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Communication

PARP inhibition in ovarian cancer: what is still missing?

Matteo Morotti[1,2,*], Eleonora Ghisoni[1,3]

[1]Ludwig Institute for Cancer Research, Bâtiment AGORA, 1005 Lausanne, Switzerland
[2]Department of Gynecology, CHUV-Centre Hospitalier Universitaire Vaudois, 1011 Lausanne, Switzerland
[3]Department of Oncology, Immuno-Oncology Service, CHUV-Centre Hospitalier Universitaire Vaudois, 1011 Lausanne, Switzerland
*Correspondence: drmorottimatteo@gmail.com (Matteo Morotti)
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1. Introduction

The addition of anti-angiogenic agents (bevacizumab) and poly (ADP-ribose) polymerase inhibitors (PARPi) to chemotherapy following debulking surgery have represented a step-change in the management of newly diagnosed high-grade serous ovarian cancer (HGSOC) [1].

PARPi are drugs exploiting *BRCA* mutations and DNA damage response deficiencies [2]. Cells with defective *BRCA* proteins are deficient in repairing double-stranded DNA breaks by homologous recombination repair (HR) pathway and rely on the PARP pathway to repair these damages [2]. Thus, the inhibition of PARP in the presence of HR deficiency (HRD) leads to cell death due to a process called 'synthetic lethality' [2].

Approximately 50% of HGSOC are estimated to exhibit HRD [3]. Germline and somatic *BRCA1/2* mutations, *BRCA* gene promoter methylations, and inactivation of other genes such as RAD51C/D, CDK1/2, Fanconi anaemia genes, CDK12 are the main causes of HRD in HGSOC [3].

Since the preliminary phase II study suggesting a benefit from PARPi in relapsing platinum-sensitive HGSOC [4], these agents have been extended in all the settings of HGSOC treatment with four positive randomized trials investigating first-line maintenance therapy with PARPi in all comers advanced stages HGSOC between 2018 (SOLO-1) [5] and 2019 (PAOLA-1/ENGOT-OV25, VELIA/GOG-3005 and PRIMA/ENGOT-OV26 [4–6]).

Notably, the experience with PARPi in these trials demonstrated that their therapeutic effect extends beyond *BRCA* germline mutations, with a clear clinical benefit also seen in HRD patients.

Thus it is clear that the knowledge of both germline and somatic mutation status is becoming of paramount importance in the management of patients with HGSOC.

Despite the positive outcome results achieved in clinical trials, there are still several challenges to identify the optimal positioning of PARPi in the HGSOC treatment algorithms.

The identification of the correct population to treat, the selection of the right PARPi molecule, the optimal time-window of prescription of these drugs, and a better understanding of the mechanisms leading to PARPi resistance are crucial points that need to be addressed.

2. Genetic testing for *BRCA* and HRD

Since the arrival of PARPi in the clinic, genetic testing for *BRCA* germline mutations has been recommended for all women with non-mucinous epithelial ovarian cancer (EOC), as stated by multiple professional societies [7]. In addition to germline testing, tumour genetic profiling for somatic mutations (those mutations only present in the tumour) in the HR pathway has been implemented along with other independent DNA-based measures of genomic instability reflecting underlying tumour HRD such as (i) loss of heterozygosity (LOH), (ii) telomeric allelic imbalance (TAI) and (iii) large-scale state transitions (LST) [8].

The two most common commercially HRD assays are the myChoice® CDx (Myriad Genetics, USA) and the Foundation Medicine's FoundationFocus® CDx (Foundation Medicine, USA). The first combines the three metrics describe above with the classification of *BRCA1/BRCA2* (sequencing and large rearrangement) gene mutations.

The latter tests tumour DNA to detect *BRCA1/BRCA2* genes mutations and the percentage of the genome affected by LOH. Current guidelines recommending germline testing do not make specific recommendations regarding which available platform to utilize.

Unfortunately, these tests present some pitfalls that hampered their widespread use in clinical practice [9]. A discrete proportion of samples could return with an 'unknown' status, and there is a possibility of false negatives due to tumour heterogeneity and technical reasons. The high cost, unavailability/lack of access to testing, and difficulty in cross comparing the results between different assays are also important factors.

For example, in the PRIMA, PAOLA-1 and VELIA, the definitions of HRD positivity based on myChoice® test was defined with different cut-offs. Initially in the three trials an HRD score cut-off of >42 was used to determine HRD positivity. Later, in the VELIA trial, this was revised to >33 to increase the sensitivity of detecting a PARPi response. This difference in threshold might impact the reported prevalence of HRD status with important clinical consequences to accessing PARPi.

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Several academic groups are attempting to develop robust and cheaper HRD tests to identify these patients. Tumiati *et al*. [10] described a functional HRD test developed in EOC samples, which reliably predicted treatment response to PARPi and outperformed other clinical and pathological parameters. The test through the use of the signature 3 (Sig 3) and LOH was able to identify more HRD patients than available genetic screening kits. However, the multiple steps needed for the execution of this test (including culturing of primary cells, immunofluorescence and sequencing) hamper its availability beyond research purposes.

A sensible approach would be to derive an HRD signature by implementing available multigene panels from targeted sequencing. This would allow also the identification of targetable mutations beyond *BRCA*. Gulhan *et al*. [11] recently proposed a new method called Signature Multivariate Analysis (SigMA) for detecting Sig 3 (HRD-related) from targeted sequencing data of an individual tumour to be use in addition of *BRCA1/2* germline mutations. They *in-vitro* validated the method by assessing response to PARPi in cancer cell lines with or without Sig 3. The clinical validation of this method compared to available tests and its subsequent application could expand the number of patients that could benefit from PARPi by maintaining good accuracy and decreasing the costs.

3. Future combinational therapies

One current clinical challenge is to sensitize HR-proficient tumours to PARPi or to overcome PARPi resistance. This is the rationale behind a growing number of clinical trials exploring combination strategies with PARPi in HGSOC. Drugs showing promise in overcoming these mechanisms of resistance (extensively reviewed by Paes Dias *et al*. [12]) include suppression of alternative HR pathways and cell-cycle checkpoint signalling, and the implementation of immunotherapy. The mechanisms of resistance might be overall driven or by clonal selection of pre-existing drug-tolerant cells (genetic route) [13] or by the effect of the interplay of these HRD cells within the tumour microenvironment.

As of August 2021, 105 clinical trials on PARP inhibitors in EOC could be found in the ClinicalTrials.gov database, which are ongoing or completed with results yet to be published (https://clinicaltrials.gov/ct2/results?term=PARP&cond=Ovarian+Cancer&Search=Apply&recrs=a&recrs=f&recrs=d&age_v=&gndr=&type=&rslt=). Most of these studies focus on combination strategies with anti-angiogenic agents (including bevacizumab), targeted agents such as drugs disrupting cell-cycle or alternative DNA repair pathways and/or immunotherapy agents.

The DNA damage response can regulate both DNA repair and cell cycle arrest. The emerging role of cell-cycle cyclin-dependent kinases in HRR suggests that inhibition of these pathways be synthetically lethal with PARP inhibitors by inducing an HRD phenotype. Several studies have since shown that ATR, CHK1 and WEE1 inhibitors can sensitize *BRCA*-wild-type and PARP inhibitor-resistant cells to PARP inhibitors [14]. Similarly, suppression of alternative HR pathways such as PALB or RAD52 might be interesting strategies to overcome PARPi resistance [12].

A strong interplay link the immune system, DNA damage in cancer cells, and inflammation in the tumour microenvironment. HR-deficient cancers have an increased tumor mutational burden (TMB), which could possibly result in increased abundance of tumour-specific neoantigens, which can then increase immune cell infiltration [15,16]. PARP inhibition leads to the accumulation of DNA damage in cancer cells, thus triggering the STING/interferon pathway, an important mediator of systemic immune response, that induces the activation of several immune cell types [17]. Data from multiple preclinical studies showed that PARP inhibition enhances the antitumour effects of anti-PD-1 antibodies in mouse models of HGSOC [18–20]. Several ongoing clinical trials are evaluating the impact of this combination in ovarian cancer (OC) patients (reviewed in detail elsewhere [21]).

In germline *BRCA1/2* patients, the phase II basket study (MEDIOLA) evaluated the combination of durvalumab (anti-PD-L1) and olaparib in 32 patients with recurrent platinum-sensitive HGSOC (21). The PARP and PD-L1 inhibition combination showed an overall response rate (ORR) of 63% (6 CR and 14 PR) and a 12-week disease control rate (DCR) of 81%. The larger TOPACIO trial showed more modest results with the combination of pembrolizumab (anti-PD-1) and niraparib in ovarian and triple-negative breast tumours with *BRCA* mutations vs. wild-type *BRCA1/2* (35). Across all 60 patients, there was an ORR of 25% and a DCR of 68% [21]. Ongoing trials, such as the ATHENA trial, are evaluating the use of nivolumab (anti-PD-1) and rucaparib as maintenance therapy following response to upfront platinum-based therapy in stage III/IV OC (NCT03522246).

A rational combination of PARPi is with the antiangiogenic drug bevacizumab. We recently showed that in HGSOC with *BRCA* mutation and active IFNγ signalling, STING not only drives T-cell inflammation but also promotes tumour angiogenesis through intrinsic overexpression of VEGF-A, a known molecule mediating angiogenesis and tumour immune escape [16]. This evidence partially explains the reported benefit of combining PARPi and bevacizumab in *BRCA1*-mutated and HRD tumours but not in HRP tumours [4], and it has important implications for ongoing clinical studies testing the combination of PARPi, immune checkpoint inhibitors, and bevacizumab in HGSOCs. The ongoing AVANOVA trial (NCT02354131) and OVARIO study (NCT03326193) showed interesting results, with the latter demonstrating a 6-month PFS rate of 89.5% for the maintenance combination of niraparib plus bevacizumab in primary HGSOC.

In conclusion, PARP inhibitors have changed the landscape of EOC treatment. However, several issues, both from a pre-clinical and a clinical point of view, still hamper the full potential of these drugs. First of all, it becomes obvious that not only germline *BRCA* status but also HRD status is relevant for treatment decision-making for newly diagnosed HGSOC and is important for accessing these drugs. However, the accuracy and reliability of currently available tests leave room for improvement, and the development of more robust and more large-scale accessible tests is a priority. Secondly, escalation of PARPi to front-line management of patients with newly diagnosed advanced disease has raised several questions about the sequence of following treatments. The recent OReO trial data presented at ESMO 2021 showed positive results regarding the possibility to re-challenge PARPi after PARPi exposure in platinum-sensitive EOC.

Finally, PARPi plus anti-angiogenic drugs and/or immunotherapy combination could represent a novel combinatorial treatment option that might benefit the HGSOC patients in first-line setting.

Author contributions

Conceptualization—MM; Writing—MM, EG. All authors contributed to editorial changes in the manuscript. All authors read and approved the final manuscript.

Ethics approval and consent to participate

Not applicable.

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Conflict of interest

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