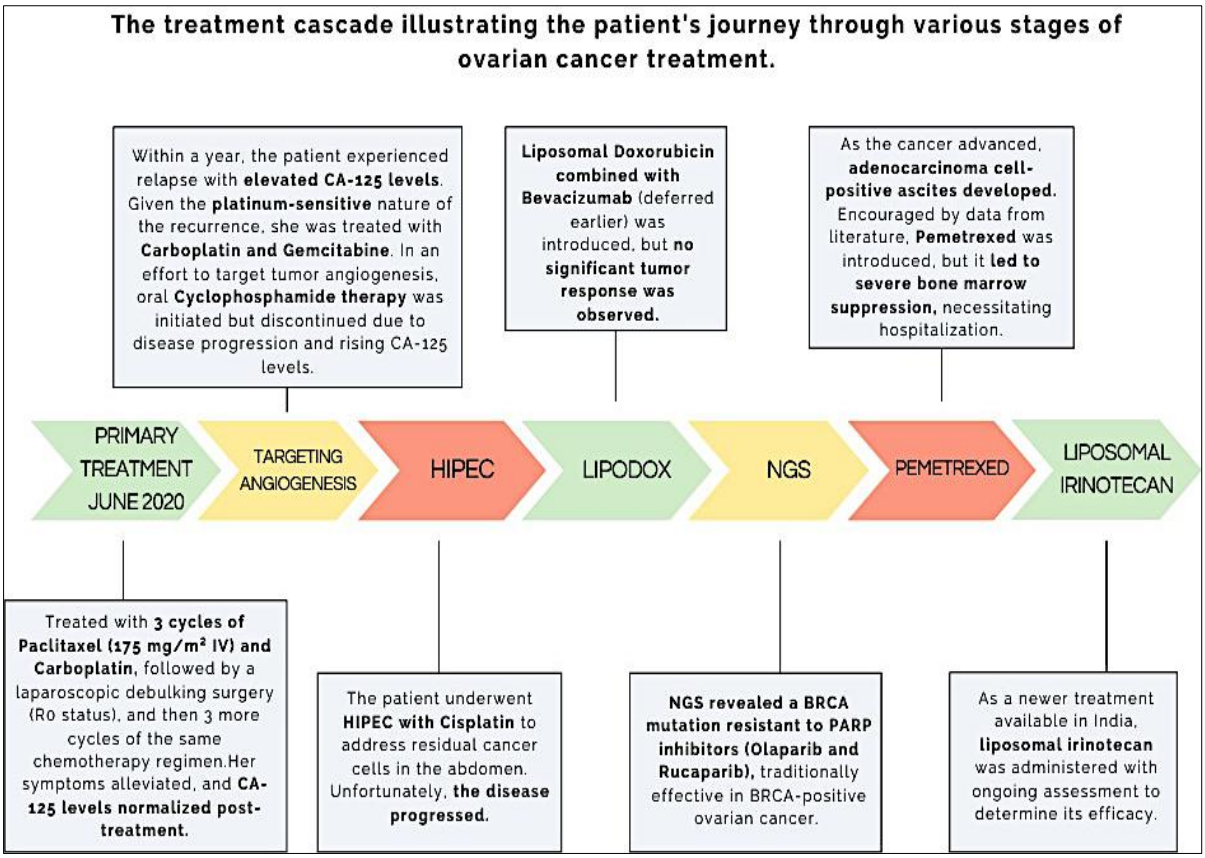

Figure 1: Treatment cascade.

Second relapse (2022)

Despite aggressive secondary cytoreductive surgery combined with hyperthermic intraperitoneal chemotherapy (HIPEC) using cisplatin, the patient experienced continued disease progression.

Third relapse (platinum-resistant, June 2023)

A third relapse occurred, now platinum-resistant due to disease progression within six months post-platinum therapy. The treatment regimen shifted to liposomal doxorubicin and bevacizumab, an anti-angiogenic agent

previously deferred due to wound healing concerns. Concurrent molecular profiling with Tempus xF+ next-generation sequencing (NGS) liquid biopsy was performed.

Molecular testing and key findings

The Tempus xF+ liquid biopsy, assessing circulating tumor DNA across 523 genes, identified a pathogenic BRCA1 mutation and a secondary BRCA1 reversion mutation. This reversion mutation partially restored BRCA1 functionality, reversing sensitivity to platinum-based chemotherapy and PARP inhibitors. The profile also revealed microsatellite stability (MSS) and low tumor mutational burden (TMB), indicating likely resistance to immune checkpoint inhibitors.

Immune and targeted therapies (2023)

Given the molecular profile, pembrolizumab (Keytruda), an anti-PD-1 immune checkpoint inhibitor, was initiated. However, minimal therapeutic benefit was observed, consistent with MSS and low TMB. Disease progression was evidenced by malignant ascites with adenocarcinoma cytology.

Experimental therapeutic approaches (late 2023)

Due to limited standard therapeutic options, pemetrexed chemotherapy was attempted, resulting in severe bone marrow suppression requiring prolonged hospitalization. Concurrently, liposomal irinotecan was initiated as an alternative, with response evaluation ongoing.

DISCUSSION

Resistance mechanisms and emerging therapeutic strategies

Poly (ADP-ribose) polymerases (PARPs) play an important role in various cellular processes, such as replication, recombination, chromatin remodeling, and DNA repair. Emphasizing PARP's role in facilitating DNA repair, the PARP pathway has been a target for cancer researchers in developing compounds which selectively target cancer cells and increase sensitivity of cancer cells to other anticancer agents, but which also leave normal cells unaffected.[11] Since certain tumors (BRCA1/2 mutants) have deficient homologous recombination repair pathways, they depend on PARP-mediated base excision repair for survival. Thus, inhibition of PARP is a promising strategy to selectively kill cancer cells by inactivating complementary DNA repair pathways.[1]

Published clinical studies suggest that germline BRCA mutation-associated (gBRCAm) breast cancers are more sensitive to DNA-damaging therapies like poly (adenosine diphosphate ribose) polymerase (PARP) inhibitors. PARP inhibitors (PARPi) are a class of anti-cancer drugs which compete with nicotinamide (NAD^+) for the catalytically active site of PARP molecules.[12] PARP inhibitors disrupt the replication fork and the subsequent HR-dependent repair of these forks. Therefore, given that BRCA1/2 mutated tumor cells have disrupted HR activity, the collapsed replication forks are unable to be repaired and cell death occurs.[12]

BRCA1/2 mutations remain the main predictive biomarkers for the majority of PARP inhibitors. Although PARP inhibition is a promising therapeutic approach for BRCA-mutated breast cancers, in some cases PARPi resistance can emerge, often via poorly understood mechanisms. Common resistance mechanisms in BRCA-mutated ovarian cancers include BRCA reversion mutations, increased drug efflux (e.g., ABCB1/P-glycoprotein), stabilization of replication forks, and activation of alternative DNA repair pathways.[4,8]

The most frequent method by which HR is restored is by the reactivation of BRCA1/2 due to secondary mutations. These reversion mutations have been identified in patients diagnosed with both germline and somatic BRCA1/2 mutated breast and ovarian carcinomas. A study of high-grade ovarian cancers showed BRCA reversion mutations were identified in the circulating cell-free DNA of 18% and 13% of platinum-refractory and platinum-resistant tumors, respectively.[8,13] Open reading frame (ORF) mutations restore BRCA function through removal of the initial deleterious mutation and subsequent HR reactivation. Increased drug efflux may also contribute, as higher expression of efflux transporters has been associated with PARPi resistance. Microhomology-mediated end-joining (MMEJ) repair was reported in 58.3% of reversion deletions in BRCA1/2 cases.[13]

Emerging therapeutic strategies

Emerging therapeutic strategies include Polθ inhibitors targeting the MMEJ pathway, WEE1 and ATR inhibitors targeting cell cycle checkpoints and replication stress, optimized selection and combination regimens for immune checkpoint inhibitors, antibody–drug conjugates such as mirvetuximab soravtansine targeting folate receptor-alpha (FRα), novel therapies including liposomal drug formulations, epigenetic modifiers, and immunotherapies like bispecific T-cell engagers (BiTEs).[14-18]

CONCLUSION

This case highlights the evolving biology of recurrent ovarian cancer under therapeutic pressure and underscores the necessity of continuous molecular profiling and tailored therapeutic strategies. Understanding resistance mechanisms and advancing innovative treatments are critical to improving outcomes in therapy-resistant ovarian cancer. This case serves as a reminder that ovarian cancer, particularly with BRCA mutations, is a dynamic disease that requires continual adaptation in treatment plans to achieve optimal outcomes.

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