Research Article

Efficacy and safety of PARP inhibitors as the maintenance therapy in ovarian cancer: a meta-analysis of nine randomized controlled trials

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Purpose: Poly ADP ribose polymerase (PARP) inhibitors can effectively kill cancer cells by restraining the activity of DNA repair enzymes and utilizing the characteristics of BRCA mutations. This article evaluates the efficacy and safety of PARP inhibitors (PARPis) in the maintenance treatment of ovarian cancer.

Method: We searched for clinical trials in electronic databases. PARPis efficacy were evaluated by the hazard ratios (HR) and its 95% confidence intervals (95% CI) of overall survival (OS) and progression-free survival (PFS) between the PARPis groups and placebo groups, while the PARPis' safety was assessed by relative risk (RR) values of adverse events (AEs) between the two arms.

Results: The immature OS data manifested that patients with BRCA mutation receiving PARPis therapy versus placebo therapy appeared to have longer OS (HR = 0.78, 95%CI = 0.61–1.01; P = 0.06). Compared with placebo group, PARP group had a significant advantage in PFS in ovarian cancer patients with BRCA wild-type (BRCAwt), BRCA mutation (BRCAm), BRCA status unclassified, BRCA1 mutation subgroup and the BRCA2 mutation subgroup (BRCAwt: HR = 0.53, 95%CI = 0.42–0.68, P < 0.00001; BRCAm: HR = 0.30, 95%CI = 0.26–0.34, P < 0.00001; BRCA status unclassified: HR = 0.52, 95%CI = 0.41–0.66, P < 0.00001; BRCA1m: HR = 0.38, 95%CI = 0.29–0.48, P < 0.00001; BRCA2m: HR = 0.23, 95%CI = 0.10–0.57, P = 0.001). Our analysis revealed the incidence rates for AEs of grade ≥3 (grades 3 to 4) and serious AEs in PARPis group were 55.19% and 26.29%, respectively.

Conclusion: Our meta-analysis demonstrates that PARPis therapy can significantly improve PFS in ovarian cancer patients, but it has no benefit in OS. However, the therapy is associated with a significant increase in the risk of AEs of grade ≥3 and serious AEs.

Background

Based on American cancer statistics in 2019, ovarian cancer is the 11th most common cancer, with approximately 22,530 newly diagnosed ovarian cancer cases, and the 5th leading cause of cancer-related death, with estimated 13,980 ovarian cancer deaths [1]. Ovarian cancer patients are characterized by late-stage presentation, easy relapse and metastasis, no chance to radical surgery, which ultimately lead to stagnation of mortality statistics. Ovarian cancer is a diverse and genomic complex disease, which has attracted worldwide attention [2]. Women with inherited mutations in BRCA1 or BRCA2 had an increased risk of ovarian cancer, and for BRCA1 or BRCA2 mutation carriers, the lifetime risk of ovarian cancer were 54% and 23%, respectively [3]. However, compared with mutation-negative patients, patients carrying BRCA mutations have an advantage in progression-free and overall survival, and more frequently
respond to both platinum-based chemotherapy and poly (adenosine diphosphate [ADP]–ribose) polymerase (PARP) inhibitors [4,5]. BRCA is known to be involved in homologous recombination [6–8], and the targeted inhibition of specific DNA repair pathways may provide an appropriate treatment for cancer [7]. BRCA-mutation positive epithelial ovarian cancer (EOC) patients appear impaired ability to repair double-stranded DNA breaks via homologous recombination, which may partly explain the molecular basis for heightened sensitivity to platinum and PARPis, as well as better survival compared with nonhereditary EOC patients [4,9–11].

PARPis are a class of molecule-targeting agents suppressing PARP enzymes activity. BRCA1 or BRCA2 dysfunction deeply appears the susceptibility of cancer cells to the inhibition of PARP enzymatic activity, leading to defects in DNA damage repair by homologous recombination, which results in cell death [6,7]. According to our latest search results, nine randomized controlled trials (RCTs) have shown that PARPis have shown impressive results in the treatment of ovarian cancer [10,12–16]. Therefore, this meta-analysis aimed to update and evaluate the efficacy of PARPis in different status of BRCA ovarian cancer, and to assess the safety of them in detail according to the grade and type of AEs.

Method
Search strategy
We systematically searched PubMed, Web of Science, Embase, Cochrane CENTRAL and ClinicalTrials.gov from inception to January 2020 for all RCTs. For database search we used “(‘ovarian cancer’ OR ‘ovarian carcinoma’ OR ‘ovarian neoplasm’ OR ‘ovarian tumor’) AND (‘parp’ OR ‘parpi’ OR ‘olaparib’ OR ‘niraparib’ OR ‘rucaparib’) AND (‘randomized’ OR ‘randomised’ OR ‘trial’ OR ‘placebo’)” as the search terms in all fields. Wherever possible, we searched for references to relevant articles to identify potential information that had not already been retrieved. The search was restricted to articles published in English.

Inclusion criteria
The relevant clinical trials on the efficacy and safety of PARPis therapy were included, if they qualified for a randomized controlled trial with or without blinding. Besides, accepted articles should also meet the following criteria: (1) The trial involved the study of high-grade serous or endometrioid ovarian cancer, primary peritoneal cancer, or fallopian-tube cancer with or without BRCA1 or BRCA2 mutations, platinum-sensitive or platinum-resistant. (2) The trial compared PARPis with other interventions such as placebo or other chemotherapy drugs. (3) The study provided available data to calculate the HR of OS or PFS and RR of AEs.

Exclusion criteria
Exclusion criteria excluded: (1) The trial was not randomized control trial. (2) Literature reviews, or Case reports, (3) Phase I clinical trial. (4) Duplicate publication. (5) Intervention only included the PARPi (PARPi) group for ovarian cancer. For example, we excluded the articles (Swisher 2017) because they aimed to investigate molecular predictors of rucaparib sensitivity, rather than to evaluate efficacy and safety by comparing it with placebo [17]. Updated and published follow-up data were considered for one trial to analyze.

Data extraction
Two investigators independently reviewed the whole content of each eligible literature, including supplements, and extracted the data using a pilot-tested data extraction sheet.

The following contents was included in the extraction sheet: first author; year of publication; phase of clinical trial; tumor type and clinical stage; number of patients enrolled; platinum status; BRCA status; interventions; hazard ratios (HR) for OS and PFS and their 95% confidence intervals (CIs); numbers of AEs with different grades and types; and other necessary information.

Statistical analysis
The data of the analysis were extracted from the selected literature, and all meta-analysis were performed using Review Manager 5.0 (http://www.cochrane.org). Statistical heterogeneity was analyzed using Cochran’s Q-test and inconsistency (I^2) statistics; P ≤ 0.10 or I^2 ≥50% indicate significant heterogeneity. If there is no heterogeneity, a fixed-effect model (P > 0.10 and I^2 < 50%) is used [18], otherwise a random effects model (P ≤ 0.10 or I^2 ≥ 50%) is used [19]. HR and 95% CI were used to analyze the OS and PFS between PARPis group and control group. In addition, pooled risk ratio (RR), 95% CI and incidence rate were used to analyze AEs with different degrees via a meta-analysis. For all analyses, P < 0.05 was refer to indicate statistical significance.
Results

Literature search

A total of 2631 records were identified from all searched databases, and 2321 articles were automatically deleted by selecting the type of articles for clinical trials about human. About 166 articles were retained after excluding duplicates and phase I trial by reading titles and abstracts. After assessing the titles, abstracts and full texts of the article of retained articles, 157 were excluded for the following reasons: reviews; single-arm trials; non-randomized control; non-clinical studies of PFS and OS; non-research ovarian cancer and others do not meet the selection criteria. Finally, 9 randomized controlled trials were included in the final analysis [13,20–28]. The flowchart of the trial selection process is shown in Figure 1.

Characteristics of the included studies

The characteristics of the nine selected trials are summarized in Table 1. Among nine randomized controlled trials, two were phase II trials, and the other seven were phase III trials, involving 4526 patients in the pooled analyses. In the nine trials included, the therapeutic effects and safety of PARPis including olaparib, rucaparib, veliparid and niraparib as maintenance therapy were evaluated, and that of olaparib were evaluated in five trials. The last four trials including Moore 2018, Coquard 2019, Martin 2019 and Coleman 2019 focused on PARPi as the maintenance therapy for newly diagnosed advanced ovarian cancer, while the earlier five trials including Ledermann 2014, Oza 2014, Mirza 2016, Lauraine 2017 and Coleman 2017 investigated PARPis for recurrent and refractory platinum-sensitive ovarian cancer. When comparing olaparib with placebo in BRCA mutation patients, the HR is gradually reduced with increasing therapeutic doses of olaparib in these studies [13,21,23,24,26], which means a positive dose–response relationship between clinical efficiency and olaparib dosage. In Oza 2014 and Coleman 2019, the intervention regimen of the experimental group was PARPi combined with chemotherapy, followed by PARPi alone for maintenance therapy, while the control group was not further treated in the maintenance phase of the study after chemotherapy. Coquard 2019 reported the efficacy and safety of combination maintenance olaparib and bevacizumab in patients. Although Oza 2014 and Coleman 2019 [13] assessed not only AEs in the treatment phase of PARPi combined with chemotherapy, but also AEs in the maintenance phase of PARPi monotherapy, in this meta-analysis, we only analyzed the AEs at monotherapy maintenance phase. In Miza 2016 [22], ovarian cancer patients with homologous recombination deficiency plus somatic BRCA mutation (HRD positive/sBRCA mutation) and with a germline BRCA mutation (gBRCA
Table 1 Characteristics of the trials included in the meta-analysis

<table>
<thead>
<tr>
<th>Trial</th>
<th>Phase</th>
<th>Year</th>
<th>Treatment arms</th>
<th>Therapeutic schedule</th>
<th>Patients (Exp/Con)</th>
<th>Platinum status and clinical stage</th>
<th>BRCA status</th>
<th>Median PFS (BRCA mutation group)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oza 2014</td>
<td>II</td>
<td>2014</td>
<td>Olaparib plus chemotherapy vs Chemotherapy</td>
<td>Experimental: olaparib (200 mg capsules bid) plus chemotherapy, then olaparib monotherapy (400 mg bid) Control: chemotherapy then no further treatment</td>
<td>81/81</td>
<td>platinum-sensitive recurrent, high grade serous ovarian cancer</td>
<td>BRCA1/2 mutation</td>
<td>Experimental: not reported</td>
</tr>
<tr>
<td>Mirza 2016</td>
<td>III</td>
<td>2016</td>
<td>Niraparib vs Placebo</td>
<td>Experimental: niraparib (300 mg) qd Control: placebo</td>
<td>372/181</td>
<td>platinum-sensitive recurrent, high grade serous ovarian cancer</td>
<td>gBRCA mutation non</td>
<td>Experimental: 21.0 months</td>
</tr>
<tr>
<td>Lauraine 2017</td>
<td>III</td>
<td>2017</td>
<td>Olaparib vs Placebo</td>
<td>Experimental: olaparib (300 mg) bid Control: placebo</td>
<td>196/99</td>
<td>platinum-sensitive relapsed ovarian cancer patients</td>
<td>BRCA1/2 mutation</td>
<td>Experimental: 19.1 months</td>
</tr>
<tr>
<td>Coleman 2017</td>
<td>III</td>
<td>2017</td>
<td>Rucaparib vs Placebo</td>
<td>Experimental: rucaparib 600 mg bid Control: placebo</td>
<td>375/189</td>
<td>platinum-sensitive recurrent, high grade ovarian carcinoma</td>
<td>BRCA1/2 mutation</td>
<td>Experimental: 16-6 months</td>
</tr>
<tr>
<td>Moore 2018</td>
<td>III</td>
<td>2018</td>
<td>Olaparib vs Placebo</td>
<td>Experimental: olaparib (300 mg) bid Control: placebo</td>
<td>260/131</td>
<td>platinum-sensitive high grade serous or endometrioid ovarian, primary peritoneal, or fallopian tube carcinoma</td>
<td>BRCA1/2 mutation</td>
<td>Experimental: 36 months longer</td>
</tr>
<tr>
<td>Coquard 2019</td>
<td>III</td>
<td>2019</td>
<td>Olaparib plus bevacizumab vs Bevacizumab</td>
<td>Experimental: olaparib (300 mg) bid plus bevacizumab Control: placebo plus bevacizumab</td>
<td>537/269</td>
<td>platinum status unknown high-grade serous or endometrioid ovarian cancer, primary peritoneal cancer, or fallopian-tube cancer</td>
<td>BRCA1/2 mutation</td>
<td>Experimental: 37.2 months</td>
</tr>
<tr>
<td>Martin 2019</td>
<td>III</td>
<td>2019</td>
<td>Niraparib vs placebo</td>
<td>Experimental: niraparib (200 mg) qd Control: placebo</td>
<td>487/246</td>
<td>platinum status unknown high-grade serous or endometrioid ovarian cancer, primary peritoneal cancer, or fallopian-tube cancer</td>
<td>BRCA1/2 mutation wild-type</td>
<td>Experimental: 22.1 months</td>
</tr>
<tr>
<td>Coleman 2019</td>
<td>III</td>
<td>2019</td>
<td>Veliparib vs placebo</td>
<td>Experimental: veliparib (400 mg) bid Control: placebo</td>
<td>382/375</td>
<td>platinum status unknown high-grade serous epithelial ovarian, fallopian tube, or primary peritoneal carcinoma</td>
<td>BRCA1/2 mutation wild-type</td>
<td>Experimental: 34.7 months</td>
</tr>
</tbody>
</table>

gBRCA mutation means the presence of a germline BRCA mutation; non gBRCA mutation means the absence of a germline BRCA mutation; bid means twice a day; qd means once daily.

Overall survival (OS)

Oza 2014, Ledermann 2016, Lauraine 2017, Moore 2018 and Martin 2019 had assessed OS in ovarian cancer patients, while the maturity of OS analysis data in these four trials was 49%, 70%, 24%, 21% and 10.8% respectively, which means that the OS data were immature. By pooling the data from Oza 2014, Ledermann 2016, Lauraine 2017 and Moore 2018, OS in PARPi group seemed to have an advantage over placebo group in BRCA mutation setting (HR = 0.78, 95%CI = 0.61–1.15, fixed-effect model; P = 0.06, which did not meet the required threshold for statistical significance [P < 0.05]) (Figure 2A). The analysis data for the BRCA status unclassified group were extracted from Oza 2014, Ledermann 2016 and Martin 2019, and disappointingly there was no statistically significant beneficial effect for OS between the two groups (HR = 0.84, 95%CI = 0.61–1.15, P = 0.27, random effect model) (Figure 2B).
Figure 2. Pooled HRs of OS comparing PARPis maintenance therapy arm with Placebo maintenance therapy arm in ovarian cancer patients with BRCAm (A) and BRCA status unclassified (B)

Progression-free Survival (PFS)

After pooling the data, it showed that there were 1319 patients with ovarian cancer with BRCA wild-type, including 750 in PARPis group and 569 in control groups, and PFS was significantly improved in the PARPis group than in the placebo group (HR = 0.53, 95%CI = 0.43–0.68, P < 0.00001, random effect model) (Figure 3A). Especially, data from all RCTs were pooled to analyze ovarian cancer patients with BRCA mutations, and when comparing the two groups (PARPis group, n = 1270; placebo group, n = 699), the median PFS HR was 0.30 (95%CI = 0.26–0.34, P < 0.00001, fixed-effect model) (Figure 3B). Six trials also analyzed the PFS of the BRCA status unclassified mainly consisting of BRCA mutation and BRCA wild-type, and the pooled HR of median PFS was 0.52 (95%CI = 0.41–0.66, P < 0.00001, random effect model) (Figure 3C). Significantly, three trials classified BRCA mutation status in more detail, and in patients with BRCA1m and with BRCA2m, the HRs of median PFS were 0.38, 0.23, respectively (95%CI = 0.29–0.48, P < 0.00001, fixed effect model; 95%CI = 0.10–0.57, P = 0.001, random effect model) (Figure 3D,E).

Adverse event (AEs)

Data of AEs extracted from selected literature were used to risk analysis, as details are shown in Table 2. In total, a treatment-emergent adverse event of any grade occurred in 2685 of 2725 patients (98.53%) who received PARPis and in 1495 of 1602 patients (93.32%) who received placebo (RR = 1.05, 95%CI = 1.03–1.07, P < 0.00001, fixed-effect model). Most notably, PARPis significantly increased the overall risk to suffer grade ≥3 AEs and serious AEs compared with placebo (grade ≥3 AEs: incidence rate = 55.19%, RR = 2.16, 95%CI = 1.47–3.18, P < 0.0001, random effect model; serious AEs: incidence rate = 26.29%, RR = 1.82, 95%CI = 1.32–2.51, P < 0.00001, random effect model). In PARPis group, for any grade events, the five most common AEs of any grade were nausea, fatigue, anaemia, vomiting and thrombocytopenia, and for grade ≥3 AEs, they were anaemia, thrombocytopenia, neutropenia, fatigue and nausea. Considering the incidence and relative risk of AEs, we found that hemotoxicity and gastrointestinal reactions may be the main obstacles to the clinical use of PARPis.

Discussion

Rapid progression or lower OS after cytoreductive surgery plus conventional cytotoxic chemotherapy for ovarian cancer patients indicates an urgent need for a new and effective treatment regimen. In addition to BRCA mutation related to the sensitivity of PARPis therapy, many studies have demonstrated that loss of DNA repair proteins of other tumor suppressor factors, many of which are related to homologous recombination deficiency, also induces such sensitivity to PARPis [29–32]. These studies suggested that the effectiveness of PARPis was mainly based on the defect of homologous recombination pathway, not only on the mutation of BRCA [29–32]. Through the results of clinical trials of PARPis in cancer patients and the growing understanding of various DNA repair defects, it was found that these drugs were effective for patients regardless of the mutation status of BRCA [33,34]. In ovarian cancer, these
Figure 3. Pooled HRs of PFS comparing PARPis maintenance therapy arm with Placebo maintenance therapy arm in ovarian cancer patients with BRCAwt (A), BRCAm (B), BRCA status unclassified (C), BRCA1m (D) and BRCA2m (E)
targeted inhibitors were the standard treatment for advanced serous ovarian cancer with BRCA mutation [35,36], and could also be used as alternative treatment for many patients other than BRCA germline mutation carriers [33,36].

At present, some scholars have analyzed the effect of PARPis on the treatment of ovarian cancer patients through meta-analysis [37,38]. However, more randomized controlled trials have been included in this study, including some of the latest clinical trials. What’s more, we analyzed the PFS and OS of ovarian cancer patients treated with PARPis more specifically, as well as the AEs related to PARPis in more detail. By integrating data from 9 RCTs,
this meta-analysis discussed the efficacy and safety of various PARPis maintenance therapy including olaparib, niraparib, veliparib, and rucaparib in patients with ovarian cancer. Our research revealed an impressive efficacy of the PARPis maintenance therapy in treatment ovarian cancer patients with BRCAm or BRCAwt, in which the pooled HRs for PFS were 0.30 (95%CI = 0.26–0.34, \(P < 0.00001\), fixed-effect model), and 0.53 (95%CI = 0.42–0.68, \(P < 0.00001\), random effect model), respectively, comparing with placebo. The lifetime risk of ovarian cancer was different between BRCA1 and BRCA2 mutation carriers [3,39,40]. Consequently, their prognosis may be different. Bolton et al. [41] discovered that the 5-year overall survival of ovarian cancer was 44% for BRCA1 carriers and 52% for BRCA2 carriers. Similarly, Somlo et al. [42] confirmed that the clinical benefit and median PFS was a statistically higher for BRCA2 versus BRCA1 patients with metastatic breast cancer when treated with PARPi veliparib. Similarly, we confirmed that treating with PARPis, the clinical efficacy of patients with BRCA2m was better than that of patients with BRCA1m, with HRs for PFS being 0.23, 0.38 (BRCA2m: HR = 0.23, 95%CI = 0.10–0.57, \(P = 0.001\), random effect model; BRCA1m: HR = 0.38, 95%CI = 0.29–0.48, \(P < 0.00001\), fixed-effect model), respectively. A recent meta-analysis explored the impact of BRCA1 and BRCA2 mutations on survival of ovarian and breast cancer, and claimed that these mutations should be considered when designing appropriate treatment strategies [43]. Although many researchers believed that PARPis can be used to treat ovarian cancer without considering the BRCA status [33,36], the mutation status of BRCA provides a strong basis for the design of reasonable individualized targeted therapy for ovarian cancer. Therefore, to provide suitable treatment for ovarian cancer patients, it is suggested that ovarian cancer specimens after surgery need not only routine means for pathological examination, but also need gene testing to identify the relevant genotypes.

Earlier, Kaye et al. claimed that olaparib 400 mg twice per day was more suitable for patients because they found that 400 mg (8.8 months, 95% confidence interval = 5.4–9.2 months) was better than 200 mg (6.5 months, 95% confidence interval = 5.5–10.1 months) for median PFS time [44]. Thus, does the dosage of PARPis affect the prognosis of patients with ovarian cancer? Five groups of clinical trials involving olaparib maintenance therapy showed that compared with the control group, the hazard ratio of PFS ultimately obtained seemed to be positively correlated with the maintenance dose. Therefore, the appropriate treatment dose was also an aspect to be considered in the follow-up study. In addition, OS did not seem to differ significantly between patients treated with PARPi versus placebo, but the total number of patients was small and overall survival data was immature so that the study was not powered to make formal comparisons.

Our meta-analysis also provided an overview of the expected safety and tolerance of single-agent PARPi that could be of value to discuss treatment risk and benefit ratio with patients. PARPis have been gradually approved for clinical applications, so the evaluation of treatment-emergent AE is indispensable. AEs may lead to dosage adjustment, discontinuation of treatment, and even affect the health and safety of patients. A meta-analysis of 2479 patients treated with PARPis from 12 randomized controlled trials showed that incidences of severe neutropenia, thrombocytopenia, and anemia in patients receiving PARPis were 32.9%, 15.9% and 9.1%, respectively, which indicated that PARPis treatment increased the risk of severe hematologic toxicities [45]. Hematologic toxicities caused by PARPis are more common and serious, so it is necessary to monitor complete blood counts regularly. Because PARP inhibition is not selective to cancer cells, it eliminates the important mechanism of DNA repair of blood cells which are replaced more frequently like cancer cells, thus enhancing blood toxicity. In addition to increasing the risk of hematologic toxicities, another study showed that PARPis treatment significantly increased the risk of gastrointestinal toxicities at all levels in patients with ovarian cancer, except for constipation [46]. The frequent AEs recorded in these nine clinical trials that led to discontinuation of treatment and death in patients with PARPis were similar, which included anemia, thrombocytopenia, neutropenia, abdominal pain, intestinal obstruction, myelosuppression, nausea and vomiting. However, there are fewer cases of interruption of treatment and death due to AEs. Overall, PARPis seems to have a tolerance profile suitable for long-term maintenance therapy, but the high incidence rates for grade≥3 AEs and serious AEs are a trouble that cannot be ignored in clinical application.

**Competing Interests**
The authors declare that there are no competing interests associated with the manuscript.

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Author Contribution
Fengping Shao, Jun Liu and Shanyang He put forward ideas, designed research, searched literature and collected data, planned statistical analysis. Fengping Shao and Jun Liu wrote the first draft. Liu Liquin and Cai Zhang analyzed and interpreted the data. Yaoyun Duan and Li Li helped to draft and revise the final manuscript. All authors read and approved the final manuscript.

Abbreviations
95% CI, 95% confidence interval; AE, adverse event; HR, hazard ratio; NA, not applicable; NE, not estimable; OS, overall survival; PARP, poly ADP ribose polymerase; PFS, progression-free survival; RR, relative risk.

References