Currently Approved Poly (Adenosine Diphosphate-Ribose) Inhibitors in Ovarian Cancer: Current Status and Future Directions

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Abstract: Background: Poly (adenosine diphosphate [ADP]-ribose) polymerase inhibitors have entered into the clinic rapidly and are becoming a powerful therapeutic tool, especially in the management of BRCA associated ovarian cancers. PARP inhibitors have exploited the homologous recombination deficiency, present in up to 50% of ovarian cancers, through synthetic lethality: A novel therapeutic approach to this disease.

Objective: Through an extensive review of PARP inhibitors we evaluated the existing evidence in the clinical trial as monotherapy and combined with chemotherapy in ovarian cancer.

Conclusion: PARP inhibitors have demonstrated to fulfill the characteristics of the ideal maintenance therapy agent. Understanding biomarkers in this scenario holds maximum importance to allow its foresee potential, although “platinum-sensitivity” shows to be a “functional biomarker", reflecting a homologous recombination deficiency phenotype, thus, proving sensitivity to PARP inhibitors. Many clinical studies are ongoing marking its future directions and analyzing its effect on several combinations. Numerous questions remain unanswered, such as mechanisms of resistance or sequential use, and need to be explored completely through ongoing research.

Keywords: Ovarian cancer, PARP inhibitors, homologous recombination deficiency, synthetic lethality, polymerase inhibitors, disease free survival.

1. INTRODUCTION

Ovarian cancer remains the most lethal gynecological cancer with around 30% of patients (pts) alive 5 years after diagnosis. Different phase III trials have explored diverse ways of delivering Chemotherapy (CT): Intraperitoneally [1, 2], dose dense [3-5] or adding anti-angiogenic agents [6-9]; or the combination of both strategies [10] with no benefit in overall survival (OS), and only prolonging Disease-Free Survival (DFS), specially benefitting those pts rendered with residual disease (R1) after primary cytoreductive surgery.

Therefore, since relapse is an event that will eventually occur in more than three quarters of pts within the first 2 years of diagnosis after optimal debulking surgery and standard adjuvant carboplatin/paclitaxel every 3 weeks for 6 cycles [11, 12], the focus of research in ovarian cancer has been the “maintenance therapy”, defined as the treatment during the period between complete or partial response to progression [13]. The ideal agent for such a treatment should not only prolong the CT-free intervals but at the same time, preserve patients’ Quality-of-Life (QoL).

PARP inhibitors (PARPi) have demonstrated to be effective in this scenario, fulfilling the characteristics of the ideal maintenance therapy agent [14-19]. Nevertheless, this is mostly due to the fact that they are particularly active in ovarian cancer because this disease has a defect that makes it more sensitive to these agents: Homologous Recombination Deficiency (HRD), which is present in up to 50% of cases of High-Grade Serous Ovarian Cancer (HGSOC).

2. HOMOLOGOUS RECOMBINATION DEFICIENCY IN OVARIAN CANCER

DNA damage is a frequent event in metabolically active cells but even more in cancer cells under replicative stress and free-radicals of oxygen generated within the hypoxic environment of a tumor [20]. Single-strand DNA damage is repaired by base-excision repair and PARP plays a key role in activating this mechanism through PARilation of different nucleo-proteins involved in DNA repair [21-25].

Homologous recombination (HR), on the other hand, is a much more intricate mechanism through which the cell repairs more lethal lesions to its genetic material, as double-strand damage. Its complexity resides in the fact that cells have to create an exact copy of the damaged segment using the sister chromatid as a template. This process requires its recognition among thousands of genes that are replicating at the same time and the activation of the machinery to assemble this restoration [20, 26]. It is in this procedure that BRCA 1 & 2 proteins play a key role, among other proteins involved in HR: BARD 1, BRIP 1, RAD 51 and PTEN.
Genome sequencing of HGSOC showed that germline BRCA 1 & 2 mutations (gBRCA\textsuperscript{mut}) were prevalent in up to 14% of cases. Considering somatic mutations (sBRCA\textsuperscript{mut}), which account for approximately 6-8% of cases, the prevalence of BRCA 1 & 2 mutations ascends to 22% [27]. As mentioned before, there are other genes that encode proteins involved in HR and can create an HRD phenotype (BRCAness syndrome), yet the low prevalence of each individual mutation hinders its clinical use and the understanding of its relationship with PARPi sensitivity [28]. Collectively, it is considered that 50% of HSGOC are HRD [27]. When the cell cannot repair double-strand DNA through HR, it uses a more error-prone mechanism known as Non-Homologous End Joining (NHEJ) in which the injured segment is simply cut and the 3’ and 5’ ends proximal and distal to it are joined, with the subsequent loss of genetic material [29, 30].

There is clinical evidence that ovarian cancer is an HRD disease and that the mutations generating this phenotype are an early event in the genesis of relapse:

- Platinum-salts, specially diamino-cyclohexane (DACH) platinum, injure DNA by forming inter-catenary adducts [31]. This is equivalent to double strand damage and an efficient HR is required to repair its consequences. Ovarian cancer responds to platinum even in 2\textsuperscript{nd} or 3\textsuperscript{rd} lines, with high overall response rates (ORR). This platinum-sensitivity shows that ovarian cancer fails in the mechanism needed to repair platinum-damage: HR, holding true especially for BRCA\textsuperscript{mut} ovarian cancer, the paradigm of HRD [32-34].

- Even in pts with early-relapses (considered "platinum-resistant"), ORR of 30% has been reported with platinum-combinations, as cisplatin/gemcitabine [35, 36]. This fact suggests that the acquisition of HRD phenotype occurs early (<6 months) upon repopulation of the tumor at relapse (from cancer stem cells?) [13, 37].

**2.1. PARP Inhibitors and Synthetic Lethality**

PARPi exploit HRD creating an irreversible situation that cells are not able to solve. After single-strand breaks, frequently generated by free-oxygen radicals, PARPi arrives at the site of the lesion to activate the other repair proteins. But PARPi like Olaparib, Niraparib and Rucaparib, trap it within the histone complexes. Thus, when the replication fork arrives to replicate the damaged-DNA, it is stopped by the complex PARP/PARPi. The interruption transforms the single-strand damage into a double-strand lesion: the originally injured strand and the copy that could not continue its replication. In normal conditions, if the cell has an efficient HR, the damage is repaired and the cell survives. This is what happens in cells that retain at least one non-mutated allele of the BRCA 1 or 2 genes, even if the other is mutated, like in non-tumoral cells of gBRCA\textsuperscript{mut} carriers [38, 39].

But in a tumour that is HRD, most commonly after losing the normal copy of the BRCA allele, the cell cannot repair the double-strand damage that has been generated by PARPi (synthetic lethality). This leads to a situation of chromosomal instability due to loss of genetic material, large-scale transitions and allelic telomeric misbalances in which the cell can hardly survive [21] (Fig. 1).

For ovarian cancer, being an HRD disease in a very important proportion of pts, PARPi are attractive oral agents that have been evaluated in different scenarios.

**3. CLINICAL ACTIVITY OF PARPi**

**3.1. Classification of PARPi**

Depending on whether they exert a catalytic inhibition or their trapping capacity of PARPi, they can be classified into class 1 (Veliparib) or class 2 (olaparib, niraparib and rucaparib) (Table 1) [40].

PARPi trapping capacity translates clinically in greater toxicity and makes class 1 veliparib the candidate to be evaluated with fist-line CT and low dose cyclophosphamide in later ovarian cancer [41-43].

**3.2. Single Agent Activity of PARPi**

Since the first reports by Farmer et al. [21] of selective activity of Olaparib in BRCA 1 & 2\textsuperscript{mut} cells, demonstrating that homozygous mutated cells were 100 times more sensitive to this agent than the BRCA\textsuperscript{mut} cells that were heterozygous for the mutation, multiple phase II trials have been conducted with this agent in Relapsed Ovarian Cancer (ROC). Promising single agent activity (ORR 33%, PFS 5.8 m) was detected in heavily pre-treated population (50% of patients with more than 4 previous lines) with a toxicity profile different from CT and an orally taken agent [44]. Response rates were considered very important as a significant proportion were classified as platinum-resistant [45]. Kauffmann et al. showed in this poor prognosis population, especially in the most sensitive phenotype to PARPi (gBRCA\textsuperscript{mut}) [39], an ORR of 26.4% in a phase II trial that also included other BRCA\textsuperscript{mut} tumors, with a good toxicity profile (mostly anaemia), in a heavily pre-treated, large-volume disease, relapsed pts.

Martulonis et al. performed a pooled analysis of Olaparib activity in gBRCA\textsuperscript{mut} pts as monotherapy for ROC. There was an inverse relationship between ORR and the number of previous lines received, with responses being more frequent in platinum-sensitive relapses [46].

Although there have been no “head-to-head” comparisons among them, 4 clinically available drugs have been evaluated in this scenario, Olaparib being the most extensively studied therapy in ovarian cancer. A summary of single agent activities of PARPi in BRCA\textsuperscript{mut} ovarian cancer is presented in Table 2.

Each drug is metabolized differently and other drugs that the pts are taking may influence their PARPi levels. Drug interactions can occur, based on CYP induction or inhibition. Effect on renal transporters MATE1 and MATE 2-K can increase serum creatinine [47].

Toxicity profile among them varies, but the majority of toxicities are manageable and less than 45% are grade 3-4. Anaemia, asthenia and cephalea are common in olaparib, rucaparib and niraparib. Hypertension and increased creatinine (not necessarily related to renal insufficiency) are frequent with rucaparib [16, 48] and hypertension and dyspnea are more frequently observed with niraparib [14].
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Fig. (1). PARP inhibitors and synthetic lethality.

SSB: single strand breaks; DSB: double strand breaks; HRD homologous recombination deficient

Table 1. Classification of PARP inhibitors.

<table>
<thead>
<tr>
<th>PARP inhibitors</th>
<th>Catalityc Inhibition (IC50 nM)</th>
<th>Citotoxicity (IC90 μ M)</th>
<th>PARP Trapping Potency (Related to olaparib)</th>
<th>Class</th>
</tr>
</thead>
<tbody>
<tr>
<td>Veliparib</td>
<td>30</td>
<td>&gt; 50</td>
<td>&lt; 0.2</td>
<td>Class 1</td>
</tr>
<tr>
<td>Olaparib</td>
<td>6</td>
<td>4.5</td>
<td>1</td>
<td>Class 2</td>
</tr>
<tr>
<td>Rucaparib</td>
<td>21</td>
<td>3</td>
<td>1</td>
<td>Class 2</td>
</tr>
<tr>
<td>Niraparib</td>
<td>60</td>
<td>2.3</td>
<td>≈ 2</td>
<td>Class 2</td>
</tr>
</tbody>
</table>

Based on ORR of 34% and 55.8% for Olaparib [39] and Rucaparib [48], respectively in gBRCA<sup>mut</sup> pts, FDA granted approval of these agents after progression to 3 or 2 lines of therapy in this subgroup of BRCA<sup>mut</sup> pts.

Study 9 was a phase II trial that compared two doses of Olaparib versus Pegylated Liposomal Doxorubicin (PLD) in BRCA<sup>mut</sup> pts, showing nonsignificant differences in PFS, but this might be simply because BRCA<sup>mut</sup> pts are more “chemosensitive” [45]. In fact, there have been reports of higher ORR in these pts than in BRCA<sup>wt</sup> pts [49]. Nevertheless, the possibility of using a well-tolerated oral agent in heavily-pretreated pts (if they are BRCA<sup>mut</sup>), even if they are platinum-resistant, still make early knowledge of BRCA status in ovarian cancer pts a “must” regardless of their age at diagnosis or family history [50-52].

3.3. PARPi in Combination with Chemotherapy

There have been 2 phase II trials randomizing platinumsensitive relapsed ovarian cancer pts to platinum-based CT
+/- olaparib and then maintenance in the experimental arm [53]. The lack of difference in terms of ORR between the CT+placebo vs the CT+olaparib, and the separation of the PFS curves right after the concurrent phase ends, suggest that the role of this PARPi is in the maintenance phase (median 12.2 months [95% CI 9.7–15.0] vs 9.6 months [9.1–9.7]; HR 0.51 [95% CI 0.34–0.77]; p=0.0012). Even though, this lack of synergistic/additive effect may be attributed to the fact that due to toxicity, Carboplatin AUC had to be reduced to 4 and Olaparib dose was 200mg capsules twice daily concurrently and 400mg capsules twice daily during maintenance phase.

The Velia Trial is a phase III first-line trial, which has recently ended accrual across the world, randomizing pts after primary or interval debulking surgery for recently diagnosed ovarian cancer to CT +/- Veliparib and class I PARPi as maintenance therapy [54]. This agent, due to its function as a catalytic inhibitor of PARP is believed to be associated with less toxicity. Evidence from Study 42, evaluating class II PARPi (Olaparib) combination with platinum-based CT, showed elevated toxicity and frequent carboplatin dose reductions [53]. At the moment, there are trials evaluating its combination with chronomodulated oral-cyclophosphamide in ROC pts [41].

3.4. PARPi as Maintenance Therapy

Since the combination with CT proved to be too toxic and with no synergistic effect, the role of PARPi seems to be predominantly as “maintenance therapy”: The treatment between the maximum response achieved by platinum-based CT (either complete response or partial response), and subsequent progression. Information of trials in this scenario is summarized in Table 3.

So far, median PFS with either CT or CT + Bevacizumab is between 8 to 12 months [7, 9, 55-57], of which the patients spend 4-6 months receiving CT, just to find out six months later it has progressed. Consequently, extending that “CT-free” period with a well-tolerated agent with no major deleterious impact in QoL is a goal we need to achieve in these relapsed pts, in whom we know, progression is going to occur at shorter intervals and with larger-volume disease [58].

Study 19 was a phase II trial evaluating the role of olaparib as maintenance therapy in platinum-sensitive relapsed ovarian cancer irrespective of their BRCA status. 265 pts who responded to platinum-based CT for platinum-sensitive relapse were randomized to maintenance with Olaparib dose of 400 mg twice daily (in 50 mg capsules) versus placebo [59]. At the moment of randomization, only a third of pts were known to harbor a deleterious BRCA 1 or 2 mutation. In the ITT analyses, pts who received olaparib maintenance had a better PFS (8.4 vs 4.8m) with an HR 0.35 (95%CI 0.25 to 0.49; P<0.001). Although OS was not a primary endpoint of this trial and therefore was not designed to detect a difference between the arms in that end-point, there was no difference in OS between the two arms. Given that BRCA 1 & 2mut pts seemed to get the greatest benefit in PFS (11.2 months [95%CI 8.3–not calculable] vs 4.3 months [3.0–5.4]; HR 0.18 [0.10–0.31]; p=0.0001), a subanalysis of these BRCA mutated pts (which retrospectively constituted 56% olaparib group population and 50% of placebo group) was carried out. This was the greatest benefit ever observed with an agent in OC, but mostly due to the fact that it is a biomarker-driven therapy: With BRCA mutation, being the biomarker of the therapy.

At the final analyses of data with more than 70% of the events, showed no benefit in terms of OS in the olaparib arm, not even in BRCA\textsuperscript{mut} pts [60]. Whether this was an effect of the 23% of cross-over to the olaparib arm or to the fact that it was a CT-sensitive population (subsequent cancer treatments had been received by 89 (65%) of 136 patients from the olaparib group and 111 (86%) of 129 patients from the placebo group) we do not know. What evidence clarifies

Table 2. Summary of single agent activities of PARPi in BRCA\textsuperscript{mut} OC.

<table>
<thead>
<tr>
<th></th>
<th>Olaparib</th>
<th>Rucaparib</th>
<th>Niraparib</th>
<th>Veliparib</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of patients</td>
<td>137</td>
<td>106</td>
<td>20</td>
<td>50</td>
</tr>
<tr>
<td>Number of lines of prior therapy</td>
<td>At least 3</td>
<td>At least 2 (43% 3 or more lines)</td>
<td>Not described</td>
<td>1 line: 34% 2 or more lines: 68%</td>
</tr>
<tr>
<td>Response rate</td>
<td>34%</td>
<td>54%</td>
<td>40%</td>
<td>26%</td>
</tr>
<tr>
<td>Response rate based on platinum sensitivity</td>
<td>Unknown</td>
<td>Sensitive 66% Resistant 25% Refractory 0%</td>
<td>Sensitive 50% Resistant 33% Refractory 0%</td>
<td>Sensitive 35% Resistant 20%</td>
</tr>
<tr>
<td>Median duration of response (months)</td>
<td>7.4</td>
<td>9.2</td>
<td>12.9</td>
<td>8.18 (Median PFS)</td>
</tr>
</tbody>
</table>

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is that in all secondary endpoints, olaparib arm was significantly benefited (Time to first systemic progression median 8.3 months vs. 3.7 months; HR 0.35; 95% CI, 0.25 to 0.47; P<0.001). This was achieved with a good toxicity profile (fatigue 8% vs. 3% and anemia 6% vs. 1%), with less than 10% of pts withdrawing from treatment because of toxicity and less than 45% of grade 3-4 events.

Olaparib-treated pts experienced more nausea during the first few months of treatment compared with placebo-treated pts; however, over time, differences between treatment groups were minimal. Olaparib maintenance treatment had no detrimental impact on QoL as compared with placebo, both for the overall study population of SOC patients and for BRCAmut pts [61].

The results of this trial led to EMA and many other countries of the world (like Argentina, Costa Rica, Panamá, Ecuador, etc.) [62] approval of Olaparib as maintenance therapy after showing complete or partial response to platinum-based CT in BRCA 1 or 2 mutated pts, for platinum-sensitive relapsed ovarian cancer at a dose of 400 mg B.I.D.

SOLO-2 was a phase III trial which enriched its population by recruiting only BRCA 1 or 2mut pts, randomizing 295 patients, after achieving a response to platinum-based CT for platinum-sensitive ROC, to either placebo or Olaparib (in the 150mg tablet formulation) 300 mg B.I.D until progression. The median of previous lines in both arms was 2 and 46% achieved a complete response to previous platinum therapy. In this trial, maintenance with olaparib reduced the risk of progression by 70% [17]. Main toxicities were anemia (19% grade 3-4), asthenia (4% grade 3-4) and GI symptoms (3% grade 3-4), but the treatment had no negative impact in QoL, as presented in ASCO 2017 [63].

Given the results of this trial as well as Study 19, FDA recently approved Olaparib 150 mg tablets at a dose of 300 mg B.I.D, after showing a response to platinum-based chemotherapy; with an “all comers” criteria as maintenance therapy regardless of their BRCA status [64].

Table 3. Summary of phase II and III trials with PAPRP inhibitors as maintenance therapy.

<table>
<thead>
<tr>
<th>Trial (Drug)</th>
<th>Population</th>
<th>Sample Size</th>
<th>Progression Free Survival (Months)</th>
<th>Hazard Ratio (CI95%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Study 19 (Olaparib)</td>
<td>Relapsed platinum sensitive ovarian cancer</td>
<td>265</td>
<td>8.4 vs 4.8</td>
<td>0.35 (0.25-0.49)</td>
</tr>
<tr>
<td>SOLO-2 (Olaparib)</td>
<td>BRCA mutated relapsed platinum sensitive ovarian cancer</td>
<td>295</td>
<td>19.1 vs 5.5</td>
<td>0.30 (0.22-0.41)</td>
</tr>
<tr>
<td>NOVA (Niraparib)</td>
<td>Relapsed platinum sensitive ovarian cancer</td>
<td>533</td>
<td>gBRCA 21.0 vs 5.5</td>
<td>0.27 (0.17-0.41)</td>
</tr>
<tr>
<td>NOVA (Niraparib)</td>
<td>Relapsed platinum sensitive ovarian cancer</td>
<td>533</td>
<td>Non-gBRCA HRD 12.9 vs 3.8</td>
<td>0.38 (0.24-0.59)</td>
</tr>
<tr>
<td>NOVA (Niraparib)</td>
<td>Relapsed platinum sensitive ovarian cancer</td>
<td>533</td>
<td>Non-gBRCA 9.3 vs 3.9</td>
<td>0.45 (0.34-0.91)</td>
</tr>
<tr>
<td>ARIEL 3 (Rucaparib)</td>
<td>Relapsed platinum sensitive ovarian cancer</td>
<td>564</td>
<td>ITT 10.8 vs 5.4</td>
<td>0.37 (0.30-0.45)</td>
</tr>
<tr>
<td>ARIEL 3 (Rucaparib)</td>
<td>Relapsed platinum sensitive ovarian cancer</td>
<td>564</td>
<td>BRCAmut 16.6 vs 5.4</td>
<td>0.23 (0.16-0.34)</td>
</tr>
<tr>
<td>ARIEL 3 (Rucaparib)</td>
<td>Relapsed platinum sensitive ovarian cancer</td>
<td>564</td>
<td>HRD (BRCAmut or BRCAmut/LOH high) 13.6 vs 5.4</td>
<td>0.32 (0.24-0.42)</td>
</tr>
<tr>
<td>ARIEL 3 (Rucaparib)</td>
<td>Relapsed platinum sensitive ovarian cancer</td>
<td>564</td>
<td>BRCAmut/LOH high 9.7 vs 5.4</td>
<td>0.44 (0.29-0.66)</td>
</tr>
<tr>
<td>ARIEL 3 (Rucaparib)</td>
<td>Relapsed platinum sensitive ovarian cancer</td>
<td>564</td>
<td>BRCAmut/LOH low 6.7 vs 5.4</td>
<td>0.58 (0.40-0.85)</td>
</tr>
</tbody>
</table>

ARIEL 3 (Rucaparib) was a phase III trial which enriched its population by recruiting only BRCA 1 or 2 mut pts, randomizing 295 patients, after achieving a response to platinum-based CT for platinum-sensitive ROC, to either placebo or Olaparib (in the 150mg tablet formulation) 300 mg B.I.D until progression. The median of previous lines in both arms was 2 and 46% achieved a complete response to previous platinum therapy. In this trial, maintenance with olaparib reduced the risk of progression by 70% [17]. Main toxicities were anemia (19% grade 3-4), asthenia (4% grade 3-4) and GI symptoms (3% grade 3-4), but the treatment had no negative impact in QoL, as presented in ASCO 2017 [63].

Given the results of this trial as well as Study 19, FDA recently approved Olaparib 150 mg tablets at a dose of 300 mg B.I.D, after showing a response to platinum-based chemotherapy; with an “all comers” criteria as maintenance therapy regardless of their BRCA status [64].

NOVA [14], was a phase III trial which randomized 553 pts with platinum-sensitive ROC who showed a “fairly good” response to platinum-based CT. Fifty percent of complete responders in each arm and partial responders were randomized after a major response, rendering the pts to a lesion of 2cm by RECIST. The trial allowed the enrollment of BRCA 1 & 2 mut pts (37%), as well as BRCA wild-type. In fact, not only a test for somatic BRCA mutation was performed, but also a test to evaluate the effect of HRD in the tumor was conducted (LOH+LST+ATTI) [65]. Pts were randomized to receive Niraparib vs placebo until progression. All pts benefited from Niraparib maintenance (21.0 vs. 5.5 months in the gBRCA cohort [HR 0.27; 95%CI 0.17 to 0.41], 12.9 vs. 3.8 months in the non-gBRCA cohort with HRD [HR 0.38; 95%CI, 0.24 to 0.59] and 9.3 vs. 3.9 months in the overall non-gBRCA cohort [HR 0.45; 95%CI, 0.34 to 0.61]) P<0.001 for all three comparisons. The greatest benefit was seen in BRCAmut pts (with no difference between germline or somatic mutations). Yet, even those classified as HRD negative had a significant reduction in the risk of progression. The treatment was well tolerated, with no impact
on QoL. The most common grade 3 or 4 adverse events reported in the niraparib group were thrombocytopenia (in 33.8%), anemia (in 25.3%) and neutropenia (in 19.6%), which were managed with dose modifications. After trial publication, FDA approved Niraparib as a maintenance therapy after response to CT in platinum-sensitive relapse.

The PRIMA trial (NCT 02655016) is evaluating the efficacy of Niraparib as maintenance after first-line CT in recently diagnosed ovarian cancer pts.

Rucaparib was also evaluated as maintenance after platinum-sensitive ovarian cancer relapse in ARIEL 3. This phase III trial presented at ESMO 2017 [66], evaluated this agent randomizing 564 pts 2:1 at a dose of 600mg B.I.D. Similar to NOVA trial, an HRD biomarker focusing on LOH performed in the tumor (previously evaluated in ARIEL 2 [48]) was applied to BRCA\(^{wt}\) pts. Maintenance with Rucaparib showed a benefit in terms of PFS of 10.8 vs 5.4 months (HR 0.37 [95% CI 0.30–0.45]; p<0.0001). Once more, BRCA\(^{mut}\) (the paradigm of HRD) benefited the most, but the other groups (HRD LOH high vs low), had also significant reductions in the risk of progression (BRCA\(^{mut}\) 16.6 vs 5.4 months; HR 0.23; p=0.0001 and HRD 13.6 vs 5.4 months; HR 0.32; p=0.0001). The toxicity profile was slightly different (elevation in transaminases, elevated serum creatinine, hypertension). The authors concluded that this agent should be considered as a maintenance therapy after platinum-sensitive relapse.

4. BIOMARKERS FOR PARPi SENSITIVITY

According to the TCGA, near 50% of HGSOC have mutations that confer HRD phenotype [27]. The most prevalent are BRCA 1 & 2 (14%) [27]. But are there ways to test HRD and detect pts that even being BRCA\(^{wt}\) may benefit form PARPi strongly?

Evaluating the effects on the genome of HRD either focusing on LOH or a combination of scores (myChoice\(^{HD}\)), has not been useful as biomarkers to detect a population that can benefit form PARPi as BRCA\(^{mut}\) pts do. In fact, even pts who tested negative for HRD through these tests had a significant reduction in the risk of progression.

Actually, the biomarker was already established at the time of randomization: Platinum-sensitivity. All PARPi trials randomized pts who responded to platinum and that is in itself a proof of HRD. HR is the mechanism through which the cell repairs platinum-damage on DNA, so if the tumor responds to platinum, it will probably benefit from PARPi maintenance since it has already demonstrated HRD indirectly.

This consistent evidence, for example in Study 19 in which both gBRCA\(^{mut}\) as well as BRCA\(^{wt}\) had a statistically significant benefit in PFS with Olaparib maintenance after responding to platinum-based CT in platinum-sensitive relapse, has generated that both the FDA and EMA approved Olaparib maintenance regardless of the BRCA status [64, 67].

5. CURRENT INDICATIONS OF PARPi

5.1. Olaparib

By FDA:

- “as monotherapy for the treatment of patients with deleterious or suspected deleterious germline BRCA-mutated advanced ovarian cancer who have been treated with three or more prior lines of chemotherapy” [68].
- “as maintenance therapy after achieving a complete or partial response to platinum-based CT for platinum-sensitive relapse, regardless of BRCA status” [64].

By EMA: “as monotherapy for the maintenance treatment of adult patients with platinum-sensitive relapsed high-grade epithelial ovarian, fallopian tube, or primary peritoneal cancer in response (complete or partial) to platinum-based chemotherapy” [67].

5.2. Niraparib

By FDA: “maintenance treatment 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” [69].

By EMA: “monotherapy for the maintenance treatment of adult patients with platinum-sensitive relapsed high grade serous epithelial ovarian, fallopian tube, or primary peritoneal cancer who are in response (complete or partial) to platinum-based chemotherapy” [70].

5.3. Rucaparib

By FDA:

- “maintenance treatment of recurrent epithelial ovarian, fallopian tube or primary peritoneal cancer who are in a complete or partial response to platinum-based chemotherapy”.
- “treatment of adult patients with deleterious BRCA mutation (germline and/or somatic)- associated epithelial ovarian, fallopian tube, or primary peritoneal cancer who have been treated with two or more chemotherapies. Selected patients for therapy based on an FDA-approved companion diagnostic for Rubraca” [71].

By EMA: “monotherapy treatment of adult patients with platinum-sensitive, relapsed or progressive, BRCA mutated (germline and/or somatic), high-grade epithelial ovarian, fallopian tube, or primary peritoneal cancer, which have been treated with two or more prior lines of platinum-based chemotherapy, and which are unable to tolerate further platinum-based chemotherapy” [72].

6. FUTURE DIRECTIONS

6.1. Combination with Antiangiogenic Agents

Since the reports by Liu et al. revealing that the combination of cediranib + olaparib was effective in platinum-sensitive relapse and with better results with the combination in BRCA\(^{wt}\) pts [73], the concept of ”contextual synthetic lethality” emerged as provocative. Anti-angiogenic agents create a situation in which PARP and PARPi play a key role: the repairment of single-strand DNA breaks. It is like the HRD cell forced to show this deficiency [20]. Moreover, it has been shown that hypoxia downregulates the expression of genes at the replication as well as the transcriptional level, involved in HR like MMA, BRCA 1& 2, RAD 51, among others [74].
Since then, several trials are exploring this combination of anti-angiogenic: bevacizumab +/- olaparib (PAOLA-1 NCT02477644) after 1st line treatment; cediranib+olaparib vs each of them or vs CT in platinum-resistant relapse (OC-TOVA NCT03117933).

6.2. Combinations with Cell-cycle Checkpoint Inhibitors

Ovarian cancer is almost invariably associated with mutations in p53 creating a situation of genetic instability due to disruption in the cell cycle. Several proteins are involved in the control of cell-cycle check-points in the transition from G2/M, like Wee1. Association of PARPi and Wee1 inhibitor-AZD1775 may generate a more intense cell cycle arrest.

There is a trial underway combining Wee1 inhibitor with Olaparib in p53 mutated ovarian cancer or the combination of this agent with carboplatin (NCT02511795), thus, exploiting in our favor, this genomic chaos. Furthermore, associations with ATM/ATR inhibitors are also underway (AZD6738 NCT02264678 and AZD0156 NCT02588105).

6.3. Combination with Immunotherapy

Given the frequent translocations that occur during efficient DNA replications in ovarian cancer, many neo-antigens emerge, making BRCAmut and ovarian tumors in general some of the most immunogenic. Since the new trend in oncology is incorporating anti-PDL1/PD 1 in every combination, PARPi have not been the exception. Durvalumab and tremelimumab are being evaluated in association with Olaparib in phase II trials with promising results (NCT02953457).

6.4. Other Trials Ongoing

- The QUADRA trial is evaluating Niraparib monotherapy after 3 or more lines of CT (NCT02354586).
- Veliparib phase II trial in gBRCA mut pts after 3 or more lines of therapy (NCT01472783)

7. MECHANISMS OF RESISTANCE TO PARP INHIBITORS

Resistance to drugs is a complex mechanism that has become a major problem for new target therapies. Studies have identified 4 main mechanisms of resistance to PARPi in preclinical models:

1. Restoration of BRCA function by secondary mutations or epigenetic re-expression: BRCA1 truncated forms play an essential role in PARPi resistance as it maintains the integrity of RAD51 binding region for DNA repair [75]. Moreover, a single amino acid mutation at the RING domain C61G disrupts the BRCA1 function as a tumor suppressor but also promotes PARPi resistance and decreases the sensitivity of cancer cells to platinum DNA damage [76]. Another RING domain mutation of I26A does not abolish the binding ability to BARD1 and E3 ligase activity [77]. RING-deficient BRCA1 proteins are capable of contributing to PARPi and platinum resistance when expressed at high levels. Epigenetic re-expression of BRCA1 may confer drug resistance to PARPi. Detected RAD51 foci, BRCA1 gene fusions and target locus amplification in resistant tumors suggest that HR-mediated genome arrangement may re-activate BRCA1 transcription through epigenetic regulation [78].

2. Overexpression of P-glycoprotein (Pgp) (3, 5): Being a member of ABC family, Pgp transports molecules, nutrients, drugs and toxins across the cell membrane. Pgp is encoded by ABCB1 (MDR1) gene, which is upregulated in cancer cells resistant to chemotherapy. Increased expression of ABC genes is associated with Olaparib resistance in several studies [79].

3. Loss of 53BP1 with the restoration of HR: Expression loss of 53BP1 is generated by truncating mutations, duplications, frame-shifts and silencing. Its suppression inhibits NHEJ and increases HR-mediated repair, suggesting that 53BP1 may help regulate the choice between these two repair mechanisms [80].

4. Regulation of repair mechanisms by microRNA: MicroRNA (miRNA) is a type of non-coding RNA which inhibits expression of target genes contributing to activation or repression of signaling pathways. Recently, PARPi resistance has been identified through suppression of NHEJ by miR-622 expression. Overexpression of this miRNA is correlated with decreased expression of genes such as 53BP1, Ku70, and Ku80 [81]. The conventional NHEJ pathway is blocked, leading to the activation of HR repair mechanism by the accumulation of Mre11 foci at the sites of double-strand damage.

CONCLUSION

PARPi have emerged as new personalized therapy for ovarian cancer, a disease characterized by HRD. Although BRCAmut pts benefit the most, it seems that platinum sensitivity is by itself a biomarker of benefit for these agents. Many questions are still unanswered and some areas need to be explored further:

- Should they be used alone or as maintenance?
- What is the best scenario for PARPi?: Monotherapy? Maintenance after the first line? Maintenance after platinum-sensitive relapse?
- Do pts who received one PARPi benefit from re-exposure? [82]
- Is “switching” an option?
- Where to test, the germline, the tumor or both?

These types of agents represent a new development in ovarian cancer treatment. Their use so far has prolonged the CT-free interval, but in combination with other agents may prove to be as effective as CT in this heavily pre-treated population where preservation of QoL is of utmost importance.

CONSENT FOR PUBLICATION

Not applicable.

CONFLICT OF INTEREST

The authors declare no conflict of interest, financial or otherwise.
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