Commentary

Overcoming resistance to PARP inhibitor in epithelial ovarian cancer, are we ready?

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Poly(ADP-ribose) polymerase (PARP) inhibitors (PARPi) exploit BRCA mutations and DNA damage response (DDR) deficiencies. Inhibition of PARP leads to propagation of single-strand DNA breaks and accumulation of double-strand breaks, which require homologous recombination (HR) repair mechanisms. PARP inhibitors were initially developed as maintenance therapy in patients with sustained complete or partial response after platinum-based chemotherapy for recurrent epithelial ovarian cancer (EOC). The remarkable improvement in PFS in three randomized phase III trials — SOLO-2, NOVA and ARIEL3 \(^{1–3}\) — led to regulatory approval of olaparib, niraparib and rucaparib, respectively, as maintenance therapy for platinum-sensitive recurrent ovarian cancer, regardless of biomarker status. After the success of PARPi in relapse, the PARPi jumped into 1st line therapy as maintenance therapy. In Solo1, olaparib demonstrate selective activity in ovarian cancer patients with germline or somatic BRCA1/2 mutations \(^4\). In 2019, 3 other international randomized clinical trials (PAOLA-1, PRIMA, and VELIA) \(^{5–7}\) reported efficacy of PARPi (alone or in combination) as maintenance 1st line therapy irrespective of BRCA1 mutation status.

Although all the four trials were in the front-line setting and used PFS as primary end point, no head-to-head comparison was possible because of their considerable differences, particularly the control arms (placebo or bevacizumab), patient populations, and timing of PARPi initiation (concomitant with chemotherapy versus maintenance only). However, the 3 most recent publications have revealed new subgroups of patients beyond BRCA. The PARPi maintenance benefit was stronger for BRCA mutated and HR-deficient (HRD) tumors as compared to HR-proficient (so called HRD-negative) tumors. The HRD-negative subgroup benefits less also a significant hazard ratio was reported with niraparib maintenance (compared to placebo) whereas it was not significant with the combination Olaparib/bevacizumab (compared to bevacizumab alone). Unfortunately, as with platinum chemotherapy, many patients recur. There is consequently an urgent need to elucidate the mechanisms of PARPi resistance in EOC to improve patient stratification for therapeutic strategies that target molecular vulnerabilities to overcome treatment resistance.

A key resistance mechanism appears to be the restoration of the HR repair pathway, through BRCA reversion mutations and epigenetic upregulation of BRCA1. Alterations in non-homologous end-joining (NHEJ) repair, replication fork protection, upregulation of cellular drug efflux pumps, reduction in PARP1 activity and alterations to the tumor microenvironment have also been described. These resistance mechanisms reveal molecular vulnerabilities, which may be targeted to re-sensitize EOC to PARPi treatment. Promising therapeutic strategies include ATR inhibition, epigenetic re-sensitisation through DNMT inhibition, cell cycle checkpoint inhibition, combination with anti-angiogenic therapy and BET inhibition. In this article of EBioMedicine \(^8\), Goldie Yiu and colleagues focused on PARPi in combination with potential sensitizers as BET inhibitor (BETi, here inhibiting BRD4) plus or less dasatinib (a dual Src/Abl kinase inhibitor) and a combination of rucaparib plus BCL2 inhibitor (navitoclax\(^{5}\)) for patients with HR pathway mutations. They reported how BETi enhanced the effect of rucaparib irrespective of clinical subtype or HRD status, and adding dasatinib increased the effects of the doublet, proposing a potential triple-drug combination for high-grade serous (HGSC) and clear cell ovarian carcinomas (OCCC).

Bromodomains are small protein domains that recognize and bind to acetylated histone tails, change the chromatin structure, and lead to upregulation of target genes to drive oncogenesis. Inhibition of BRD4 shortcuts the communication between super-enhancers and target promoters with a subsequent cell-specific repression of oncogenes and subsequent cell death. To date, this is the most credited mechanism of action of BET inhibitors which are currently in clinical trials in several cancer settings \(^9\). However, recent evidence indicates that BRD4 relevance in cancer goes beyond its role in transcription regulation and identifies this protein as a keeper of genome stability. Indeed, a non-transcriptional role of BRD4 in controlling DNA damage checkpoint activation and repair as well as telomere maintenance has been proposed, throwing new lights into the
multiple functions of this protein and opening new perspectives on the use of BETi in cancer. The expression of BRD4 is often upregulated and predicts poor prognosis in HGSC patients. BRD4 inhibitor effectively prolonged tumor control in multiple patient-derived tumor xenograft models including HR proficient ovarian and breast cancers [10]. The current paper suggested that double and triple combinations between rucaparib, CPI-0610 (BRD4i), more or less dasatinib were effective for both HGSC and OCCC patients regardless of HRD status. Exploring several combinations with PARPi herein provide a good rationale for future efforts to assess the efficacy, tolerability, and toxicity of the proposed combinations in additional clinical trials.

These data increasing our capability to restore sensitivity to PARPi raise 2 important questions: (i) The need of careful assessment of dose intensity for each drug combination (both double and triple combinations), in addition to identification of optimal clinically tolerable dosing regimens for patients, and (ii) Identification of the best candidates for double or triple therapies including strong biomarkers and stratification. More particularly, do we have to consider to restore sensitivity (i.e patients already treated with PARPi but presenting a “secondary” resistance to parpi) or to treat subgroups of patients with initially low efficacy of PARPi (i.e HR proficient ovarian patients)? Based on the studies, patients who have ovarian cancers with different genetic backgrounds and histologies, as well as patients previously treated with PARPi, are likely to benefit from these approaches and to reveal the best candidates for the combination. The incorporation of translational research into the future clinical trials involving such new drugs would help to elucidate these mechanistic questions and will be our priority in the near future.

**Contributors**

IRC literature search, data analysis, data interpretation, writing; HV literature search, data interpretation, writing; OLS literature search, data interpretation, writing; OT literature search, data interpretation, writing

**Declaration of Competing Interest**

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