Comment on evolutionary dynamics of cancer multidrug resistance in response to olaparib and photodynamic therapy

Ainhoa Madariaga a,*, Lawrence Keshmeran b,c,d, Michelle McMullen e, Luisa Bonilla f

a Department of Medical Oncology, Breast and Gynecologic cancer unit, Hospital Universitario 12 de Octubre, Cordoba Avenue, Madrid 28041, Spain
b Department of Medical Oncology, St George Hospital, Kogarah, New South Wales, Australia
c St George and Sutherland Clinical Schools, University of New South Wales, Kogarah, New South Wales, Australia
d Department of Medical Oncology, Illawarra Cancer Care Centre, Wollongong, New South Wales, Australia
e Department of Medical Oncology, Sir Charles Gardiner Hospital, Nedlands, Western Australia, Australia
f Department of Medical Oncology, Health Science North, Sudbury, Ontario, Canada

Poly-ADP ribose polymerase (PARP) inhibitors have transformed the treatment landscape of patients with high grade serous and high grade endometrioid ovarian cancer [1]. Landmark phase III randomized trials assessing the role of PARP inhibitors—olaparib, niraparib, rucaparib, veliparib—as an oral maintenance strategy in the front-line and platinum sensitive recurrent setting, have demonstrated benefit in progression free survival without major differences in quality of life when compared to placebo [1]. More recently, long-term follow-up from SOLO-2 study (NCT01874353), demonstrated a benefit in overall survival with maintenance olaparib, compared to placebo, in patients with mutations in BRCA1/2 and a platinum sensitive relapse [2]. Despite this promising activity, ultimately the majority of patients with recurrent disease will develop resistance to PARP inhibitor therapy. Alterations in BRCA1/2 and other genes related to homologous recombination repair have emerged as biomarkers of response to PARP inhibition in ovarian cancer [1], but a current challenge includes the lack of accessible biomarkers to detect acquired resistance in individual patients and collectively. There is additionally unmet need for development of new drugs or combination strategies to overcome PARP inhibitor resistance.

Globally, three main mechanisms of PARP inhibitor resistance have been proposed: 1) Drug-target related mechanisms, including upregulations of drug-efflux pumps, 2) Restoration of homologous recombination, such as reversion mutations in BRCA1/2, and 3) Loss of DNA end protection and/or restoration of the replication fork (Fig. 1) [3,4]. Among the drug-target related mechanisms, upregulation of the ABCB1 pump, also called P-glycoprotein, reduces cellular drug availability, and is proposed to be a mechanism of acquired resistance to chemotherapy and PARP inhibition in ovarian cancer (Fig. 1). The frequency of upregulations in ABCB1 in pre-treated ovarian cancer is not well established and depends on prior therapy exposure, such as taxanes and PARP inhibitors [4]. Patch et al. performed whole genome sequencing in matched ovarian cancer samples (primary and recurrence) showing that 8% of recurrence samples harboured upregulations in ABCB1 [5]. Similarly, in a post-PARP inhibitor phase II clinical trial assessing the combination of olaparib and cediranib (an oral, small molecule selective vascular endothelial growing factor tyrosine kinase inhibitor) in patients with ovarian cancer previously treated with PARP inhibitors, 15% of the population presented with upregulations in ABCB1 at baseline [6]. Those with ABCB1 overexpression had comparatively poorer outcomes. Intriguingly, half of the patients with ABCB1 upregulation also harboured other resistance mechanisms, suggesting that multiple cellular pathways may contribute to acquired PARP inhibitor resistance [6].

Targeting ABCB1 in ovarian cancer is an intriguing strategy. In the manuscript accompanying this commentary, Baglo and colleagues propose that the combination of olaparib and photodynamic therapy (PDT) may be synergistic, and that PDT using a lipidated photosensitizer, which has reduced efflux through the ABCB1 pump, may be able to overcome drug-target related resistance to PARP inhibition in ovarian cancer [7]. PDT is purportedly able to activate photosensitizers within tumours to induce chemical damage and tumor death [8]. Single-agent PDT has a limited role in advanced ovarian cancer. However, combining PDT with current standard of care therapy may prove to be promising in managing multidrug resistance [8].

Baglo and colleagues assessed the combination of olaparib and PDT in ovarian cancer cell lines [7]. Two kinds of photosensitizers were used, the benzoporphyrin derivate (BPD) and its lipidated formulation. While BPD is a substrate of the ABCB1 pump, its lipidated formulation can reduce the BPD efflux and may help abrogate P-glycoprotein resistance [7,9]. In the study, two matched fluorescent high grade serous ovarian cancer cell lines were used to assess cell viability. The sensitive subline
PARP inhibition, and vulnerable to death given the synthetic lethality effect of blocking PARP.

2. DNA end protection loss and/or replication fork restoration, which may occur due to loss of nucleases recruitment and fork reversal degradation.

2B. Homologous recombination restoration, represented mainly by the acquired somatic mutations or epigenetic changes, restoring the function of homologous recombination proteins.

2C. Drug-target mechanisms, including diminishment of trapping of PARP and increase of the drug efflux. The former is secondary to the overexpression of the ABCB1 trans-membranal drug efflux pump. The PARP inhibitor is diffused into the cell, without the need of any mediator. The ABCB1 pump is overexpressed in the cell membrane, increasing the efflux of the PARP inhibitor, and reducing the intracellular PARP inhibitor concentration.

Fig. 1. Mechanisms of acquired PARP inhibitor resistance in ovarian cancer. 1. PARP enzymes are responsible for single strand break repairs in the DNA through base excision repair pathway. DNA double strand break repair is impaired in homologous recombination deficient (HRD) cells. The HRD cancer cells are sensitive to PARP inhibition, and vulnerable to death given the synthetic lethality effect of blocking PARP. 2. Acquired resistance to PARP inhibition is represented by: 2A. DNA end protection loss and/or replication fork restoration, which may occur due to loss of nucleases recruitment and fork reversal degradation. 2B. Homologous recombination restoration, represented mainly by the acquired somatic mutations or epigenetic changes, restoring the function of homologous recombination proteins. 2C. Drug-target mechanisms, including diminishment of trapping of PARP and increase of the drug efflux. The former is secondary to the overexpression of the ABCB1 trans-membranal drug efflux pump. The PARP inhibitor is diffused into the cell, without the need of any mediator. The ABCB1 pump is overexpressed in the cell membrane, increasing the efflux of the PARP inhibitor, and reducing the intracellular PARP inhibitor concentration.

As the indications for PARP inhibitors in ovarian cancer expand rapidly, a focus on drug development in the post-PARP space, particularly in the face of acquired drug resistance, is paramount. A rational re-sensitization approach seeks to exploit synergistic biology, particularly in patients where PARP inhibitors are likely to have ongoing therapeutic effect. Recent examples of such work include: the CAPRI trial (NCT03462342), which examined the combination of olaparib with ceralasertib, an ATR inhibitor, specifically in recurrent, platinum-sensitive homologous recombination-deficient ovarian cancer population [11]; and the EFFORT trial (NCT03579316), which was a randomized, non-comparative, two-arm phase II trial of adavosertib, a wee1 inhibitor, with or without olaparib in any recurrent high-grade serous ovarian cancer patients who had previously progressed on PARPi [12]. The robust preclinical work in PDT and ovarian cancer completed by Baglo and colleagues has the potential to translate to successful early-phase clinical trials – another important potential development to add to the armamentarium of therapeutics rationally designed to overcome PARP inhibitor resistance.

CRediT authorship contribution statement

Ainhoa Madariaga: Conceptualization, Writing – original draft, Writing – review & editing. Lawrence Kasherman: Writing – review & editing. Michelle McMullen: Writing – review & editing. Luisa Bonilla: Writing – review & editing.

Declaration of Competing Interest

AM has received honoraria from AstraZeneca. The rest of authors have no conflicts of interest to declare.
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