European Journal of Gynaecological Oncology

Review

BRCA-guided therapy of ovarian cancer

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DOI:10.31083/j.ejgo.2021.03.2210

Submitted: 4 August 2020 Revised: 24 September 2020 Accepted: 27 October 2020 Published: 15 June 2021

Advanced (FIGO stages III and IV) epithelial ovarian cancer (aEOC) accounts for the majority of deaths from gynecological cancers in western countries. Although the prognosis of this disease has been considerably improved in the last two decades, the majority of women will still die from progression of EOC. Optimal cytoreductive surgery and cytotoxic chemotherapy remains the mainstay of treatment in the front-line setting. Approximately 18% of EOCs harbor germline mutations of the tumor suppressor genes Breast Cancer Susceptibility Gene 1 (*BRCA1*) and 2 (*BRCA2*), while another 3–6% of these tumors have somatic mutations of these genes. These mutations lead to increased predisposition of multiple cancers. In addition, *BRCA1* and *BRCA2* genes encode proteins that are implicated in the Homologous Recombination (HR) mechanism, which is responsible for the repair of DNA Double Strand Breaks (DSBs), which is a common mechanism of action of chemotherapy. The incorporation of *BRCA*-targeted therapies, such as poly ADP ribose polymerase (PARP) inhibitors in the treatment algorithm of advanced EOC has further improved outcomes and represents a successful strategy of individualization of treatment in EOC. In this review, we summarize current treatment recommendations for patients with EOC and a *BRCA1/2* mutation.

Keywords

BRCA; Ovarian cancer; PARP inhibitors

1. Introduction

Epidemiologic studies demonstrate that ovarian cancer (OC) remains the deadliest gynecological cancer in developed countries [1]. Nearly 90% of all cases are epithelial in origin (EOC) [2]. Although carcinogenesis of EOC has not been clarified yet, it has been found that it is a distinctively heterogeneous malignancy comprising several histologic subtypes that have unique molecular biology [3]. Thus, type I tumors, such as low grade serous, endometrioid, clear cell carcinomas and mucinous carcinomas harbor mutations in Kirsten rat sarcoma 2 viral oncogene homolog (*KRAS*), Phosphatidylinositol 3-kinase (*PIK3CA*), Phosphatase and tensin homolog (*PTEN*), and v-Raf murine sarcoma viral oncogene homolog B (*BRAF*) genes [4]. Clinically, the majority of low grade and early stage type I tumors are indolent, while high grade and advanced stage are more aggressive. On the contrary, type II tumors include high grade serous carcinomas (HGSC), undifferentiated carcinomas and carcinosarcomas. HGSCs account for approximately 70% of cases of EOC. Type II tumors are characterized by an aggressive clinical behavior, advanced stage at diagnosis, genetic instability and high prevalence of *p53* mutations [5].

Approximately 18% of EOCs occur due to germline mutations, which are largely attributable to Breast Cancer Susceptibility Gene 1 (*BRCA1*) and Breast Cancer Susceptibility Gene 2 (*BRCA2*). *BRCA1* and *BRCA2* germline mutations (g*BRCA*m) are observed in all ovarian epithelial pathologies, but are most commonly identified in HGSCs [6]. *BRCA 1/2* genes are significant components of the Homologous Recombination (HR) DNA repair machinery, a high precision mechanism which mainly repairs Double Strand Breaks (DSBs), the most lethal form of DNA damage than can be generated in response to anti-tumor therapies. On the other hand, the Poly (ADP-ribose) polymerase (PARP) 1 protein is a crucial participant in the repair of single strand DNA breaks (SSBs), the most common type of DNA damage, which originate either from intracellular metabolites or spontaneous DNA destruction [7]. Inhibition of PARP leads to accumulation of SSBs and stalled replication forks, which subsequently transform to DSBs, requiring HR for repair [8, 9]. Thus, in the case of germline or somatic mutations of *BRCA1/2* genes or other abnormalities in HR proteins (HR deficiency), inhibition of PARP might result in DSB misrepair, genetic instability, apoptosis and cell death [8, 10].

Following the implementation of *BRCA* status in the management of EOC, the objective of this review is to provide guidance on treatment decisions regarding women with *BRCA*-associated EOC.

2. *BRCA1/2* mutations, HR deficiency and ovarian cancer

BRCA 1/2 are tumor suppressor genes; *BRCA1* is located on chromosome 13 and *BRCA2* on chromosome 17. They encode proteins which are crucial components of major complexes involved in DNA damage repair by HR [11]. In addition, they play an important role in other biological processes, including transcriptional regulation, regulation of cell cycle progression, autophagy and chromatin remodeling [12]. Since *BRCA* genes are caretakers of genomic stability, cells with alterations in *BRCA* acquire chromosomal abnormalities and have a predisposition to malignant transformation [13].

g*BRCA*m carriers have a high risk of developing primarily breast and ovarian cancer and secondarily other cancers, such as prostate, pancreatic and colon cancer [14]. More specifically, the cumulative risk of developing OC by the age 70 is 39–54% in women harboring *BRCA1*m and 11–23% in women harboring *BRCA2*m [15]. The incidence of OC in women younger than 50 years old is elevated in *BRCA1* carriers; however, overall, OC rarely occurs in *BRCA* carriers at a young age ($\leq$40 years old) [16].

Approximately 18% of HGSCs occur due to g*BRCA*m [17]. However, a number of sporadic HGSCs display alterations of *BRCA1/2* genes caused by either somatic mutations (6%) or epigenetic modifications (approximately 10%). The Cancer Genome Atlas (TCGA) reported the first results of sequencing data from 316 HGSC biopsies in 2011 [18]. It was revealed that g*BRCA1*m were present in 9% and g*BRCA2*m in 8% of the specimens, while 3% of the samples had somatic *BRCA1/2* mutations [18]. In addition, approximately 11% of HGSC tumors exhibit HR deficiency (HRD) due to germline mutations in other HR-associated genes, such as (a) core HR RAD genes [*RAD50, RAD51 paralog C* (*RAD51C*) and *RAD51 paralog D* (*RAD51D*)], (b) DNA damage response genes involved in HR [*Ataxia-Telangiectasia Mutated* (*ATM*), *Ataxia Telangiectasia and Rad3 related* (*ATR*), *Checkpoint Kinase 1* (*CHEK1*), *Checkpoint Kinase 2* (*CHEK2*), *BRCA1-associated RING domain 1* (*BARD1*)] and (c) Fanconi anemia genes [*partner and localizer of BRCA2* (*PALB2*), *BRCA-interacting protein 1* (*BRIP1*), *Fanconi Anemia group A* (*FANCA*), *Fanconi Anemia group I* (*FANCI*)] [9, 11]. Of note, germline mutations in genes implicated in the DNA repair mechanism mismatch repair (*MLH1, MSH2, MSH6, PMS2*) can cause hereditary OC (mainly of endometrioid pathology), but are not associated with *BRCA1/2* genes or HRD [19].

Pennington *et al.* [20] used genomic sequencing to analyze 390 ovarian carcinoma specimens. It was found that 24% had germline mutations, among which 56% were in *BRCA1*, 19% in *BRCA2*, and 25% were in other HR-associated genes (*BARD1, BRIP1, CHEK1, CHEK2, NBN, PALB2, RAD51C* and *RAD51D*). In addition, 9% of OCs had somatic mutations, mainly in *BRCA1* (54%) and *BRCA2* (17%).

Overall, patients with g*BRCA*m have a tendency to present with OC at a younger age [21, 22]. Following development of OC, there is some discrepancy regarding prognosis of patients with g*BRCA*m as compared to non-*BRCA*m counterparts. The majority of published studies report a more favorable outcome in patients with g*BRCA*m [23–27]. However, several studies show contradictory results [28–30]. A more recent meta-analysis of 14 studies that assessed survival in association with *BRCA1/2* mutations demonstrated an improved OS for *BRCA1/2*m carriers (*BRCA1*: HR: 0.76, 95% CI: 0.70–0.83; *BRCA2*: HR: 0.58, 95% CI: 0.50–0.66) without indicating if somatic mutation carriers were included [31]. On the other hand, several studies report a survival advantage and increased sensitivity to platinum-based chemotherapy for g*BRCA2*m as opposed to g*BRCA1*m carriers [15, 32, 33] depicting a different functional role in HR between the two genes. Nevertheless, it has not been clarified yet whether impact on survival is due to direct influence of *BRCA1/2*m or increased sensitivity to platinum-based chemotherapy and implementation of PARP inhibitors in everyday clinical practice.

3. Treatment of ovarian cancer and implementation of *BRCA* mutational status

3.1 Surgical management

Primary surgery is the cornerstone of treatment in advanced OC. Staging and initial surgical management should be preferably performed by a gynecologic oncologist because surgical procedures and survival outcomes have been shown to be superior compared to patients treated by general gynecologists or general surgeons [34, 35]. Of note, studies from the Mayo Clinic had a great impact on the development of new surgical paradigm [36]. Importantly, surgical treatment does not differ in women with *BRCA*m as opposed to their *BRCA* wild type (*BRCA*wt) counterparts [37]. In *BRCA*m carriers without OC, risk reducing surgical options such as prophylactic salpingo-oophorectomy should be discussed at childbearing or by age 35–40 [38]. Despite a higher likelihood of presenting with bulky peritoneal metastases and abdominal lymphnodes, retrospective studies suggest that rates of optimal cytoreduction are similar between women with g*BRCA*m and those with non-*BRCA*m associated tumors [39].

3.2 Chemotherapy

Combination of platinum and paclitaxel cytotoxic chemotherapy remains the standard of care for EOC either as adjuvant, neoadjuvant or first line treatment. Platinum antineoplastic drugs bind to nuclear DNA and form interstrand cross-links that produce bulky DNA adducts. Subsequently, the cell responds to the formation of DNA damage lesions either by DNA repair or apoptosis [40]. Preclinical studies have shown increased sensitivity of *BRCA* mutant cells to platinum salts, possibly due to malfunction of DNA repair machinery that causes cell death [41]. In addition, patients with *BRCA* mutant EOC display remarkable sensitivity to platinum-based chemotherapy compared to patients with no *BRCA*m. Alsop *et al.* [42] conducted a population-based case-control study where patients with OC were tested for g*BRCA*m. It was found that 14.1% of enrolled patients had g*BRCA*m and that these patients had a better response to platinum and non-platinum-based chemotherapy in the relapse setting. In addition, patients with no g*BRCA*m who showed good responses to platinum-based chemotherapy were more likely to harbor a somatic *BRCA*m (s*BRCA*m) [42]. In another retrospective study, patients with g*BRCA*m who received neoadjuvant chemotherapy had increased PFS and OS compared to patients with no mutations and patients with unknown *BRCA* status [43]. In contrast, a more recent study found no difference in response rate (RR) between g*BRCA*m carriers and non-*BRCA*m carriers in a cohort of patients with EOC who were treated with

neoadjuvant chemotherapy [44]. Of note, the presence of g*BRCA2*m was associated with higher response rate to first line chemotherapy compared to g*BRCA1*m and non-*BRCA*m in an observational study [15].

On the other hand, data from several studies indicate that patients with EOC that harbor *BRCA*m may derive greater benefit from intraperitoneal chemotherapy (IP) compared to their *BRCA*wt counterparts. The concept of IP chemotherapy is based on the tendency of EOC to spread into the peritoneal cavity; it is delivered through an implanted subcutaneous port that drains into the abdominal cavity, allowing direct access and greater exposure of chemotherapy in the peritoneum [45]. IP chemotherapy has been initially shown to improve PFS and OS in the landmark phase III Gynecologic Oncology Group (GOG) 172 trial, where it was compared to intravenous (IV) cisplatin and paclitaxel [46]. Although more recent trials failed to demonstrate a statistically significant survival benefit [47], IP chemotherapy is recommended by the National Comprehensive Cancer Network (NCCN) guidelines for patients with stage III/IV EOC that have had optimal surgical debulking.

Initial evidence that patients with *BRCA*m benefit more from IP chemotherapy was provided from a retrospective analysis of the GOG 172 trial, which showed that patients whose tumors had increased *BRCA1* protein expression on archival specimens (as assessed by immunohistochemistry) had better survival when treated with IP chemotherapy (median OS 84 months in the IP group vs 47 months in the IV group, $p = 0.0002$) [48]. In addition, in a retrospective study from a single institution, among 100 patients with HGSC that received IP chemotherapy between 2005 and 2016, 77 had *BRCA* testing and 25 were found to have *BRCA*m (either germline or somatic). It was found that patients with *BRCA*m had a longer PFS compared to *BRCA*m non-carriers (not reached (NR) vs 17.3 months respectively, HR: 0.38, 95% CI: 0.11–0.73) [49].

3.3 PARP inhibitors

3.3.1 Mechanism of action

PARP enzymes are responsible for the identification of SSBs and the recruitment of DNA repair proteins during HR. PARP inhibitors (PARPi) act by blocking the synthesis of poly (ADP-ribose) (PAR) chains (PARylation) and PARP1 release, increasing the binding affinity of PARP1 to the damaged lesion and causing PARP1 trapping. PARP1 trapping leads to constant SSBs, accumulation of DSBs, replication fork collapse, DNA damage misrepair and cytotoxicity [8, 50]. In *BRCA* mutant or HR deficient cells, PARP inhibition leads to dysfunction of two mechanisms, a term known as synthetic lethality and cell death [51, 52].

3.3.2 Front-line maintenance

It is essential for all patients with newly diagnosed EOC to receive genetic counseling for *BRCA*. It is recommended for women with a germline or somatic *BRCA*m and a response to front-line platinum-based chemotherapy to receive maintenance with a PARPi. Moreover, in women with a *BRCA*m that are regarded as high risk for recurrence and will be most likely treated with chemotherapy in combination with bevacizumab, the PARPi olaparib can be added to bevacizumab maintenance in countries where the combination has received approval (USA).

The SOLO-1 trial evaluated the efficacy of olaparib vs placebo as maintenance therapy in patients with newly diagnosed FIGO stage III–IV HGSC or endometrioid OC with predominantly germline (and a small proportion of somatic) *BRCA*m that were in complete (CR) or partial response (PR) after front-line platinum-based chemotherapy [53]. Patients could stop olaparib at 2 years if they had no evidence of disease. This trial showed a dramatic improvement in median PFS with the addition of olaparib (NR vs 13.8 months, HR: 0.30, 95% CI: 0.23–0.41, $p < 0.01$). The robustness of this finding led to immediate approval of the drug by the Food and Drug Administration (FDA) as maintenance treatment in newly diagnosed EOC with *BRCA*m following response to first-line chemotherapy. Grade 3 or 4 adverse events (AEs), mainly anemia and neutropenia, were more frequent with olaparib (39% vs 18%).

Following SOLO-1 trial, two different trials sought to address the role of PARPi in the first line setting regardless of *BRCA* status. PRIMA was a pure maintenance trial that assessed the role of niraparib vs placebo in patients with FIGO stage III–IV EOC who achieved PR or CR after platinum therapy, while PAOLA-1 trial enrolled patients with advanced EOC who were treated with first line chemotherapy and bevacizumab and were randomized to either bevacizumab in combination with olaparib or bevacizumab alone following CR or PR to first line treatment [54, 55]. With regards to their design, these trials had several main differences. First, the PRIMA trial enrolled patients with residual disease following primary debulking surgery, while in the PAOLA-1 trial, all patients were eligible regardless of residual disease. Second, niraparib was given for a total of three years in the PRIMA trial; on the contrary, olaparib was administered for 2 years in the PAOLA-1 trial. Last, in the PAOLA-1 trial, the primary endpoint was PFS (determined by the investigator) in the intent-to-treat population. In the PRIMA trial, the primary endpoint was PFS (determined by blinded independent central review, focused only on the RECIST criteria) initially in the HRD population and subsequently in the overall population if PFS was improved in the HRD population [54, 55].

Both PRIMA and PAOLA-1 trials were enriched with the *BRCA* population, since 30% of enrolled patients were *BRCA* mutant, which is higher than expected in the general population. In the intention to treat population, niraparib reduced the risk of recurrence by 38% compared to placebo (PRIMA trial) and the addition of olaparib to bevacizumab reduced the risk of relapse by 40% (PAOLA-1 trial) [54, 55]. The evaluation of PFS in the HRD population was hierarchical in the PRIMA trial, and the HR for PFS was 0.42 [54]. In the PAOLA-1 trial, the evaluation of PFS in the HRD popu-

lation was a predefined exploratory analysis and the HR for PFS was 0.33 [55]. Regarding the *BRCA* mutant population, in the PRIMA trial, the HR for PFS for niraparib maintenance was 0.40, whereas in the PAOLA-1 trial, the HR for PFS for olaparib and bevacizumab maintenance was 0.31, similar to the SOLO-1 trial (HR = 0.30). Thus, the most important question that needs to be addressed in *BRCA* mutant patients is what is the contribution of bevacizumab to the combination in patients with *BRCA*m. Indeed, in the Society of Gynecologic Oncology (SGO) 2020 meeting, SOLO-1 and PAOLA-1 trials were retrospectively compared and it was shown that median PFS was longer in *BRCA* mutant patients that received the combination of olaparib/bevacizumab (as in PAOLA-1 trial) as compared to olaparib monotherapy (as in SOLO-1 trial) [56].

Of note, the majority of patients enrolled in trials evaluating olaparib in the first line setting were g*BRCA*m carriers. For example, in SOLO-1 trial, only 2 out of 391 patients had a s*BRCA*m. Therefore, the use of front-line olaparib as maintenance treatment in patients with s*BRCA*m is practically extrapolation from the recurrent setting.

Veliparib is another PARPi currently tested in clinical trials. In the recently reported placebo-controlled phase III VELIA trial, patients with FIGO stage III–IV HGSC were randomized to either carboplatin/paclitaxel chemotherapy (control arm), chemotherapy plus veliparib (chemotherapy only arm), or chemotherapy plus veliparib followed by maintenance veliparib (veliparib throughout arm) [57]. The trial assessed the efficacy of veliparib initially in the *BRCA*m population and found that patients in the veliparib throughout arm had longer PFS (35 vs 22 months; HR: 0.44, 95% CI: 0.28–0.68). Similarly, PFS was prolonged in the HRD population (HR: 0.57). However, veliparib has not received regulatory approval in any country yet.

3.3.3 Platinum-sensitive relapse

During a typical treatment course of advanced EOC, approximately 70–80% of patients will experience relapse or disease progression within 3 years of time. Patients whose disease recurs within more than six months after completion of platinum-based chemotherapy and for whom treatment with platinum is an option are known as "platinum-sensitive", while patients who progress within less than six months after completion of platinum-based chemotherapy and for whom platinum is not a treatment option are deemed "platinum-resistant".

Patients with platinum-sensitive relapse who have achieved a CR or PR after treatment with platinum-based chemotherapy, can receive maintenance therapy with a PARPi, such as olaparib, niraparib and rucaparib, which have all been approved by the FDA and the European Medicines Agency (EMA). These agents represent a major breakthrough in the treatment of *BRCA*m EOC and despite improving outcomes in all comers, their efficacy is more prominent in *BRCA* carriers.

Study 19 was a randomized, placebo-controlled phase II study, which evaluated the efficacy of olaparib as maintenance therapy in patients with platinum-sensitive HGSC following response to a platinum-based therapy [58]. This study enrolled patients regardless of *BRCA* status. In a preplanned retrospective subanalysis that compared *BRCA*m carriers to their *BRCA*wt counterparts, median PFS was 11.2 months with olaparib vs 4 months with placebo in patients with *BRCA*m (HR: 0.18, 95% CI: 0.10, 0.31, $p < 0.0001$) as compared to 7.4 months with olaparib vs 5.5 months with placebo in *BRCA*wt patients (HR: 0.54, 95% CI: 0.34, 0.85, $p = 0075$) [59]. Patients with a *BRCA*m also had a trend toward prolonged OS (HR: 0.73, 95% CI: 0.45–1.17), whereas non-*BRCA* carriers showed no OS benefit (HR: 0.99, 95% CI: 0.63–1.55) [60]. Interestingly, a second report from the same trial demonstrated an OS benefit in *BRCA*m carriers when all placebo patients that received post progression olaparib were excluded for the analysis in an effort to explore whether crossover had a confounding effect on survival (HR: 0.52, 95% CI: 0.28–0.970) [61].

Olaparib has been shown impressive results as maintenance treatment in recurrent platinum-sensitive g*BRCA*m EOC in the phase III SOLO-2/ENGOT-Ov21 trial, which was conducted in patients who had received at least two lines of chemotherapy and have achieved a CR or PR to most recent platinum-based therapy. Olaparib resulted in a dramatic improvement of investigator-assessed PFS of 13.6 months (19.1 vs 5.5 months; HR: 0.30, 95% CI: 0.22–0.41) [62]. At final data cut-off with a median follow-up of 65 months, olaparib also let to a prolongment in OS (52 months with olaparib vs 39 months with placebo, HR: 0.74, 95% CI: 0.54–1.00) (Poveda, JCO 2020). The most frequent $\geq$grade 3 AEs with olaparib were fatigue (4.1% vs 2% with placebo), anemia (20% vs 0% with placebo), vomiting (2.6% vs 1% with placebo) and abdominal pain (2.6% vs 2% with placebo) [62].

Niraparib was evaluated as maintenance treatment in patients with recurrent platinum-sensitive disease in the phase III, placebo-controlled NOVA study, which included a cohort of patients with g*BRCA*m and a cohort of non-*BRCA*m carriers. In the g*BRCA* mutant cohort, niraparib was associated with an impressive improvement in median PFS (21 months vs 5.5 months with placebo, HR: 0.27, 95% CI: 0.17–0.41). The most frequent grade 3–4 AEs were hematologic (34% thrombocytopenia, 25% anemia, 20% neutropenia) [63]. Compared to olaparib, niraparib caused more severe AEs in the platinum-sensitive setting (74% with niraparib in the NOVA trial vs 34% with olaparib in the SOLO2 study) and more AEs leading to dose reduction (67% in the NOVA trial vs 25% in the SOLO2 study).

Efficacy of rucaparib as maintenance therapy in the recurrent platinum-sensitive setting was assessed in the phase III ARIEL3 trial that had similar design as the previous SOLO-2 and NOVA trials [64]. The primary endpoint was investigator-assessed PFS separately in the *BRCA* mutant, HRD and intention to treat (ITT) cohorts. In the *BRCA* mu-

tant cohort, median PFS was prolonged with rucaparib as compared to placebo (16.6 vs 5.4 months; HR: 0.23, 95% CI: 0.16–0.34); similar results were observed both in the HRD (13.6 months vs 5.4 months, $p < 0.0001$) and ITT cohorts (10.8 months vs 5.4 months with placebo, $p < 0.0001$). Fifty-six percent of patients in the rucaparib group experienced grade 3–4 adverse events, the most common being anemia (19%) and increased concentration of hepatic enzymes (10%) [64].

The three aforementioned maintenance trials have certain differences in the inclusion criteria, design and primary endpoints. For example, SOLO-2 and NOVA studies only enrolled patients with residual disease <2 cm [62, 63]. As described above, SOLO-2 included only patients with *BRCA*m. Regarding Cancer antigen 125 (CA-125) tumor markers levels, ARIEL3 solely included patients with a normal level following response to platinum-based therapy, NOVA trial enrolled patients with a 90% decrease and SOLO-2 permitted registration to all patients who did not have a rising Ca125 after platinum-based treatment [62–64]. Last, in the NOVA trial, patients with s*BRCA*m were included in the HRD subgroup, whereas in the ARIEL3 study, they were included in the *BRCA* mutant subgroup.

Taking into consideration indirect comparisons based on retrospective data, there is a recommendation that *BRCA*m OCs should be preferably treated with a PARPi as maintenance therapy in the platinum-sensitive setting, as compared to bevacizumab [65]. However, after the regulatory approval of PARPi in newly diagnosed EOC, there are no prospective trials to assess the use of a PARPi in platinum-sensitive relapse following administration of a PARPi as maintenance in the front-line setting. For a patient that has not received a PARPi as front-line maintenance, there are no prospective trials directly comparing bevacizumab to a PARPi in platinum-sensitive disease. Notably, certain important differences are observed regarding the design and the patient population included in maintenance PARPi [62–64] as compared to maintenance bevacizumab trials [66, 67] in the platinum sensitive setting and cross-comparisons must not be done. First, PARPi maintenance trials were restricted to patients who achieved a response to platinum-based chemotherapy, whereas bevacizumab trials were addressed to all comers. Second, there were no subanalyses in *BRCA* mutant subgroups in bevacizumab trials. Last, bevacizumab trials included patients with EOC and any histology, whereas PARPi trials were restricted to patients with HGSC and endometroid OC.

Olaparib can be used as a single agent in *BRCA*m carriers with platinum-sensitive relapse who are unfit for platinum-based chemotherapy. Data from the phase III SOLO-3 trial, where olaparib was compared to nonplatinum chemotherapy in the platinum-sensitive context, indicate that olaparib increases objective response rate (ORR) (72 vs 51% with nonplatinum chemotherapy) and PFS (13 vs 9 months; HR: 0.62, 95% CI: 0.43–0.91) [68]. Similarly, rucaparib has demonstrated high ORR (66%) as single-agent in the platinum-sensitive setting, as shown in a pooled analysis of phase II studies that included patients with *BRCA* mutant advanced EOC that had not received a PARPi [69]. In addition, in the phase II ARIEL 2 trial, the efficacy of rucaparib as monotherapy was evaluated in recurrent platinum sensitive EOC in three HRD subgroups: *BRCA* mutant, *BRCA* wt and high genomic loss of heterozygosity (LOH high subgroup) and *BRCA* wt and low LOH (LOH low subgroup). It was shown that PFS was prolonged in patients receiving rucaparib in the *BRCA* mutant and LOH high subgroups as compared to LOH low subgroups [70].

3.3.4 Platinum-resistant relapse

Single agent PARPi can be used in patients with platinum-resistant EOC with *BRCA*m. In a phase II study that included patients with *BRCAm* and advanced cancer, olaparib yielded promising results in platinum resistant EOC; ORR was 26.2% and stable disease (SD) was achieved in 40% of patients [71]. In addition, in a pooled analysis of phase I/II trials of olaparib monotherapy in advanced *BRCA* mutant cancer, it was shown that patients with heavily pretreated EOC who were naïve to PARPi had relatively durable responses (RR 31%, median duration of response 7.8 months) [72]. Rucaparib has been also FDA approved as monotherapy in *BRCA* mutant platinum-resistant disease following promising results from a pooled analysis of phase II trials that has shown a RR of 25% in this context [69].

Moreover, in the phase III QUADRA trial, niraparib was evaluated as monotherapy in relapsed OC in 4th or later line of therapy. In the *BRCA* mutant cohort that had not received any previous PARPi, ORR was 33% in patients with platinum-resistant disease and 19% in patients with platinum-refractory disease (defined as progression within one month of the last dose of platinum), with a median duration of response of 9.2 months in the *BRCA* mutant population [73]. Thus, in October 2019 niraparib has been approved by the FDA as monotherapy in platinum resistant and platinum refractory disease.

3.3.5 Toxicity of PARPi

Patient education is critical to acceptance and ongoing compliance with maintenance PARPi in particular, because there is a common perception that "non-chemotherapy" options are nontoxic. Before treatment initiation with a PARPi, it is essential to clearly explain to patients which AEs are likely to occur, potential drug interactions, the likely duration and severity of AEs and the need for regular monitoring. The most common AEs for PARPi are hematologic (anemia, neutropenia, thrombocytopenia), gastrointestinal (nausea, vomiting, anorexia, dysgeusia) and fatigue. These AEs may vary in incidence, severity and time of onset depending on type of PARPi and prior lines of treatment. For example, gastrointestinal AEs usually have an early onset and may persist, whereas hematologic toxicity might occur within the first 12

weeks. In addition, the setting and population included in each clinical trial can have a profound impact on toxicity.

Regarding the platinum-sensitive setting, in the SOLO-2 trial where olaparib was given as a maintenance treatment, any grade nausea occurred in 80% of patients with olaparib, any grade anemia in 44% and grade fatigue in 66% of patients; dose interruptions were essential in 45% of patients and dose reductions in 25% of patients [58]. Eleven percent of patients were obliged to discontinue the drug due to AEs. In the NOVA trial, which evaluated niraparib as maintenance treatment, the most frequent any grade AEs were nausea (74%), thrombocytopenia (61%), fatigue (59%) and anemia (50%), whereas grade 3/4 AEs occurred in 74% of patients leading to discontinuation in 15% and dose reduction in 67% [63]. In ARIEL3 trial, the most common any grade AEs with rucaparib were nausea (78%), fatigue (78%), vomiting (49%) and anemia (48%) and the most common grade 3/4 AEs were anemia (29%), fatigue (10%) and increased hepatic enzymes (10%) [64].

Long term and severe toxicities such as acute myeloid leukemia (AML) and myelodysplastic syndrome (MDS) merit special mention as they have been reported in patients receiving PARPi. The incidence of these hematologic malignancies varies depending on agents used and the setting of each clinical trial. In the platinum sensitive setting, olaparib was associated with MDS/AML in 2% of patients [62], niraparib in 1.4% of patients [63] and rucaparib in 1% of patients [64]. In newly diagnosed OC, respective percentages were 1% for olaparib [53] and 0.2% for niraparib [54]. Of note, due to previous treatment with chemotherapy, it is difficult to identify PARPi as the specific cause of MDS/AML [74]. However, these potential side effects need to be discussed with every patient as part of the informed consent process.

Lack of compliance might be due to AEs, increased number of oral tablets and high cost and is usually associated with worse outcomes. Nevertheless, the most robust predictor of better adherence is satisfaction with clinician communication, trust and confidence in physician care and good understanding of disease behavior. Since the majority of AEs can be easily managed with symptomatic treatment and dose modifications, treating physicians must focus on patient education, familiarity with common AEs and good communication with patients.

3.3.6 PARPi resistance

Acquired resistance to PARPi is a commonly encountered phenomenon in advanced OC after a period of successful treatment. However, the mechanisms that govern resistance to PARPi are not fully understood. Inactivation of p53-binding protein 1 (53BP1) has been shown to drive the development of resistance through restoration of HR in preclinical studies [75]. Secondary *BRCA1/2* mutations, such as *BRCA2* c.9106C>G, which restore the opening reading frame of the gene and reestablish HR function have been found in patients treated with olaparib using DNA sequencing in pre- and post- olaparib treatment biopsies [76]. In triple negative breast cancer cell lines, upregulation of RAD51 protein was associated with resistance to olaparib [77]. Similarly, overexpression of zeste homolog 2 (EZH2) in *BRCA* mutant breast cells, an enzyme that catalyzes H3 lysine trimethylation and directly interacts with PARP1 has been implicated in PARPi resistance [78]. Finally, increased replication fork stabilization in *BRCA* mutant cancers, mediated by certain proteins, can lead to PARPi resistance through activity of alternative DNA repair mechanisms [50].

4. Conclusions—future perspectives

In conclusion, the presence of germline or somatic *BRCA*m is currently considered key important information for treatment planning in advanced EOC. Although patients with *BRCA* mutant EOC gain great benefit from PARPi in any disease context, patient selection remains a challenge. In an effort to maximize the impact of these drugs, we need to understand what makes a super-responder, mechanisms of drug resistance, optimal treatment timing and development of effective combinations to enhance the efficacy PARPi. Several resistance mechanisms, such as increased drug efflux, loss of PARP protein owing to mutation, and HR function restoration have been already reported [79]. Clinical trials that combine these drugs with Wee1 inhibitors, ATR inhibitors or immunotherapy aim at a greater understanding of novel combinations in order to produce landmark changes in the outcome of advanced EOC [80].

Author contributions

PE wrote the manuscript. IK and PE analyzed the data. AB contributed in concept and design and supervised this work. 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.

Acknowledgment

Not applicable.

Funding

This work was funded by the National and Kapodistrian University of Athens, School of Health Sciences.

Conflict of interest

The authors declare no conflict of interest.

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