The role of PARP inhibitors in ovarian cancer: therapeutic mechanisms and clinical data

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Ovarian cancer is the most lethal gynecologic cancer with a high rate of recurrence. Poly(ADP-ribose) polymerase inhibitors (PARPis) are the most active therapeutic options available for patients with recurrent epithelial ovarian cancer. The treatment is based on the mechanisms of synthetic lethality and PARP trapping, especially in cancer patients with deficiencies associated with homologous recombination (HR) including cancer with BRCA mutations. The treatment is associated with high survival rates. Our review highlights the role of BRCA 1/2 mutations in tumorigenesis. We further discussed the recent clinical data of PARPis including olaparib, niraparib and rucaparib in ovarian cancer. However, resistance to PARPis is an emerging problem, and several resistance mechanisms are significantly associated with alternating drug availability, affecting the PARylation enzyme, restoring HR or replication fork stability. PARPis represent emerging and interesting therapies for recurrent epithelial ovarian cancer.

Keywords

BRCA mutation; PARP inhibitor; Homologous recombination; Synthetic lethality; Ovarian cancer

1. Introduction

Ovarian cancer constitutes 2.5% of all female malignancies, with a poor survival rate of approximately 5% due to the high rate of cancer death [1]. The five-year survival rate of advanced-stage ovarian cancer was only 29.2% [2]. Treatment of ovarian cancer therefore is a challenge in the United States (US). Epithelial ovarian cancer is especially lethal and most patients present in advanced stages [2]. Despite standard first-line chemotherapy, most patients experience disease recurrence with a median progression-free survival (PFS) of 18 months [3]. Despite advances in surgical cytoreduction and adjuvant cytotoxic chemotherapy, more than 70% of these patients will relapse with limited therapeutic options subsequently [3].

Recent insights into the molecular biology of cancer significantly increased the focus on genetic pathways predicting response to targeted therapy. Thus, the profound understanding of oncogenesis and therapeutic strategies suggest several target therapies as novel therapeutic options for ovarian cancer [4].

Poly (ADP-ribose) polymerase (PARP) inhibitors (PARPis) are small molecule inhibitors of PARP enzymes playing a crucial role in DNA repair of single-stranded breaks (SSBs) via base excision repair (BER) pathway [5]. The standard therapy for epithelial ovarian cancer is based on clinical data, which significantly improved the PFS and tolerability [6].

Breast Related Cancer Antigen (BRCA) 1 and BRCA 2 are two key tumor suppressors associated with DNA repair of double-stranded breaks (DSBs) via homologous recombination (HR) repair pathway [7]. PARPis provide significant therapeutic benefits in patients with BRCA 1/2 mutations by increasing the cumulative DNA damage, resulting in cell-cycle arrest and apoptosis. Thus, the BRCA mutations are thought to be powerful molecular indicators of sensitivity to PARPi therapy. PARPis are now approved by the European Medicines Agency (EMA) and the US Food and Drug Administration (FDA) in both therapeutic and maintenance settings for relapsed ovarian cancers, and has gained widespread adoption [8].

This review summarizes the molecular roles of PARP enzyme in DNA repair pathways and mechanisms of action underlying several PARPis in cancer cells with BRCA 1/2 mutations. Clinical trials of various PARPis in patients with relapsed ovarian cancers are also described. Further insights into the mechanisms of resistance to PARPis are provided.

1.1 DNA repair pathway, BRCA and PARP

Human genome is constantly influenced by various internal and external elements of stress resulting in DNA damage mediated via lesions such as SSBs and DSBs. As mentioned above, BER is the major SSB repair mechanism. DSB repair is mostly mediated via two main SSB repair mechanisms including homologous repair (HR) as a high-fidelity system and non-homologous recombination end-joining (NHEJ) as another rapid and error-prone pathway [9, 10]. Defective SSB repair leads to DSBs due to abnormal DNA replication. Under this condition, two different pathways including HR and NHEJ for DSB repair are activated to repair the DNA lesions (Fig 1).

BRCA genes 1 and 2 are essential for DSB repair via HR pathway [11]. However, the functional loss of BRCA 1/2 interrupts HR and DSB repair, leading to activation of NHEJ. The error-prone pathway NHEJ does not lead to effective re-
Table 1. PARP inhibitors used to treat ovarian cancer: a summary of clinical data.

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OC, ovarian cancer; PFS, progression-free survival; BRCA, BReastCaNCer gene; HR, homologous recombination; HGSOC, high grade serous ovarian carcinoma; HGEOC, high grade endometroid ovarian carcinoma; OR, overall response rate; wt, wild type; HRD, homologous recombination deficiency; ITT, intent-to-treat.
pair of DSBs in the tumor cells. Thus, tumor cells carrying BRCA1/2 mutations tend to be HR-deficient and exhibit genomic instability.

PARP plays an important role in DNA repair and genomic integrity [12]. PARP-1 is the most important of the 18 members belonging to the identified PARP family, and plays a dominant role in DNA repair. PARP is associated with SSB repair via BER pathways, by binding DNA at the location of the excised base. It also plays a role in re-initiating the stalled DNA-fork replication and BRCA1/2-mediated HR. Several data suggest that PARP also regulates DSB repair.

![Fig. 1. DNA repair mechanisms in cells.](image)

Effective repair of SSBs is crucial for tumor cell survival. Unrepaired SSBs are converted to DSBs, which are lethal to cells. Homologous repair is one of the DSB repair mechanisms during cell replication. HR-proficient cells enable effective repair of DSBs from SSBs leading to cell survival. No DSB repair occurs in HR-deficient cells, thereby resulting in cell death.

1.2 PARP inhibition and synthetic lethality

PARPis induce the accumulation of unrepaired SSBs and stalled DNA replication forks by trapping PARP at the SSB via formation of PARP-DNA complex and interrupting the progression of DNA replication [13]. The stalled DNA replication forks remain unrepaired and are converted to DSBs, which are lethal to cells. The accumulation of DSB ultimately results in cell death via apoptosis. PARP trapping via PARP-DNA complexes interfering with DNA replication is an important factor contributing to the cytotoxic activity of PARPis [14–16]. Thus, cancer cells lacking the ability to repair DSBs due to BRCA 1/2 mutation are more sensitive to PARPis (Fig. 2).

Isolated BRCA 1/2 mutations or PARP inhibition in the cell are not deleterious; however, their concomitant activity results in lethal outcomes. This phenomenon is known as “synthetic lethality” as a potential cause of cell death, due to the combination of two events such as BRCA mutations and PARP inhibition [17–19]. PARP inhibition has been investigated in BRCA 1/2 wild type as well as in mutant tumor cells. The mutant cells exhibit nearly 1000-fold increased sensitivity due to “synthetic lethality” compared with BRCA wild-type tumor cells.

1.3 PARP inhibitors

1.3.1 Olaparib

Olaparib is a PARPi, used in maintenance therapy of ovarian cancer, based on several phase III randomized-controlled trials. The anti-tumor activity of PARPis is associated with platinum sensitivity [20]. Thus, tumors deficient in DNA repair are expected to be highly sensitive to both platinum and PARPi. Clinical data mainly focus on PARPi maintenance therapy in patients with ovarian cancer who respond to platinum-based chemotherapy (Table 1).

A randomized placebo-controlled, phase II study investigated the clinical impact of olaparib as maintenance therapy in patients with recurrent, platinum agent-sensitive relapsed ovarian cancer [21]. The results showed that PFS was significantly improved in ovarian cancer patients with BRCA 1/2 mutations with a median PFS of 8.4 months versus 4.8 months (hazard ratio [HR], 0.35; 95% confidence Interval [CI], 0.25–0.49; P < 0.001). Moreover, the BRCA mutation status significantly improved PFS in patients carrying mutant BRCA receiving olaparib therapy compared to placebo (11.2 vs. 4.3 months; HR, 0.18; P < 0.0001). Similar results were found in a proportion of patients without BRCA mutations, who may also benefit from olaparib treatment (PFS, 7.4 vs. 5.5 months; HR, 0.54; P = 0.0075). However, no significant overall survival (OS) benefit was observed.

The SOLO-2 is a double-blind, randomized phase III study of maintenance therapy using olaparib in platinum agent-sensitive, relapsed ovarian cancer patients with BRCA 1/2 mutations treated with at least two lines of previous chemotherapy [22]. Two hundred ninety-five patients with BRCA 1/2 mutation were randomly allocated to receive olaparib (n = 196) or placebo (n = 99). Patients carrying germline BRCA mutations showed a significant improvement in PFS...
when treated with olaparib than placebo. The median PFS in the olaparib group was 19.1 months compared with 5.5 months in the placebo group (HR, 0.30; 95% CI, 0.22–0.41; \( P < 0.0001 \)). This finding may suggest that olaparib is a second-line therapeutic option for maintenance therapy among patients receiving platinum-based chemotherapy, in spite of BRCA mutation status.

Recently, PAOLA-1 trial demonstrated the beneficial role of maintenance therapy using the combination of olaparib and bevacizumab in women with newly diagnosed advanced ovarian cancer carrying a BRCA mutation in a randomized phase III study \[23\]. Of the 806 patients who underwent randomization, 537 were assigned to receive olaparib and 269 received placebo. After a median follow-up of 22.9 months, PFS was 22.1 months with olaparib plus bevacizumab versus 16.6 months with placebo plus bevacizumab (HR, 0.59; 95% CI, 0.49–0.72; \( P < 0.001 \)). In patients with advanced ovarian cancer receiving first-line standard therapy including bevacizumab, the addition of maintenance olaparib extended the PFS.

In the recent ongoing SOLO-3 study, olaparib was compared with chemotherapy only in patients with advanced ovarian cancer carrying germline BRCA mutations and previously treated with two or more previous chemotherapy regimens \[1\]. The results demonstrated a superior objective response rate of 72% in the olaparib group compared with 51% in the chemotherapy group. The median PFS was 13.4 months and 9.2 months in the two groups, respectively.

### 1.3.2 Niraparib

Niraparib is a potent and selective inhibitor of PARP-1 and 2. It is primarily metabolized by carboxylesterase to form a major inactive metabolite, which subsequently undergoes glucuronidation. It was approved by the FDA in 2017 for maintenance therapy of patients with recurrent ovarian cancer who showed complete or partial response to platinum-based chemotherapy.

ENGOT-OV16/NOVA is a randomized phase III study comparing niraparib with placebo as maintenance therapy in patients with recurrent ovarian cancer undergoing two or more lines of previous platinum-based chemotherapy \[24\]. Patients were separated according to their germline BRCA mutation status (gBRCA and non-gBRCA cohorts) and the type of non-gBRCA mutation, and were randomly allocated in a 2 : 1 ratio to receive niraparib (300 mg) or placebo once daily. The primary end point was PFS.

The gBRCA cohort included 203 out of 553 patients, including 138 assigned to niraparib and 65 to placebo, and the non-gBRCA cohort included 350 patients (234 assigned to niraparib and 116 to placebo). The median PFS in the niraparib group was superior to that of the placebo group (21.0 vs. 5.5 months in the gBRCA cohort [HR, 0.27; 95% CI, 0.17–0.41], 12.9 vs. 3.8 months in the non-gBRCA cohort of patients with HR deficiency [HR, 0.38; 95% CI, 0.24–0.59], and 9.3 vs. 3.9 months in the overall non-gBRCA cohort [HR, 0.45; 95% CI, 0.34–0.61; \( P < 0.0001 \) for all the three comparisons]). The data demonstrated a significantly higher PFS in the niraparib group than in the placebo group, in spite of gBRCA mutations or HR deficiency in patients with platinum-sensitive, recurrent ovarian cancer.

In QUADRA, a multicenter, phase II study, the safety and activity of niraparib were evaluated in patients with recurrent gynecological cancer treated with three or more prior therapeutic regimens \[25\]. Niraparib monotherapy in the delayed therapy setting yielded an overall response rate (ORR) of 27.5%, a disease control rate of 68.5%, and response duration of 9.2 months.

### 1.3.3 Rucaparib

Rucaparib is a potent PARPi, approved by FDA and EMA for treatment as a single agent in high-grade ovarian carcinoma (HGOC) patients carrying BRCA mutations relapsing after at least two chemotherapy lines.

Study 10 provides clinical data for the investigation of oral rucaparib \[26\]. The phase I was designed to determine the recommended phase II dose (RP2D) of rucaparib and to explore the preliminary efficacy. In phase I, RP2D was established at 600 mg bid. Meanwhile, a phase II study was performed to determine ORR in patients with platinum-sensitive HGOC associated with gBRCA1/2 mutations managed via two or more previous treatments. The phase II data showed an ORR of 59.5% and a median duration of response of 7.8 months in 42 patients with platinum-sensitive HGOC with gBRCA mutations. Further, rucaparib was found to be tolerable and effective in HGOC patients with platinum-sensitive gBRCA1/2 mutations.

ARIEL-2 study is a phase II trial designed to evaluate the clinical impact of rucaparib in relapsed HGOC or endometroid ovarian cancer after one or more therapeutic regimens \[27\]. In ARIEL-2 Part 1, recurrent, platinum-sensitive, HGOC patients were separated into one of three HR deficiency groups according to mutations: BRCA mutation (BRCam, \( n = 40 \)), BRCA wild-type and LOH high (BRCAwt/LOH high, \( n = 82 \)), or BRCA wild-type and LOH low (BRCAwt/LOH low, \( n = 70 \)). The BRCam group (HR, 0.27; 95% CI, 0.16–0.44; \( P < 0.0001 \)) and BRCAwt/LOH high (HR, 6.2; 95% CI, 4.2–9.0; \( P = 0.011 \)) showed a significantly longer PFS than the BRCAwt/LOH low group (5.2 months). Rucaparib treatment in patients with BRCam or BRCAwt/LOH high platinum-sensitive OC was more effective for PFS than in patients with BRCAwt/LOH low cancer. LOH as a molecular biomarker was used to identify patients with BRCAwt platinum-sensitive OC treated with rucaparib.

The phase III ARIEL-3 study evaluated the efficacy of rucaparib as maintenance treatment in patients with platinum-sensitive, relapsed HGOC, endometrioid ovarian fallopian and primary peritoneal cancers undergoing at least two previous platinum-based chemotherapies \[28\]. The enrolled 564 patients were randomized to rucaparib (\( n = 375 \)) or placebo (\( n = 189 \)). The PFS was investigated as the primary end-
point in three nested cohorts: patients with BRCA mutation (BRCAm), patients with HR deficiencies (BRCAm or BRCA wild-type and high loss of heterozygosity), and the intention-to-treat (ITT) population. In the subgroup with BRCAm, the median PFS in rucaparib group \( (n = 130) \) was 16.6 months compared with 5.4 months in the placebo group \( (n = 66) \) (HR, 0.23; 95% CI, 0.16–0.34; \( P < 0.0001 \)). In the subgroup with HR deficiency, the PFS was 13.6 months in the rucaparib group versus 5.4 months in the placebo \( (n = 118) \) (HR, 0.32 95% CI, 0.24–0.42; \( P < 0.0001 \)). In ITT population, it was 10.8 months versus 5.4 months (HR, 0.36 95% CI, 0.30–0.45; \( P < 0.0001 \)). Rucaparib significantly improved PFS in patients with platinum-sensitive ovarian cancer, who were responsive to platinum-based chemotherapy.

1.4 Resistance mechanism of PARP inhibition

Although PARPi have a significant therapeutic effect on HR-deficient cancers, several clinical data focused on drug resistance equivalent to the efficacy. Because drug resistance is a challenge in patients undergoing repetitive treatment, understanding the resistance mechanisms of PARP inhibition is important for early and effective prevention of drug resistance in patients.

Recently, various resistant mechanisms to PARPi were described including HR restoration, influence of replication fork protection and upregulation of drug efflux pump (p-glycoprotein, Pgp).

HR restoration is the most common acquired resistance mechanism to PARPi. Truncated genetic reversion of BRCA 1/2 genes is the most accepted mechanism of resistance underlying PARP inhibition. The reversal of critical HR genes including BRCA 1, 2 and RAD51D and RAD51C was reported in drug-resistant tumor cell models [29–33]. Further, HR was restored to increase the activity of downstream effector molecules without BRCA mutations. Johnson et al. showed that PARPi-resistant clones restored RAD51 as a critical step in HR function downstream of BRCA 1 [34]. Another resistance mechanism involves loss of P53-binding protein 1 (53BP1), a nuclear protein playing an important role in maintaining the balance between HR and NHEJ. Other data showed that 53BP1 was a key player in NHEJ, and induced resistance to PARP inhibition in mouse mammary tumor cells with BRCA 1 mutation [35]. Another study reported that 53BP1 loss-induced HR restoration depends on hypomorphic BRCA 1 proteins to achieve PARPi resistance [36]. It is assumed that loss of 53BP1 is significantly linked to resistance to PARP inhibition.

BRCA 1/2-deficient tumor cells develop therapeutic resistance to PARPi via pathways protecting the replication forks. Some studies reported the crucial roles of BRCA 1 and 2 and Fanconi anemia-associated proteins in protecting the replication forks [37, 38]. Importantly, previous studies showed that BRCA 1 cells were resistant to PARPi by reducing the recruitment of nuclease, MRE11 [39]. Reduced MRE11 recruitment correlated with improved replication fork stability.

The final resistance mechanism is pharmacological and mediated via multidrug efflux transporters such as Pgp. Pgp is encoded by the MDR1 gene, and upregulation of Pgp expression is a known mechanism of resistance to chemotherapy [40, 41]. The increased expression of Pgp and the resulting elevation in drug efflux rate diminish the intracellular therapeutic effect of PARPi in BRCA 1/2 mutant cancers.

2. Discussion

Approximately 50% of cases diagnosed with ovarian cancer are characterized by defective DNA repair via HR, which has important implications for disease management [42]. BRCA mutations are the most common molecular phenomenon associated with HR deficiency, and other mechanisms are linked to mutations in ovarian cancer. The extraordinary efficacy of PARPi in patients with ovarian cancer with HR deficiency is maximized by synthetic lethality. PARPi are approved as molecular targeted therapies.

Before PARPi inhibitors, bevacizumab was used only as an efficient maintenance therapy for ovarian cancer [43–45]. However, the SOLO-2 study showed that the PFS was improved to 15 months [22]. SOLO-1 also showed that the PFS was further improved to 3 years [46]. A recent study using real-world data also demonstrated that the median PFS in the real-world trials of olaparib ranged from 12.7 to 15.6 months [47].

In 2014, olaparib was first approved in the European Union (EU) as a maintenance therapy for patients with platinum-sensitive, recurrent BRCA1/2-mutated HGOC [48]. Meanwhile, rucaparib was first approved in the USA for the treatment of ovarian cancer patients with g/sBRCA mutations treated with two or more prior chemotherapy regimens and as a maintenance therapy for adult patients with recurrent ovarian cancer [49]. Moreover, niraparib was approved in the USA as maintenance therapy for patients with recurrent ovarian cancer who responded to platinum-based therapy [50]. Thus, the PARPi in EU are used only to treat patients with platinum-sensitive, relapsed HGOC. Rucaparib is used as a third-line therapy in BRCA mutation-associated ovarian cancer. Meanwhile, olaparib and niraparib are used only as maintenance therapy. In the US, olaparib is used as the fourth-line therapy for advanced ovarian cancer with BRCA1/2 mutations, maintenance therapy for recurrent ovarian cancer and first-line maintenance treatment for newly-diagnosed, BRCA1/2-mutated advanced ovarian cancer. Rucaparib is used as both a third-line therapy for BRCA1/2 mutation-associated ovarian cancer and as a maintenance therapy for recurrent ovarian cancer. Niraparib is used only as maintenance therapy for recurrent ovarian cancer.

However, PARPi such as olaparib, rucaparib and niraparib are characterized by similar efficacy in maintenance setting for patients with platinum-sensitive ovarian cancer. Thus, the adverse effects (AEs) of each agent need to be identified. Olaparib increases the serum levels of creatinine in about 44% of patients. Meanwhile, rucaparib has been shown
to elevate liver enzymes in 75% of patients while nearly 30% of those receiving niraparib exhibited grade 3/4 thrombocytopenia [51].

Deficiencies of DNA repair are common in cancers. Combinations of other DNA repair-targeting treatments need to be further investigated to overcome the resistance associated with PARPi monotherapy. Currently, PARPis combined with immunotherapy significantly increase the efficacy against cancers compared with combinations of other targeted drugs. Combining PARPis and targeted agents such as CDK1, CDK12, PI3K, AKT, WEE1, CHK1, and HSP90 inhibitors may have a deadly effect against tumor cells via synthetic lethality interaction [52]. Recent data showed that BRD4 inhibitor and PARPi showed synergic therapeutic effect in several types of cancer [53]. Other data showed that combining BET inhibitor with PARPi reversed drug resistance in BRCA 1/2 wild-type ovarian cancer [54]. Moreover, as PD-L1 is one of the major inhibitory ligands associated with evading tumor cells in host immune system, the combined therapy of PARPi with anti-PD-L1 antibody was more effective than monotherapy both in vivo and in vitro [55]. Another potential target for immunotherapy is cytotoxic T-lymphocyte associated protein 4 (CTLA-4). Combination of PARPis and anti-CTLA-4 antibody enhances long-term systemic T-cell immunity. Recent data showed that PARPis directly induce tumor cell damage and the anti-tumor T cell response is amplified by CTLA-4 blockade [56, 57].

PARPis are the first approved agents targeting DNA damage repair in patients with ovarian cancer. Close monitoring is required for clinical applications using PARPis. Moreover, combination therapy should be considered to overcome drug resistance of PARPi monotherapy. As additional data accumulate, we hope that precision medicines will be available for patients with ovarian cancer.

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MKS analyzed previous data and wrote the paper.

Ethics approval and consent to participate
Not applicable.

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