PARP inhibitors and epithelial ovarian cancer: Molecular mechanisms, clinical development and future prospective (Review)

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Abstract. Epithelial ovarian cancer (EOC) has a poor prognosis. Since the introduction of paclitaxel as antineoplastic agent >20 years ago, only a few phase III randomized trials have shown challenging data regarding different therapeutic options for facing its aggressive clinical course and granting active therapies to patients. Different studies have shown the utility of poly(ADP-ribose) polymerase (PARP) inhibitors in women with EOC with or without *BRCA* mutations, both germline and somatic. Three PARP inhibitors, olaparib, rucaparib and niraparib, have been recently approved by the Food and Drug Administration for clinical use in EOC patients, though with different clinical indications and profiles of toxicity, while two other molecules, veliparib and talazoparib, are still under clinical investigation. The aim of the present paper is to evaluate the current status of PARP inhibitors in terms of molecular activity, pharmacodynamic properties and clinical applications.

Contents

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1. Introduction

Since the introduction of paclitaxel >20 years ago for the treatment of epithelial ovarian cancer (EOC), only a few phase III trials testing other therapeutic agents have demonstrated notable data in terms of clinical outcome (1). Two studies demonstrated an increase in progression-free survival (PFS) time and, in a selected subgroup of patients, overall survival (OS) time (2) or only in PFS time (3), with the introduction of the anti-vascular endothelial growth factor (VEGF) monoclonal antibody, bevacizumab, using a therapeutic schedule based on paclitaxel (2-5).

More recently, poly(ADP-ribose) polymerase (PARP) inhibitors have begun to be used as a new therapeutic approach in the management of EOC (6), particularly for patients with assessed defects in the homologous recombination (HR) DNA repair process, which is strictly linked to *BRCA*1/2 gene mutations (7). Considering the few available therapeutic options for EOC treatment, this important discovery has addressed scientific research into novel strategies exploiting DNA repair deficiencies and PARP inhibitors are the first drugs with this peculiar mechanism of action and are active in patients with recurrent EOC with HR deficiencies (6,7). In spite of this potentially revolutionary evidence, these molecules have been demonstrated to be also active in patients without HR deficiencies (8). Three PARP inhibitors, olaparib, rucaparib and niraparib, are commercially available and approved by the Food and Drug Administration (FDA) for the treatment of patients with recurrent EOC, with different clinical indications and toxicity profiles. In addition, two other molecules, veliparib and talazoparib, are still under clinical investigation. In the literature, to the best of our knowledge, no comparisons among the three commercial drugs have been made so far; however, ongoing trials are now focusing their attention on new clinical indications and on additional therapeutic strategies in combination with conventional antineoplastic drugs.

The aim of the present review was to discuss the current status of PARP inhibitors in terms of the mechanisms of action, molecular activity and clinical applications, as well as to evaluate their future prospective in oncological therapy.

2. *BRCA* mutations and cancer risk

Previous studies have demonstrated the association between germline mutations of *BRCA*1 and *BRCA*2 genes and the early development of both breast and ovarian cancer (9), as well as other neoplasms caused by either germline or somatic mutations (10).

The techniques used for the detection of *BRCA* gene mutations depend on DNA sequencing procedures, which are, however, susceptible to yielding false-positive results. In fact, these genes can also be affected by certain benign non-pathogenic variations, termed variants of unknown significance, which represent ~13% of *BRCA*1 and *BRCA*2 mutations, suggesting clinical uncertainty and ambiguity in the risk assessment of patients undergoing the analysis (11,12). As a consequence, different polymorphisms of these genes complicate the identification of *BRCA* mutations.

Breast cancer-related to *BRCA*1 mutation is more likely estrogen receptor (ER)-negative when compared with *BRCA*2 and non-*BRCA*1 tumors (13). This evidence is substantial as estrogens influence certain genes controlling growth regulation; therefore, both breast and ovarian cancer are assessed for ER status to predict prognosis, future treatment or preventive and curative measures in both *BRCA* and non-*BRCA* tumors. The failure of *BRCA* function and estrogen signaling, together with other subcellular mechanisms, causes tumor growth due to the lack of appropriate DNA surveillance. Silencing the *BRCA*1 gene leads to increased expression of the gene codifying the aromatase enzyme that is responsible for the conversion of steroids into active estrogens, promoting their synthesis and biological activity (14).

3. Molecular mechanisms of PARP enzymes

Tumor genomic instability results in DNA aberrations consisting of point mutations, tandem duplications and translocations, which induce carcinogenesis and tumor progression (15,16). The integrity of chromosomal structure, transcription, replication, recombination and DNA repair are under the control of a pool of 17 enzymes, constituting the PARP family of proteins (17,18) (Fig. 1).

Human cells have at least five primary mechanisms of DNA repair (19), such as mismatch repair (MMR), base excision repair (BER), nucleotide excision repair (NER) and double-strand break (DSB) recombination repair, including both non-homologous end-joining (NHEJ) and homologous recombination repair. The dysfunction, reduction or absence of proteins involved in these pathways may lead to dangerous cellular implications, determining mutagenesis and toxicity (20).

Different insults can affect DNA, although single alterations are the most recurrent and are repaired by a combination of BER, NER and MMR pathways using the undamaged DNA strand as a template. The predominant mechanism of single-strand break (SSB) repair is BER with the activity of PARP enzymes (21).

PARP-1 and PARP-2 are activated by DNA damage. In particular, PARP-1 functions as a molecular sensor binding the N-terminal zinc finger domains to DNA SSBs and subsequently, by increasing its activity, catalyzes the transfer of ADP-ribose (poly ADP-ribosylation) to target proteins through their C-terminal catalytic domain. Following the activation of the nicotinamide-adenine-dinucleotide (NAD^+), PARPs form PAR polymer chains that play an essential role for recruiting intermediates for the DNA repair pathway (20) (Fig. 2). PARP-1 covalently attaches PAR chains to several different proteins, in the process known as PARylation. Due to its role in DNA repair, PARP inhibition results in genomic instability and the accumulation of damaged cells in cell cycle arrest (22-26).

If PARP activity is lacking, more deleterious DSBs can multiply, beginning from damaged SSBs, which require other different pathways for repair (19).

4. Biological link between PARP and angiogenesis inhibition

Ample experimental data have indicated a link between PARP enzymes and angiogenesis. Angiogenesis is an important driver of EOC development and progression and it is a main target of antitumor therapy (27). In this regard, since 2011, anti-VEGF therapy with bevacizumab combined with paclitaxel and carboplatin has been the backbone of treatment with monoclonal antibodies in patients with locally advanced and metastatic EOC (FIGO classification stage III and IV) (28).

The PARP-1 pathway is able to regulate gene expression, controlling angiogenesis through hypoxia-inducible factor-1α (HIF-1α) (29). Experimentally, PARP-deficient mice have been shown to exhibit a decreased level of HIF-1α. This transcription factor plays a major role in stimulating tumor angiogenesis and is a subunit of the heterodimer HIF-1 together with HIF-1β. HIF-1β is a nuclear constitutively expressed protein that does not undergo regulation by the oxygen level (30); by contrast, HIF-1α is a cytoplasmic protein whose activation is dependent on the oxygen concentration. In particular, in oxygenated microenvironmental conditions, HIF-1α undergoes hydroxylation by prolyl hydroxylases on its prolyl residues in the oxygen-dependent degradation domain and this event leads to its binding to von Hippel-Lindau protein, before being degraded in the ubiquitin-proteasome pathway. Meanwhile, at low oxygen tension, prolyl hydroxylase is inactive, resulting in HIF-1α stabilization, which allows its migration to the nucleus, where it binds HIF-1β, finally forming the HIF-1 complex (31). The HIF-1 complex targets a consensus hypoxia response element in the promoter of several pro-angiogenic genes, in particular VEGF, activating their transcription (32).

From a biological point of view, *in vivo* and *in vitro* data have suggested that angiogenesis and tumorigenesis in EOC is promoted by PARP-1 overexpression and due to the increasing level of VEGF-A, PARP-1 can be considered a potential therapeutic target (33).

Experimental data employing reverse transcription-quantitative polymerase chain reaction demonstrated that SKOV3 human ovarian cancer cells transfected with PARP-1 small interfering RNA express lower levels of VEGF-A mRNA compared with SKOV3 cell cultures transfected with negative

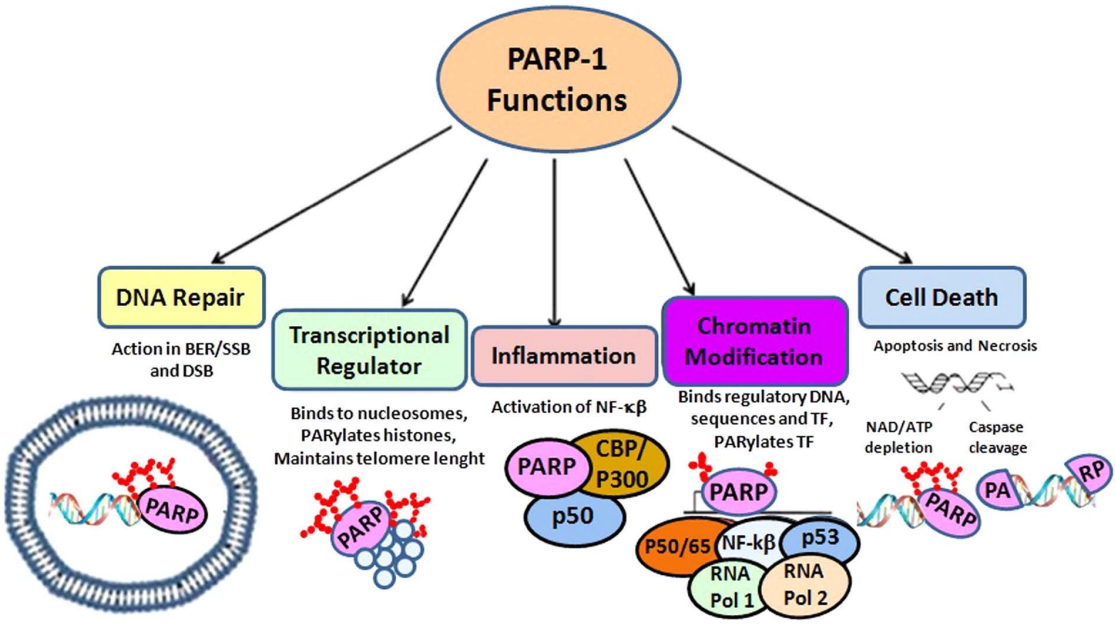

Figure 1. Schematic summary delineating the multifaceted nature of PARP actions: DNA repair, chromatin modification, inflammation, transcriptional regulation and cell death. PARP, poly(ADP) ribose polymerase; SSB, single-strand break; DSB, double-strand break; BER, base excision repair; TF, Tissue Factor.

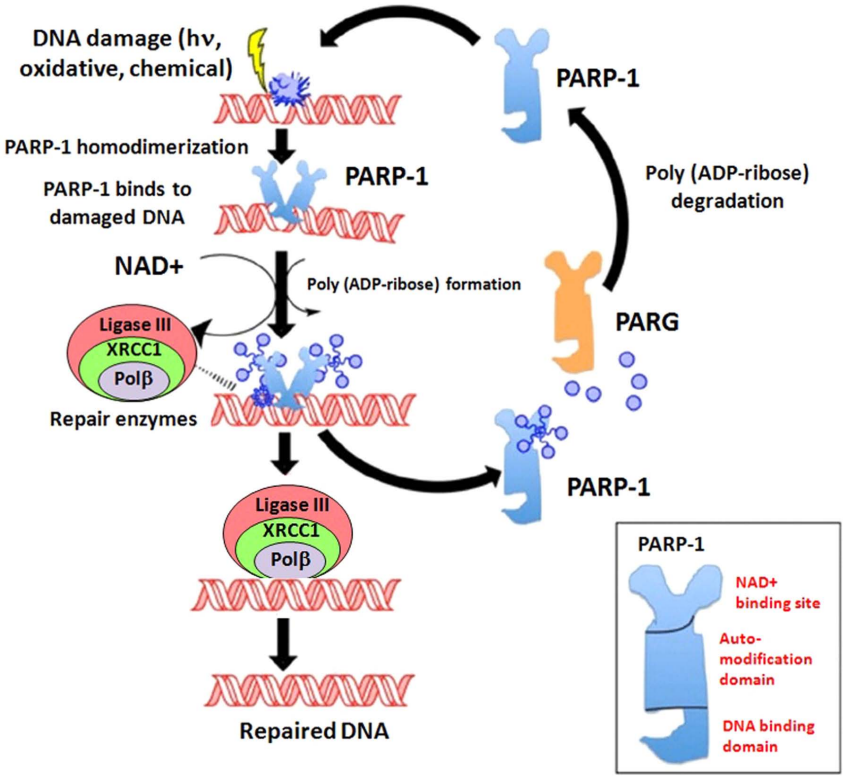

Figure 2. Clinical significance of PARP-1 inhibitors in cancer chemotherapy. PARP, poly(ADP) ribose polymerase. hν, photon energy (light); PARG, poly(ADP-ribose) glycohydrolase.

control-small interfering-RNA (26). Moreover, the knockdown of PARP-1 was shown to decrease VEGF-A levels in SKOV3 cells, as demonstrated by western blot analysis. These results were confirmed by ELISA, revealing the presence of VEGF-A in the supernatant of SKOV3 cell cultures transfected with negative control-small interfering RNA.

Notably, in addition to these data, the PARP inhibitor, N-(6-Oxo-5,6-dihydro-phenanthridin-2-yl)-N,N-dimethylacetamide (PJ-34), has been demonstrated to be endowed with anti-angiogenic activity by the *in vitro* inhibition of growth and migration of human umbilical vein endothelial cells (34), probably due to the reduction of nitric

oxide, guanylylcyclase and the cGMP pathway, which represent the drivers of the VEGF effect on endothelial cells. Evidently, the effects of VEGF are also mediated by the binding to VEGF receptors that, in turn, activates the intracellular pathways of Akt, ERK1/2 and p38 MAP kinase. *In vitro* studies have demonstrated that PJ-34 inhibits the phosphorylation of these kinases, suggesting that in the VEGF response in endothelial cells, PARP exerts a key role. Similarly, the PARP inhibitor, GPI 15427, has been found to exert anti-angiogenic effects in PARP-1-knockout mice (35).

5. Clinical application of PARP inhibitors in *BRCA* mutations, mechanisms of activity and resistance

PARP inhibitors prevent the repair of persistent SSBs and the reconstitution of DSBs, through the replication fork. PARP inhibitors have been developed for targeting cancer related to *BRCA*1 or *BRCA*2 gene mutations, these genes being responsible for the synthesis of proteins involved in the HR repair pathway. Individuals with the wild-type phenotype have both functioning copies of the *BRCA* genes; by contrast, patients carrying a *BRCA* mutation have only one functioning copy, which allows the correct process of DNA repair and viability. When a mutation occurs in the only functioning gene copy, cells lose their mitotic control, become susceptible to tumor growing and are unable to undertake HR (36).

When tumor cells carry both abnormal copies of the gene, being homozygous for *BRCA1* or *BRCA2* mutations, cells undergo inadequate DNA repair and become sensitive to PARP inhibitors. In the presence of an oncogene mutation, targeted drugs or gene therapy should theoretically induce synthetic lethality in neoplastic cells; in other words, synthetic lethality occurs when two cellular events occur independently, but permit cell survival, whereas in combination, they result in cell death (37-39).

All PARP inhibitors can inhibit both PARP-1 and PARP-2 by suppressing PARP catalytic activity, avoiding the formation of PAR polymers and, consequently, blocking the binding of NAD^+ at the site of DNA damage. These effects compromise the cellular ability to overcome DNA damage (20). Recent studies have investigated possible biomarkers of the response to PARP inhibition by measuring both the biosynthesis of RAD51 foci and PAR poly(ADP-ribose) and 53BP1 expression levels in cancer cells (37). However, efforts to identify an efficient and more specific biomarker are imperative in order to optimize clinical outcomes to PARP inhibitor treatment.

PARP inhibitors share similar toxic effects with other chemotherapeutic agents, such as nausea, fatigue, vomiting, anemia and abdominal pain, which are the most frequently reported adverse effects (40).

Recent evidence has shed light on an acquired resistance to PARP inhibitors developed by neoplastic cells. A number of mechanisms of pharmacological resistance have been proposed; these include, in particular, the ability of tumor cells to reverse the mutation in the *BRCA* gene, which restores HR function (41). Other possible mechanisms of resistance to PARP inhibitors can be either a decrease in NHEJ, the reduction of PARP-1 enzymatic activity or the increased activity of RAD51, an essential protein involved in HR function (37). In the light of all considerations and hypotheses, the resistance mechanisms to PARP inhibitors are important aspects to ascertain knowledge for, in order to forecast the efficacy of treatments.

6. Clinical trials with PARP inhibitors in EOC

DNA repair processes induced by both *BRCA* and PARP pathways are considered key elements for tumor aggressiveness. If PARP is inhibited by a molecule that modifies its function, cells genetically deficient in *BRCA* die, and this occurs in EOC with *BRCA* mutations (42).

Olaparib. Olaparib was the first PARP inhibitor to be used in clinical practice for the treatment of EOC; it acts as a single therapeutic agent, with a 30-50% response rate when used in second-line or subsequent line treatments in patients carrying *BRCA*1-2 mutations (40,43-47). The clinical activity of the drug is greater in the presence of platinum-sensitive tumors, although platinum-resistant cancer also responds to therapy. In addition, olaparib has been tested in patients with the wild-type phenotype affected by high-grade serous EOC, although the response rates have not been satisfactory in this group of patients.

A double-blind randomized controlled phase II trial enrolled patients with high-grade OC who were pre-treated with a platinum-based second-line chemotherapeutic regimen, resulting in a complete response (CR) or partial response (PR), to receive either olaparib or a placebo as the maintenance therapy (48). The study demonstrated a better outcome with regard to PFS time (median, 8.4 months vs. 4.8 months; hazard ratio, 0.35; P<0.001) in patients treated with olaparib compared with placebo. Furthermore, patients with a documented germline *BRCA* mutation experienced a tripling of the time to disease progression (median, 11.2 months vs. 4.3 months; hazard ratio, 0.18; P<0.0001) (49).

The long-term follow-up of patients enrolled in the aforementioned study (48) demonstrated a favorable impact on OS time due to the maintenance strategy. A similar outcome was recorded in a subsequent randomized phase III trial testing olaparib vs. placebo in patients with platinum-sensitive recurrent EOC, with a CR or PR after ≥2 lines of platinum-based chemotherapy (50). The overall median PFS time was 19.1 months for active maintenance therapy vs. 5.5 months for placebo, respectively (hazard ratio, 0.30; P<0.0001).

Apart from its use in the maintenance approach, olaparib has recently been approved by the FDA in monotherapy for women who carry germline *BRCA* mutations with a diagnosis of EOC and who have received a minimum of three prior lines of cytotoxic chemotherapy (51). Promising data from more recent studies might extend the clinical indications of the drug within the near future.

Rucaparib. Rucaparib is a PARP inhibitor approved by the FDA as a single-agent treatment in patients with EOC who carry either a germline or a somatic *BRCA* mutation and who have received pre-treatment with a minimum of two prior lines of chemotherapy. A phase II trial demonstrated an objective response rate (ORR) of ~80% in patients with a *BRCA* mutation (52).

By contrast, in patients with the wild-type phenotype with a high loss of heterozygosity, the ORR was reduced to 44%, while in treated patients with a low loss of heterozygosity, only 20% experienced a response (52). These data suggest that defects in DNA repair mechanisms can be considered appropriate targets for therapy with a PARP inhibitor.

A recent randomized phase III trial evaluating the effects of maintenance therapy with rucaparib following second-line chemotherapy demonstrated a significantly improved PFS time (53), highlighting the candidacy of this clinical approach to be once more a new standard of care for patients with platinum-sensitive EOC.

Niraparib. Niraparib is the third PARP inhibitor available for clinical use in the USA; it has been approved on the basis of the results of a randomized phase III trial testing the drug compared with a placebo, for maintenance therapy in patients who obtained a CR or PR after second-line platinum-based chemotherapy (54). In women affected by EOC who carry a *BRCA* mutation, the median PFS time of 21 months was higher than the 5.5 months found for patients treated with placebo (hazard ratio, 0.27). Favorable results have been observed even in the overall non-germline *BRCA* patient population, with a median PFS time of 9.3 months compared with 3.9 months (hazard ratio, 0.45) for placebo (54).

Moreover, within the same niraparib trial (54), an attempt was made to identify a biomarker to recognize patients whose tumors could be particularly susceptible to treatment, despite the absence of a germline *BRCA* mutation. In patients with the wild-type phenotype with tumors characterized by homologous recombinant deficiency (HRD), maintenance therapy with niraparib exhibited a statistically significant 12.9-month median PFS time compared with the 3.8 months (hazard ratio, 0.38) found for placebo (54). From this objective evidence, the FDA approved niraparib for clinical use as a second-line maintenance strategy, following a response to platinum-based treatment without requiring the use of a molecular biomarker, either *BRCA* mutation or HRD-positive (Table I).

Veliparib. Veliparib is a PARP inhibitor that is still under investigation. A phase II study evaluated the effects of the use of oral veliparib at 400 mg twice daily in 50 patients who underwent a maximum of three prior chemotherapy regimens, with measurable disease and who had never benefitted from another previous treatment with a PARP inhibitor. The response rate was 26%, with a median PFS time of 8.18 months (55). Another phase I/II study revealed a 65% overall response rate in platinum-resistant or partially platinum-sensitive patients with a relapse of EOC carrying a germline *BRCA* mutation treated with maintenance oral veliparib 300 mg twice daily (56). These preliminary data gave raise to other ongoing phase III clinical trials testing veliparib not only in ovarian cancer, but also in non-small cell lung and triple-negative breast cancer.

Talazoparib. Talazoparib is a new PARP inhibitor in clinical development for patients with advanced or recurrent solid tumors. *In vitro* studies have demonstrated that talazoparib exhibits potent activity in tumor cells with *BRCA* or *PTEN* mutations compared to other PARP inhibitors (57). In a multicenter phase I study, among patients with *BRCA*-mutated ovarian cancer, talazoparib exhibited a response in 5 out of 12 patients (42%), with a median PFS time of 36.4 weeks (58).

7. Selection of PARP inhibitors in EOC

To date, to the best of our knowledge, no direct trial comparing the three commercially available PARP inhibitors has been performed; therefore, a summary report about the relative efficacy or toxicity of each drug is not immediately being attempted. Thanks to the results of the discussed clinical trials and despite the different adverse events (AEs) they induce, all agents have obtained regulatory approval for use in different clinical settings. The large majority of patients enrolled in non-randomized and randomized trials for all drugs have continued treatment (if permitted by the protocol), despite recognized toxicity, often with appropriate dose modifications and treatment interruptions to permit recovery from the AEs (40,43-54).

All currently available PARP inhibitors have some common side effects, in particular low-grade nausea, fatigue and myelosuppression, which can compromise the quality of life of patients, despite no evidenced cancer-related symptoms (59).

The selection of the right PARP inhibitor remains a challenge. At the current time, olaparib is the only PARP inhibitor approved for first-line therapy owing to the results of the SOLO1 clinical trial. By contrast, for second-line treatment the matter is still under debate and the selection could be based on certain specific differences in toxicity. Niraparib exerts a more potent effect on platelet counts (54), while rucaparib induces an increase in creatinine and transaminases (52,53), both of which are essentially false-positives, as they are not associated with real kidney toxicity or liver toxicity. The cause of this peculiar effect remains under investigation, as it seems to be associated with the interaction of the PARP inhibitor with certain transport proteins, which is responsible for the difficulty in monitoring the clinical effect of the drug in patients with kidney and liver comorbidities (60-62).

More frequent toxicities of PARP inhibitors can be grouped as follows: i) Hematological: Anemia, thrombocytopenia and neutropenia (55,63,64). These outcomes provoke different degrees of bone marrow suppression, depending upon the dose, which must be prescribed only after blood counts have been taken. It is considered best practice to follow-up new patients with lower blood counts at a weekly frequency, particularly in the case of bone marrow suppression due to previous chemotherapeutic regimens. ii) Gastrointestinal: Nausea, vomiting, diarrhea, constipation, difficulty in eating and anorexia (65), which tend to reduce in severity with time. iii) Other: Fatigue.

In the SOLO-1/2 trial, 3 patients in the olaparib group developed acute myeloid leukemia (AML) or myelodysplastic syndrome (MDS). Therefore, patients who begin therapy with a PARP inhibitor must be advised about this 3% risk of developing AML or MDS (50).

Niraparib can cause hypertension, tachycardia and headaches due to its interaction with the norepinephrine dopamine carriers; therefore, patients affected by hypertension have to monitor their blood pressure regularly (66).

Rucaparib can cause a benign elevation both in liver function tests and in serum cholesterol during the first few weeks of treatment (60).

Table I. Studies of PARP-inhibitors in epithelial ovarian cancer.

First author, year	Patient Population	Therapies and doses	Outcomes	(Refs.)
Audeh *et al*, 2010	Two cohorts of women (aged ≥18 years) with confirmed genetic *BRCA1* or *BRCA2* mutations and recurrent, measurable disease.	First cohort (n=33): Continuous oral olaparib at the maximum tolerated dose of 400 mg twice daily. Second cohort (n=24): Continuous oral olaparib at 100 mg twice daily.	ORR was 11 (33%) out of 33 patients (95% CI, 20-51) in the cohort assigned 400 mg olaparib twice daily and 3 (13%) out of 24 (4-31) in the cohort assigned 100 mg twice daily.	(45)
Gelmon *et al*, 2011	Women with advanced high-grade serous and/or undifferentiated ovarian carcinoma or triple-negative breastancer were cstratified according to whether they had a *BRCA1* or *BRCA2* mutation or not. A total of 91 patients were enrolled (65 with ovarian cancer and 26 breast cancer).	Olaparib at 400 mg twice daily.	In the ovarian cancer cohorts, confirmed objective responses were seen in 7 (41%; 95% CI, 22-64) out of 17 patients with *BRCA1* or *BRCA2* mutations and 11 (24%; 95% CI, 14-38) out of 46 patients without mutations. No confirmed objective responses were reported in patients with breast cancer.	(46)
Swisher *et al*, 2017	A total of 204 patients with recurrent, platinum-sensitive, high-grade ovarian carcinoma were classified into one of three predefined homologous recombination deficiency subgroups on the basis of tumor mutational analysis: *BRCA* mutant (deleterious germline or somatic), *BRCA* wild-type and LOH high (LOH high group), or *BRCA* wild-type and LOH low (LOH low group).	Rucaparib at 600 mg twice daily for continuous 28 day cycles.	Progression-free survival was significantly longer in the *BRCA* mutant (hazard ratio, 0.27; 95% CI,0.16-0.44; P<0.0001) and LOH high (hazard ratio, 0.62; 95% CI, 0.42-0.90; P=0·011) subgroups compared with that in the LOH low subgroup.	(52)
Mirza *et al*, 2016	A total of 553 patients were enrolled and categorized according to the presence or absence of a germline *BRCA* mutation (g*BRCA* cohort andnon-g*BRCA* cohort). Of these, 203 were in the g*BRCA* cohort (with 138assigned niraparib and 65 placebo), and 350 patients were in the non-g*BRCA* cohort (with 234 assigned niraparib and 116 placebo).	Niraparib at 300 mg or placebo once daily.	Patients in the niraparib group had significantly longer median PFS times than those in the placebo group, namely 21.0 months vs. 5.5 in the g*BRCA* cohort (hazard ratio, 0.27; 95% confidence interval [CI], 0.17 to 0.41), as compared with 12.9 months vs. 3.8 months in the non-g*BRCA* cohort for patients who had tumors with homologous recombination deficiency (hazard ratio, 0.38; 95% CI, 0.24 to 0.59) and 9.3 months vs. 3.9 months in the overall non-g*BRCA* cohort (hazard ratio, 0.45; 95% CI, 0.34 to 0.61; P<0.001 for all three comparisons).	(54)

ORR, objective response rate; LOH, loss of heterozygosity.

8. Future development of PARP inhibitors in EOC

Ongoing trials are questioning the new possible clinical applications of PARP inhibitors in EOC, as first-line maintenance therapy or in combination with chemotherapy, but also the potential cross-resistance among all PARP inhibitors. In fact, the pharmacological strategy based on PARP-after-PARP could be considered in women who have failed to respond to one PARP agent or who have progressed after the initial response.

Maintenance therapy plays a central role in the clinical use of PARP agents, both as a first-line and a second-line response to platinum-based chemotherapy and as third-line maintenance.

Other clinically relevant questions to elaborate on in the treatment of EOC with PARP inhibitors are the possible combination therapies with standard platinum-based cytotoxic therapy, bevacizumab, a checkpoint inhibitor and a topoisomerase I inhibitor, such as topotecan.

The last cited strategy is based on the activity of topoisomerase I to bind DNA during its replication or repair, tempering SSBs and diminishing the associated distortional tension (67). Topotecan is still approved for EOC therapy due to its ability to induce de-stabilization of the replication forks promoting DNA lesions (68,69). PARP-1 is activated by topotecan and induces DNA lesion-reducing DNA breakage (69). In the light of these considerations, topoisomerase I inhibition with topotecan in combination with PARP inhibition could lead to a magnification and strengthening of the anti-EOC response. This therapeutic strategy has been explored in pre-clinical studies and is now under clinical investigation, as *in vitro* anti-tumor effects have been shown to be highly potentiated (70-73).

Another clinical approach involving PARP inhibitors is represented by their potential ability to radiosensitize EOC (74). In a recently published study, *BRCA*1-deficient high-grade ovarian cancer cells were shown to be more sensitive to radiotherapy alone after olaparib-mediated radiosensitization, compared with *BRCA*1-proficient cells. Furthermore, when used in association with radiotherapy, olaparib inhibited DNA damage repair and PARP-1 activity, increased apoptosis and increased OS.

All these notable and potentially revolutionary clinical applications of PARP inhibitors must be considered alongside the potential associated toxicities, first of which is the onset of MDS and AML; this toxicity seems to be due to prior DNA damage caused by cytotoxic chemotherapy. The overall risk of MDS and AML after PARP inhibitors is <3%, with a number of patients having received >5 years of continuous PARP inhibitor therapy without onset. In the future, longer treatments in a larger population of patients will be required; therefore, the incidence of these serious events must be carefully evaluated.

Finally, PARP inhibitors represent a new important weapon against EOC, which is known to be associated with a poor prognosis, with a few therapeutic options. The potential clinical efficacy of PARP inhibitors lies not only in their peculiar mechanisms of action, but also in the number of clinical approaches they are involved with. The near future may provide the answers to all questions related to PARP inhibitors in this context.

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Authors' contributions

GR and GC conceived and designed the study of comparison among PARP inhibitors. VL, AK, MDL, VDV and EN performed the literature review, selecting information and clinical trials. VL wrote the original draft of the manuscript and ML revised English language and syntaxes. EN, ML, CDG, GG, EC and GR critically revised the manuscript for important intellectual content in terms of clinical trial results, adverse reactions and future perspectives in therapy. GC, GG, EN, CDG and GR supervised the study. All authors read and approved the final manuscript.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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