Mechanisms of PARP inhibitor resistance in ovarian cancer

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Purpose of review
To summarize recently discovered PARP inhibitor resistance mechanisms and highlight the clinical relevance of these findings to date.

Recent findings
A predominant mechanism of acquired PARP inhibitor resistance in homologous recombination-deficient cancers is the acquisition of homologous recombination proficiency as a consequence of secondary genetic or epigenetic events, such as secondary mutations in BRCA1 or BRCA2, or reversal of BRCA1 promoter methylation that restores homologous recombination and leads to PARP inhibitor resistance. Multiple other potential mechanisms of acquired resistance to PARP inhibitors including loss of DNA end resection inhibition (53BP1/REV7/RIF1/Sheldin) or DNA replication fork protection (PTIP/EZH2), but also increased drug efflux or induction of a reversible senescent or mesenchymal cell state have been described in ovarian cancer models. However, only few of these mechanisms have been identified in clinical samples.

Summary
Multiple adaptive responses following PARP inhibitor treatment have been identified. Further research is needed to better understand what role these mechanisms play for clinical PARP inhibitor resistance and how these mechanisms may render ovarian cancer cells susceptible to subsequent novel combination therapies.

Keywords
homologous recombination deficiency, ovarian cancer, polyadenosine diphosphate ribose polymerase inhibitors, resistance mechanisms

INTRODUCTION

Polyadenosine diphosphate (ADP) ribose polymerase (PARP) inhibitors have been approved by the US Food and Drug Administration (FDA) for the treatment of patients diagnosed with recurrent ovarian, primary peritoneal, and fallopian tube cancer who have received previous lines of chemotherapy and as maintenance therapy for patients with recurrent epithelial ovarian, fallopian tube, or primary peritoneal cancer who achieved complete or partial response to platinum-based chemotherapy. In 2019, olaparib also received FDA approval for use as a maintenance therapy after front-line chemotherapy for patients with a BRCA1 or BRCA2 mutations. In October 2019, new data were reported at the European Society for Medical Oncology (ESMO) meeting on three clinical trials that may lead to approval of additional ovarian cancer front-line treatment strategies. The PRIMA study evaluated platinum-based chemotherapy followed by niraparib maintenance, regardless of BRCA mutation status [1▪▪]. The VELIA study evaluated platinum-based chemotherapy with veliparib followed by veliparib maintenance, regardless of BRCA mutation status [2▪▪]. The PAOLA-1 study evaluated platinum-based chemotherapy with bevacizumab followed by bevacizumab with olaparib maintenance [3▪▪]. All three studies demonstrated very promising results that may lead to approval of additional strategies in front-line therapy of ovarian cancer including use of niraparib, veliparib and bevacizumab with olaparib as maintenance therapy.

However, despite these successes, the potential of PARP inhibitors in the management of all ovarian cancer patients is mitigated by the fact that ovarian

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KEY POINTS

- The successes of PARP inhibitors are mitigated by the fact that nearly all patients with initial sensitivity to PARP inhibition develop resistance over time.
- Acquisition of homologous recombination proficiency as a consequence of secondary genetic or epigenetic events that restores homologous recombination leads to PARP inhibitor resistance.
- Multiple other mechanisms of acquired resistance including loss of DNA end resection inhibition, DNA replication fork protection, increased drug efflux or induction of senescence or EMT have been described.
- Further research is needed to better understand what role these mechanisms play for clinical PARP inhibitor resistance.

cancers with intrinsic homologous recombination DNA repair proficiency do not respond as well as homologous recombination-deficient cancers [1▪▪–3▪▪]. Additionally, responses to PARP inhibitors are all too frequently transient in homologous recombination-deficient cancers and ultimately nearly all patients with initial sensitivity to PARP inhibition develop resistance to PARP inhibition over time [1▪▪–3▪▪].

The current review summarizes recently discovered resistance mechanisms and highlights the clinical relevance of these findings to date.

REVERSION MUTATIONS

PARP is an enzyme family that posttranslationally modifies its target proteins by conjugating polymeric chains of ADP-ribose (PARylation) during a number of cellular processes including DNA repair of single-stranded DNA breaks. PARP inhibitors demonstrate synthetic lethality in ovarian cancer cells with homologous recombination deficiency and clinical efficacy has been shown for ovarian cancers harboring deleterious germline or somatic BRCA mutations as well as in those that display a BRCA-like phenotype [1▪▪,2▪▪,3▪▪].

A key resistance mechanism to platinum-based chemotherapies and PARP inhibitors in *BRCA*-mutant cancers is the acquisition of *BRCA* reversion mutations that restore protein function. Reversion mutations are somatic base substitutions or insertions/deletions that are typically close to the primary protein-truncating mutation and restore the open reading frame of the gene and functional protein, switching the neoplastic cell from homologous recombination-deficient to proficient [4–6]. Reversion mutations in multiple homologous recombination pathway genes, including *BRCA1, BRCA2, RAD51C, RAD51D*, and *PALB2*, have been reported in ovarian, prostate, and breast carcinomas as a mechanism of acquired resistance to platinum-based chemotherapies and PARP inhibitors [7–12]. Recent studies have identified somatic *BRCA* reversion mutations in circulating cell-free DNA (cfDNA) in germline *BRCA* mutation carriers with ovarian cancer [13,14]. Moreover, a recent study also identified reversion mutations in cfDNA patients harboring somatic BRCA mutations [15▪]. Interestingly, these studies have shown polyclonality of multiple reversion mutations in a single patient illustrating the profound selection pressure of these tumors to restore BRCA protein activity and overcome PARP inhibitor sensitivity.

HYPOMORPHIC BRCA PROTEINS AND BRCA ALTERNATIVE SPLICING ISOFORMS

It is unclear whether all pathogenic *BRCA1* mutations have similar effects on the response to therapy. For example, mutations in the BRCT domains of BRCA1 often prevent proper protein folding, and misfolded proteins are subject to protease-mediated degradation [16–18]. Under PARP inhibitor selection pressure, the HSP90 protein interacts with and stabilizes mutant BRCA1 proteins. The stabilized C-terminal-truncated BRCA1 protein is semifunctional and retains the protein domains necessary to mediate interactions with PALB2–BRCA2–RAD51 [19,20]. Importantly, the mutant BRCA1 protein is capable of promoting RAD51 loading onto DNA following DNA damage and maintains a partial BRCA1 function under PARP inhibitor selection pressure [21].

Further, genetically engineered mouse models mimicking the two most common *BRCA1* founder mutations, *BRCA1 (185delAG)* and *BRCA1 (5382insC)*, suggest that some N-terminal BRCA1 mutations may have some residual activity in DNA damage response. These studies in mice show that both mutations predisposed animals to mammary tumors. However, *BRCA1 (185delAG)* tumors responded significantly worse to homologous recombination-targeted therapy than the *BRCA1 (5382insC)* tumors. *BRCA1 (185delAG)* tumor cells produce a RING-less BRCA1 protein. In preclinical experiments this RING-less structure led to PARP inhibitor resistance through its residual activity in the DNA damage response pathway by activating RAD51 [22]. Nevertheless, further validation of these findings in clinical samples will be required to further substantiate the clinical significance of RING-less BRCA1 proteins and the development of PARP inhibitor resistance.

Additionally, BRCA1 mRNA isoforms generated by alternative splicing that lack specific exons may