DNA damaging agents in ovarian cancer

Maria-Pilar Barretina-Ginesta[*]

Department of Medical Oncology, Catalan Institute of Oncology (ICO) Girona, Girona Biomedical Research Institute (IDIBGI), Department of Medical Sciences, Medical School University of Girona (UdG), Spain

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ABSTRACT

Epithelial ovarian cancer (EOC) is very sensitive to upfront chemotherapy. This condition is attributable to defects in the DNA damage repair system. Agents that damage DNA are the main drugs used for its treatment. Many EOC cells have DNA repair deficiencies that confer susceptibility to these agents. Platinum is the most important agent for first-line and also for relapses, together with other drugs that can be given as monotherapy or along with platinum or other drugs. Lately, the emerging role of PARP inhibitors has changed the landscape of opportunities for patients with EOC. All these strategies will be reviewed in this article.

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1. Introduction

DNA repair deficiency confers cancer susceptibility and represents a common feature of carcinogenesis, as it drives malignant transformation with the accumulation of genomic alterations in cancer cells [1]. Conversely, normal and cancer cells rely on multiple DNA damage repair (DDR) pathways specialised in repairing specific forms of DNA damage, providing a compensating mechanism for cancer cells to avoid non-viable amounts of genotoxic stress [2]. Key DNA repair pathways include base excision repair, nucleotide excision repair, mismatch repair, homologous recombination repair (HRR), non-homologous end-joining (NHEJ), and inter-strand cross-link repair [3,4]. Many ovarian cancer (OC) histologies have some degree of DNA repair defects, particularly high-grade serous (HGS), as swell as high-grade endometrioid cancer where DNA repair defects have been found in approximately 50% of cancers [5]. This makes them more sensitive to agents damaging DNA, which will be reviewed in this paper.

2. DNA reactive agents: platinum-containing drugs

Cisplatin, carboplatin and oxaliplatin are active agents in OC. They directly modify DNA bases, intercalating between bases or forming cross-links in DNA.

Platinum agents were introduced in the late 1970s when different clinical studies reported that cisplatin doubled overall response rates (ORRs) compared with non-platinum schedules including other DNA alkylators such as cyclophosphamide [6]. At the end of the 1990s, carboplatin was considered the standard first-line therapy after being compared with cisplatin in a non-inferiority trial of platinum-taxane doublets [7].

Specifically, platinum-taxane doublets represent the gold standard of treatment (both in adjuvant and neoadjuvant

setting) in epithelial ovarian cancer (EOC). Platinum together with paclitaxel, pegylated liposomal doxorubicin (PLD) or gemcitabine has shown better results than carboplatin alone for platinum-sensitive relapses in different phase III trials [8−10].

3. Antimetabolites: gemcitabine

Gemcitabine is a pyrimidine analogue. Once incorporated to DNA, its intracellular metabolites inhibit its synthesis and induce cell apoptosis. It has been shown to be active as single agent in patients for whom platinum is not an option with progression-free survival (PFS) of 3.6 months and overall survival (OS) of 12.7months [11]. Gemcitabine also increased PFS (from 5.8 to 8.6 months) when added to carboplatin compared with carboplatin alone in a phase III trial [9].

4. Topoisomerase poisons: anthracyclines, topotecan and etoposide

Topoisomerases are enzymes that participate in the overwinding or unwinding of the DNA. When their function is limited, replication fork progression is inhibited and double strand breaks may appear.

PLD is an anthracycline that is delivered in vesicles called liposomes. This formulation allows increasing doses in the tumour. Its mechanism of action consists of poisoning topoisomerases, this is, stabilises the topoisomerase II complex after it has broken the DNA chain for replication, preventing the DNA double helix from being resealed and thereby stopping the process of replication.

PLD has shown activity as both single agent in patients with platinum-sensitive relapse (showing no inferiority as a platinum doubled compared with platinum-paclitaxel in the CALYPSO trial [10]) and as monotherapy [12].

Topotecan binds to the topoisomerase I-DNA complex and prevents religation of the DNA strand, resulting in double-stranded DNA breakage and cell death. It is active as single agent for patients for whom platinum is not an option, although its use is less common due to its higher renal and haematological toxicity compared with other alternatives as weekly paclitaxel and PLD [13].

Etoposide forms a complex with topoisomerase II and DNA. This complex induces double-stranded DNA breaks and avoids repair by topoisomerase II bindings. It acts in the G2 and S phases of the cell cycle, preventing the cell to enter in the mitotic phase of cell division, leading to cell death. Etoposide is active both in platinum-sensitive and platinum-resistant relapses of EOC, with a 26.8% and 32% response rate and 5.7 and 6.3 months in PFS. Most common toxicity is haematological [14].

5. Trabectedin

Trabectedin is a tetrahydroisoquinoline alkaloid that was isolated from the Caribbean tunicate Ecteinaiscidia turbinate in the late 1960s and is currently produced synthetically [15].

The cytotoxic effects of trabectedin depend on its binding to the minor groove of DNA at the N2 position of guanine with some sequence specificity which causes an unusual DNA helix distortion, triggering a cascade of events that interfere with several transcription factors, DNA-binding proteins, and DNA repair pathways, resulting in G_2-M cell cycle arrest and ultimately apoptosis. Trabectedin-induced DNA damage requires double-stranded DNA break (DSB) repair and HRR, suggesting a pivotal role of this pathway in drug-induced cytotoxicity, being cells lacking the hazard ratio (HR) pathway indeed extremely sensitive to the drug [16,17]. Trabectedin is approved in combination with PLD for those platinum-sensitive patients unable or unwilling to receive carboplatin due to previous toxicity or contraindications such as platinum hypersensitivity reactions based on the results of the OVA-301 trial. This phase III randomised trial compared PLD in combination with trabectedin vs. PLD alone. The combination showed a median PFS of 7.3 months versus 5.8 months [HR = 0.79, 95% confidence interval (CI) = 0.65−0.96, p = 0.019]. This difference was maintained in the platinum-sensitive population: PFS of 9.2 months vs. 7.5 months (HR = 0.73, 95% CI = 0.56−0.95, p = 0.017) [18]. Of interest, a post hoc analysis in the partially platinum-sensitive patient population suggested that platinum-free interval can be artificially prolonged using a non-platinum regimen. Trabectedin plus PLD induced a 6-month longer median OS, with a significant 36% decrease in the risk of death compared with PLD alone (22.4 months vs. 16.4 months, HR = 0.64, p = 0.0027) [19]. Based on these results, the INOVATYON phase III trial (NCT01379989) has been conducted to answer whether this combination is beneficial in terms of OS compared with standard carboplatin-PLD in the partially platinum-sensitive setting.

6. DDR and mechanisms of action of poly(ADP-ribose) polymerase inhibition

DNA damage involving single- and double-stranded breaks, occurs as part of routine cellular response to environmental and metabolic stress. Single-stranded breaks (SSBs) on DNA activate poly(ADP-ribose) polymerase (PARP) which ultimately leads to DDR. Once DDR is completed, PARP autoPARylates and is released from the repaired DNA strand [20]. Inhibition of PARP leads to stalling of the DNA replication fork, converting SSBs to DSBs. DSBs are repaired through two major pathways, the high fidelity HR pathway, and the more error-prone NHEJ pathway [21]. The interplay between the roles of PARP and HRR leads to the concept of synthetic lethality. In patients whose tumour exhibit HRR deficiency (e.g. through *BRCA1/2* mutations) inhibition of the PARP1/2 enzymes increases the demand for HR-directed repair and shifts DNA repair towards alternative error-prone repair pathways such as NHEJ, eventually leading to cellular lethality [22]. In addition to their catalytic action, PARP inhibitors also cause trapping of PARP1 and PARP2, forming PARP-DNA complexes with increased cytotoxicity leading to increased cell killing [23]. Different PARP inhibitors may vary in their specificity for PARP enzymes and PARP-trapping activity and the potency of PARP

trapping does not seem to correlate with its catalytic effect [24] (Table 1).

7. Clinical development of PARP inhibitors

PARP inhibitors have emerged as one of the most exciting new therapies for the treatment of OC.

8. Olaparib

Olaparib was the first PARP inhibitor to be approved by regulatory agencies. Olaparib first demonstrated to successfully induce cell-killing effects in BRCA-deficient cancer cells through inhibition of DDR in 2005 [25,26]. The Study 19, a randomised phase II, double-blinded placebo-controlled trial of olaparib maintenance therapy versus placebo in patients with relapsed platinum-sensitive HGS OC resulted in a significant improvement in a median PFS from 4.8 months on placebo to 8.4 months on olaparib (HR = 0.35, $p < 0.001$) [27]. In a retrospective analysis, the benefit of olaparib was shown to be more significant in BRCAm patients, including somatic BRCAm, showing a PFS benefit of 11.2 months with olaparib maintenance versus 4.3 months with placebo (HR = 0.18, $p < 0.0001$) [28]. Unfortunately, with 77% OS data maturity, the predefined study criteria for statistical significance for OS was not achieved ($p < 0.0095$). Based upon the Study 19 results, the European Medicines Agency approved olaparib in 2014 as maintenance for patients with relapsed platinum-sensitive BRCAm (germ line or somatic) OC after response to platinum-based chemotherapy. The Food and Drug Administration (FDA) conditionally granted accelerated approval for olaparib in December 2014 based on a pooled analysis from phase I and II studies of olaparib monotherapy in 300 women with relapsed ovarian, fallopian tube, or peritoneal cancer with gBRCAm who received 400 mg twice daily of olaparib monotherapy showing an ORR of 36% (95% CI: 30%–42%) and a median duration of response (DoR) of 7.4 months (95% CI: 5.7–9.1). Among patients who had received ≥3 prior lines of chemotherapy, the ORR was 31% (95% CI: 25%–38%), with a 7.8-month DoR (95% CI: 5.6–9.5) [29]. The ORR was 42% for platinum-sensitive patients versus 26% for platinum-resistant patients among those who had received ≥3 prior lines of chemotherapy.

Results from the phase III SOLO2 study, comparing olaparib vs. placebo as maintenance treatment after response to a platinum doubled in patients with platinum-sensitive

relapsed BRCAm OC, led to regulatory approval by the FDA for maintenance olaparib of adult patients with recurrent epithelial ovarian, fallopian tube or primary peritoneal cancer, who are in a complete or partial response to platinum-based chemotherapy. In the SOLO2 study, maintenance olaparib (tablets 300 mg orally twice daily) showed a 70% decrease in the risk for progression or death versus placebo, with an estimated mean PFS of 19.1 months and 5.5 months with olaparib and placebo, respectively, (HR = 0.30 [95% CI: 0.22, 0.41; $p < 0.0001$]) [30]. Olaparib has also shown benefit in PFS as maintenance after first-line treatment in the SOLO 1 trial. It included patients with BRCAm advanced HGS or endometrioid OC. HR for PFS was 0.30 (95% CI: 0.23–0.42) [31]. Olaparib has also shown benefit as maintenance treatment combined with bevacizumab in a phase III trial. The PAOLA-1 trial tested this combination as first-line treatment, resulting in a 6-month increase in PFS compared with bevacizumab with placebo in the overall population (22.1 vs 16.6 months, HR = 0.59; 95% CI: 0.49–0.72; $p < 0.001$). In this trial, patients with homologous recombination deficiency (HRD) tumours and BRCA mutations derived the greatest benefit in median PFS with olaparib compared with placebo (HRD: 37.2 vs. 17.7 months, HR = 0.33; 95% CI: 0.25–0.45; BRCA: 37.2 vs 21.7 months, HR = 0.31; 95% CI: 0.20–0.47) [32].

9. Rucaparib

Rucaparib, another potent inhibitor of PARP1, PARP2 and PARP3 has also demonstrated efficacy as single agent in OCs with both BRCA mutation (germ line and somatic subtypes) and HRR-deficient tumours. Indicated for the treatment of patients with advanced OC and BRCAm who have been treated with ≥2 prior chemotherapies, rucaparib gained accelerated approval from the FDA and came with a companion diagnostic, the FoundationFocusCDxBRCA, which was the first next-generation sequencing–based companion diagnostic approved by the FDA. The accelerated approval was based on results from two single-arm trials – Study 10 and ARIEL2 – comprising 106 patients with BRCA-mutated, advanced OC who had received treatment with ≥2 chemotherapy regimens [33,34]. In a pooled analysis of results from the two trials, the ORR was 54% with rucaparib, and the median DoR was 9.2 months. In addition, in ARIEL2 part 1, rucaparib demonstrated different efficacy profile based on three predefined HRD subgroups on the basis of tumour mutational analysis: BRCA mutant (deleterious germ line or somatic), BRCA wild-type and loss of heterozygosity (LOH) high (LOH high group), or BRCA wild-type and LOH low (LOH low group). Median PFS after rucaparib treatment was 12.8 months (95% CI: 9.0–14.7) in the BRCA mutant subgroup, 5.7 months (5.3–7.6) in the LOH high subgroup, and 5.2 months (3.6–5.5) in the LOH low subgroup. PFS was significantly longer in the BRCA mutant (HR = 0.27, 95% CI: 0.16–0.44, $p < 0.0001$) and LOH high (0.62, 0.42–0·90, $p = 0.011$) subgroups compared with the LOH low subgroup [35]. Data from ARIEL3, a randomised, double-blind, placebo-controlled, phase III trial, demonstrated improved PFS by investigator review for rucaparib compared with placebo in all three primary efficacy analyses: BRCA mutation (16.6 months vs. 5.4 months; HR': 0.23, $p < 0.001$); HRD-positive (13.6 months

Table 1 – Current PARP inhibitors.			
Drug	Company	IC50/ nM	Relative PARP trapping potency
Olaparib	AstraZeneca	6	1
Rucaparib	Clovis	21	1
Niraparib	Tesaro	60	2
Veliparib	AbbVie	30	<0.2
Talazoparib	Pfizer	4	100
PARP, poly(ADP-ribose) polymerase.			

vs. 5.4 months; HR': 0.32, $p < 0.001$); overall intent-to-treat populations (10.8 months vs. 5.4 months; HR': 0.36, $p < 0.001$) [36].

10. Niraparib

Niraparib was the first PARP inhibitor that got global FDA approval for maintenance therapy of patients with recurrent epithelial or fallopian tube cancer or primary peritoneal cancer who are in complete or partial response to platinum-based chemotherapy regardless of their BRCAm and HRD status. Regulatory approval was based on the results of the multinational, randomised, double-blinded, phase III clinical trial (ENGOT-OV16/NOVA trial) [37]. In NOVA trial, patients were dichotomised in two cohorts, each containing two arms, based on the status of gBRCAm (gBRCAm cohort and non-gBRCAm cohort) and assigned in 2:1 ratio to receive 300 mg niraparib or placebo. In gBRCA cohort, niraparib improved PFS compared with placebo from 5.5 months to 21 months (HR = 0.27; 95% CI: 0.17–0.4), whereas in the non-gBRCA cohort with HRD-positive patients, the median PFS was found to be 12.9 months and 3.8 months for niraparib and placebo groups, respectively [HR = 0.38; 95% CI: 0.24–0.59]. The overall PFS in non-gBRCA cohort regardless of HRD status was 9.3 months vs 3.9 months [HR = 0.45; 95% CI: 0.34–0.61]. Niraparib has also recently shown first-line PFS benefit as maintenance treatment after first-line platinum-based chemotherapy in the PRIMA trial [38]. The population of the study included all FIGO stage IV and stage III non operable, with residual disease at primary debulking surgery or receiving neoadjuvant treatment. The PFS in this high-risk population with homologous recombination deficiency including BRCA-mutated patients (50.9%) was significantly longer in the niraparib group than in the placebo group (21.9 months vs. 10.4 months; [HR = 0.43; CI: 0.31–0.59]). In the overall population PFS was 13.8 vs. 8.2 months (HR = 0.62; 95% CI: 0.50–0.76).

11. Other PARP inhibitors: veliparib and talazoparib

A phase I/II study of veliparib in patients with germ line BRCA mutations and platinum-resistant or partially platinum-sensitive relapse of EOC determined the maximum tolerated dose to be 300 mg twice daily and showed a 65% ORR [39]. More recently, a phase III randomised trial comparing carboplatin-paclitaxel to carboplatin-paclitaxel-veliparib followed by veliparib maintenance has shown the maximum benefit among BRCAm cohort (median PFS 34.7 vs. 22 months [HR = 0.44; 95% CI: 0.28–0.68]). For the HRD cohort, it was 31.9 vs. 20.5months (HR = 0.57; 95%CI: 0.43–0.76) and in the intention-to-treat population PFS was 23.5 vs 17.3months (HR = 0.68; 95% CI: 0.56–0.83) [40].

Talazoparib, an additional PARP inhibitor that exhibits superior PARP-trapping capabilities compared with other PARP inhibitors, demonstrated a 42% ORR in a phase 1 dose escalation, first-in-human trial [41].

Haematological toxicities are the most common class effect of PARP inhibitors and the main cause of dose modification, interruption and discontinuation although the latter is necessary in less than 15% of patients for all of them. Anaemia is the most common haematological toxicity for all PARP inhibitors (20–25% G3-4). Thrombocytopenia is more common with niraparib (34% G3-4) yet it is manageable with dose reduction and typically occurs during the first month of treatment. Gastrointestinal adverse events are also common with these drugs with nausea being the most common with only 3–4% of patients with G3 or 4. Characteristically, rucaparib produces elevation of liver enzymes without repercussion in liver function and correctable with dose reduction when indicated. This toxicity profile, its posology and metabolism can help in the decision of which PARP inhibitor offer to patients in routine practice [42].

There is no doubt about the impact of PARP inhibitors on the treatment algorithm of patients with OC. Their benefit is greater for patients with somatic or germ line BRCA mutation. It is also of bigger magnitude for patients with HRD compared with those without it. Yet, no biomarker has been able to select patients who will not benefit from this treatment.

Further understanding of the mechanism(s) of action and resistance is leading to the exploration of novel therapeutic combinations. Combination of PARP inhibitors with immunotherapy [43] and antiangiogenics [44] have shown promising activity in advanced late lines of treatment and are under evaluation together with chemotherapy in first-line (NCT03522246, NCT03602859, NCT03740165, NCT03737643) and in platinum-sensitive relapses (NCT03598270, NCT03278717).

Nonetheless, several outstanding issues still remain to be answered, which may eventually help to better define the patient populations that will benefit from treatment with PARP inhibitors and combination therapies.

12. Conclusions

Agents that damage DNA are essential for the treatment of EOC. Platinum is still one of the milestones of this treatment not only for its efficacy but also for its prediction of later benefit to PARP inhibitors. Platinum together with other agents has changed the prognosis of patients with EOC. The recent introduction of PARP inhibitors has added a significant treatment strategy to the therapeutic armamentarium. However, beyond histology and BRCA mutations, we still do not have a robust biomarker of platinum and PARP inhibitor sensitivity to select patients who will not benefit from these treatments.

The aforementioned studies, along with the results of ongoing studies combining these important drugs with other strategies, such as immunotherapy and antiangiogenics, are going to change the scenario of EOC treatment to personalise strategies and improve the results.

Conflict of interest statement

Tesaro-GSK, Clovis, Roche, AstraZeneca and PharmaMar; has received travel expenses from Tesaro-GSK, Roche, AstraZeneca and PharmaMar.

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