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Systematic Review

PARP inhibitors as maintenance therapy in newly diagnosed advanced ovarian cancer: a meta-analysis

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Background Up to 70% of patients with advanced ovarian cancer have a relapse after primary therapy. New agents and approaches are urgently needed to avoid or slow down this recurrence.

Objectives To investigate the efficacy of PARP inhibitors (PARPis) as maintenance treatment in patients with newly diagnosed advanced ovarian cancer.

Search strategy PubMed, MEDLINE, EMBASE, Cochrane Library and Web of Science databases.

Selection criteria All randomised clinical trials (RCTs) that compared PARPis with placebo as first-line maintenance therapy in ovarian cancer.

Data collection and analysis Two reviewers extracted data. Pooled hazard ratio (HR) and risk ratio (RR) with 95% confidence interval (CI) were calculated.

Main results PARPis were associated with significant improvement of progression-free survival (PFS) in advanced epithelial ovarian cancer (AeOC) (HR = 0.53, 95% CI 0.40–0.71; $P < 0.0001$). The benefit was not only in women with BRCA mutations (HR = 0.35, 95% CI 0.29–0.42; $P < 0.00001$) and homologous recombination deficiency (HRD) (HR = 0.43, 95% CI 0.32–0.60; $P < 0.00001$), but also in those with nonmutated BRCA (HR = 0.72, 95% CI 0.63–0.82; $P < 0.00001$) and even non-HRD (HR = 0.83, 95% CI 0.70–0.99; $P = 0.04$).

Conclusions PARP inhibitors are effective as maintenance therapy among patients with newly diagnosed advanced ovarian cancer after platinum-based chemotherapy, regardless of BRCA mutation or HRD status.

Keywords Maintenance therapy, ovarian cancer, PARP inhibitors.

Tweetable abstract PARPis provide a significant PFS benefit as first-line maintenance therapy in patients with newly diagnosed advanced ovarian cancer.

Linked article This article is commented on by JL Berger, p. 494 in this issue. To view this mini commentary visit https://doi.org/10.1111/1471-0528.16450.

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Introduction

Ovarian cancer is the most lethal gynaecological cancer and about 70% of affected patients present with advanced-stage disease.[1] Annually, worldwide, 239 000 women will be diagnosed and 152 000 will die.[2] The standard treatment for newly diagnosed advanced epithelial ovarian cancer is cytoreductive surgery and combination platinum-taxane chemotherapy. Recently, weekly paclitaxel therapy, intraperitoneal chemotherapy and bevacizumab therapy are also considered to be acceptable as primary therapy.[3–6] Nevertheless, approximately 70% of patients have a relapse within 3 years and overall survival remains poor.[7]

Inhibitors of poly(adenosine diphosphate-ribose) polymerase (PARP) have emerged as one of the most exciting new therapies for the treatment of ovarian cancer, based on the DNA repair vulnerability of many ovarian cancer cells. PARP inhibitors (PARPis) prevent the repair of DNA single-strand breaks and generate double-strand breaks that cannot be repaired accurately in tumours with homologous recombination deficiency (HRD). The accumulation of unrepaired DNA damage will ultimately lead to tumour-

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cell death, which is called synthetic lethality (Figure S1).[8] The most common cause of HRD is a germline or somatic mutation in BRCA1/2. However, genomic alterations and/or epigenetic silencing of other pathway genes including ATR, ATM, CHK1/2, RAD51/54, NBS1, PALB2 and PTEN have also been shown to be associated with HRD.[9–12] Thus, HRD is not limited to tumours with BRCA mutations, and BRCA-mutated or other HR-deficient patients may benefit the most from PARPis. In patients with high-grade serous ovarian cancers, approximately 50% are estimated to have HRD, with 20% of the tumours harbouring germline (15%) or somatic (5%) BRCA1/2 mutations.[11] Therefore, ovarian cancer has been the leading tumour type to gain FDA approval for PARPi therapy.

PARPis have shown efficacy as maintenance therapy among patients with recurrent platinum-sensitive ovarian cancer regardless of the presence or absence of BRCA mutations.[13–17] However, the first-line role of PARPis among patients with newly diagnosed advanced ovarian cancer is completely clear, especially with regard to their effect in different populations with different BRCA phenotype and HRD status.

Therefore, we performed this meta-analysis that incorporates all qualified relevant randomised clinical trials (RCTs) to investigate the efficacy and safety of PARPis as maintenance treatment after platinum-based chemotherapy in patients with newly diagnosed advanced ovarian cancer, paying particular attention to the population's BRCA mutational and HRD status and stratifying results into five different categories: whole population, BRCA-mutated patients, patients without BRCA mutation, HRD-positive patients and HRD-negative patients.

Methods

This systematic review and meta-analysis was conducted according to the guidelines of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA).[18] Because all analyses were performed using data from previously published studies, ethical approval, patient consent and primary authors' approval were unnecessary. Two reviewers independently performed the literature searches, data extraction and quality assessment, and any disagreements were resolved by discussion. Patients were not involved in the development of the research and a core outcome set was not used.

Literature search and selection criteria

We systematically searched the PubMed, MEDLINE, Embase, Cochrane Library, and Web of Science databases up to March 2020 using a combination of the following search terms: ovarian cancer, ovarian neoplasm, ovarian carcinoma, Poly(ADP-Ribose) polymerase inhibitors, PARPi, PARP inhibitors, olaparib, rucaparib, niraparib, veliparib. Additionally, the reference lists of the identified articles and the 'Related Articles' feature in PubMed were reviewed to maximise the probability of finding additional suitable papers. All English-language publications of RCTs that investigated the efficacy of PARPis as maintenance treatment after platinum-based chemotherapy in patients with newly diagnosed advanced ovarian cancer were included.

The exclusion criteria for the present study were as follows: (1) non-randomised clinical trials, (2) incomplete information for a quantitative analysis, (3) non-human models or non-English-language publications or (4) non-comparative studies. Two reviewers independently screened and excluded papers based on the abstracts using the inclusion and exclusion criteria. The full-text articles with potentially relevant abstracts were then retrieved and independently assessed according to the inclusion and exclusion checklists. All disagreements were resolved by discussion until a consensus was reached; if this failed, a third reviewer was consulted.

Data extraction

Two reviewers independently extracted the data from eligible primary studies and transferred them to a standard data extraction form. These data included the first author, year of publication, trial acronym, study design, number of patients enrolled, participant age, primary treatment received, intervention details, duration of maintenance, median duration of follow up, number of patients by BRCA mutational status and HRD status, outcomes including progression-free survival (PFS) and adverse events

For time-to-event data (PFS), we extracted the log of the hazard ratio, log (HR), and its standard error from trial reports. For dichotomous outcomes (e.g. adverse events), we extracted the number of women in each treatment arm who experienced the outcome of interest and the number of women assessed at endpoint, in order to estimate a risk ratio (RR).

Quality assessment

The quality levels of the included studies were independently assessed by two reviewers. Disagreements were resolved by discussion, with the involvement of an independent third review author where necessary. Briefly, the Cochrane Collaboration tool[19] was used to assess the risk of bias with respect to the following: selection bias (random sequence generation and allocation concealment), attrition bias (incomplete outcome data), performance and detection bias (blinding of participants, personnel and outcome assessment), reporting bias (selective reporting) and other biases (other sources of bias).

Statistical analysis

All data syntheses and analyses were performed using REVMAN 5.3 software (Cochrane Collaboration; Oxford, UK). For PFS, pooled hazard ratios (HR) with 95% CI were calculated; for adverse events with an incidence of grade 3 or higher, we calculated the pooled risk ratio (RR) with 95% CI. Statistical heterogeneity was assessed using both the I^2 and Chi-square tests. In cases of I^2 being greater than 50%, a random-effect model was used; otherwise, a fixed-effect model was used.[20]

Sensitivity analyses were used to assess the stability of the results, and funnel plots were used to screen for potential publication biases.

Results

Overview

Our search strategy identified 956 articles, 70 of which were duplicates and 871 that were excluded by the title and abstract screening processes. Of the remaining 15 articles, full texts were accessed and, ultimately, four RCTs met our inclusion criteria and were included in the final analysis: PRIMA, PAOLA-1, VELIA, SOLO1.[21–24] Figure 1 presents a flow chart illustrating the above search process.

Description of studies

The basic characteristics of the included studies are summarised in Table 1 and Table S1. A total of 2687 patients were included in the present analysis. The median age of patients ranged from 53 to 62 years. Patients in the SOLO1 trial, all of whom had BRCA mutations, were younger. BRCA mutation included somatic and germline mutations in all four studies. HRD was defined as the presence of a BRCA deletion mutation, a score of at least 42 on the myChoice test, or both in the PRIMA and PAOLA-1 trials; however, the VELIA trial used a lower cutoff score (≥33) for inclusion. Of the four trials, three[21–23] included both BRCA-mutated and unmutated patients, and evaluated the efficacy of PARPis according to HRD status. Only the SOLO1 trial exclusively included BRCA-mutated population. PRIMA was the only study that included the differentiated HRD without a BRCA mutation as a sub-population and enrolled patients with unfavourable advanced disease. In the PAOLA-1 trial, bevacizumab was initiated in combination with chemotherapy and was continued after randomisation as maintenance therapy, which may have extended the duration of PFS compared with standard first-line platinum-taxane chemotherapy in the other three studies. Patients in the VELIA trial were randomly assigned to three arms (control, veliparib combination only and veliparib throughout). The veliparib combination-only arm was not included in our study due to the lack of PARPi maintenance therapy.

Quality assessment

The quality assessments of the included RCTs are summarised in Table S2; the overall quality of the trials was determined to be good. Briefly, the randomisation methods were described in all the four studies. For allocation concealment and blinding of outcome, all four studies were low risk. In terms of incomplete outcome data, PRIMA and PAOLA-1 were considered to be unclear. Finally, selective outcome reporting was unclear in SOLO1 and other bias was unclear in VELIA.

Progression-free survival (PFS)

Our meta-analysis extracted HR for PFS from every study and distinguished in five subgroups: whole population, BRCA-mutated patients, patients without BRCA mutations, HRD-positive patients, HRD-negative patients.

In the overall population, all four studies, with a total number of 2687 patients (1666 PARPis and 1021 placebo), were included in this meta-analysis for evaluation of PFS. A random-effect model of analysis was used. It showed that the use of maintenance therapy with PARPis resulted in a statistically significant improvement in PFS among the whole population regardless of BRCA mutation status or HRD status (HR = 0.53, 95% CI 0.40–0.71; $P < 0.0001$; Figure 2A), but heterogeneity of results was observed ($I^2 = 86\%$; $P = 0.0001$).

All four RCTs of 1051 patients (677 PARPis and 374 placebo) evaluated the PFS in BRCA-mutated subgroup. The outcomes of PFS were pooled and compared with a fixed-effect model. The benefit of PARPis on PFS in BRCA-mutated patients was significant (HR = 0.35, 95% CI 0.29–0.42; $P < 0.00001$; Figure 2B). In addition, heterogeneity of results was not observed ($I^2 = 0\%$; $P = 0.46$).

Three studies[21–23] involving 1467 patients (889 PARPis and 578 placebo) analysed PFS in the subgroup of women without BRCA mutations. In the PRIMA trial, the cohort of patients with nonmutated BRCA comprised those with tumours that had HRD without a BRCA mutation and the HRD-negative subgroup. Therefore, both them were included for the analysis of the population without BRCA mutations. Pooling data from the three RCTs by a fixed-effect model, also showed that PARPis provided a significant PFS benefit in patients with nonmutated BRCA (HR = 0.72, 95% CI 0.63–0.82; $P < 0.00001$; Figure 2C). There was no heterogeneity in ther results among the studies ($I^2 = 0\%$; $P = 0.39$).

We identified three studies[21–23] involving 1181 patients (716 PARPis and 465 placebo) with HRD positivity for analysis of PFS. A random-effect model of analysis was used. The results indicated that PARPis were associated with significantly greater PFS in HRD-positive patients (HR = 0.43, 95% CI 0.32–0.60; $P < 0.00001$; Figure 2D). However, heterogeneity of results was observed ($I^2 = 70\%$; $P = 0.03$).

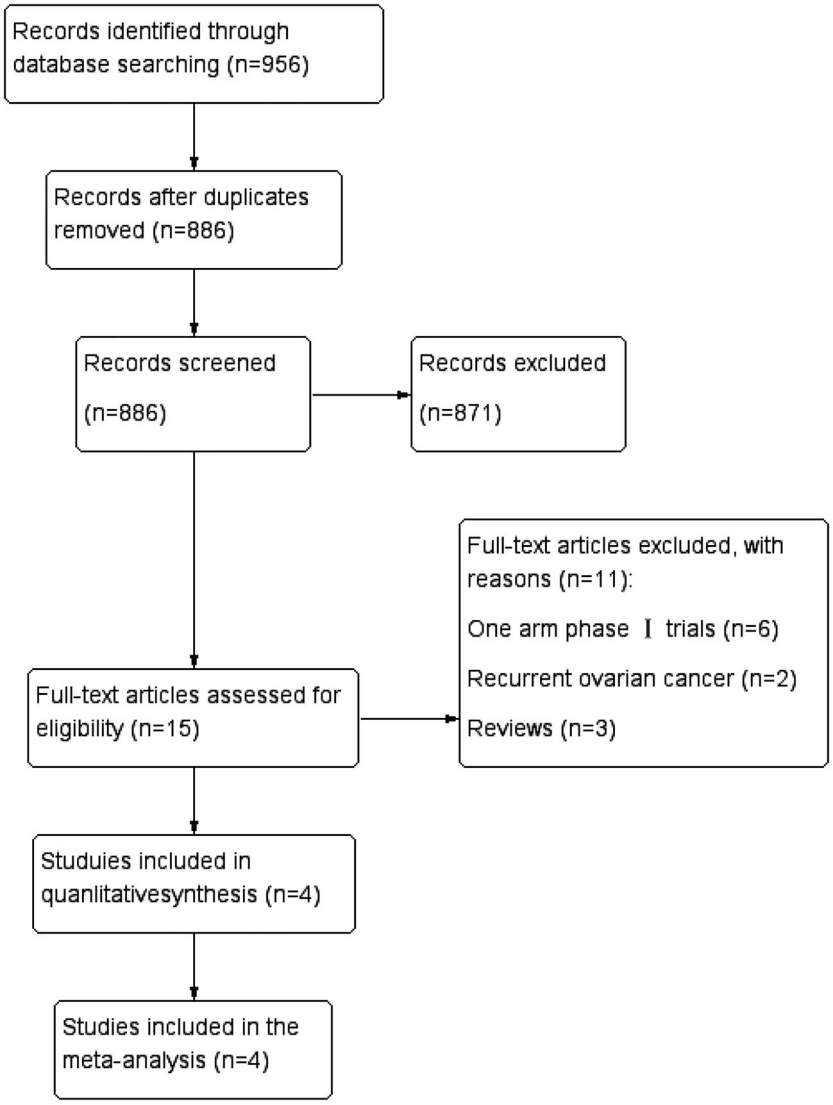

Figure 1. Flow chart of the literature search.

Finally, the PFS analysis in HRD-negative patients was based on three trials[21–23] (n = 775 patients: 486 PARPis and 289 placebo. Even in this subgroup, the results indicated that the PFS of PARPis was significantly greater than of the placebo (HR = 0.83, 95% CI 0.70–0.99; P = 0.04; Figure 2E). There was little heterogeneity of results among the studies (I^2 = 33%; P = 0.22).

Adverse events

All studies included in this meta-analysis reported common adverse events that occurred during the trials, mainly nausea (64.4% in the PARPi group and 44.8% in the placebo group), fatigue (52.8 versus 42.9%), anaemia (52.4 versus 27.5%), neutropenia (34.2 versus 32.0%) and thrombocytopenia (30.9 versus 14.3%). Adverse events of grade 3 or higher occurred in 65.1% of the patients in the PARPi group and 48.5% in the placebo group. The pooled analysis showed that grade 3 or higher adverse events were more common in the PARPi maintenance arm (RR = 1.75, 95% CI 1.05–2.93; P = 0.03; Figure 3), but heterogeneity was observed among trials (I^2 = 97%; P < 0.00001). The frequency of treatment discontinuation because of adverse events in the PARPi group and placebo group was 12.0 versus 2.5%, 20.4 versus 6%, 18.7 versus 6.1% and 11.5 versus 2.3%, respectively, in PRIMA,[22] PAOLA-1,[21] VELIA[23] and SOLO1.[24]

Sensitivity analysis and publication bias

The results of the sensitivity analyses for PFS of all subgroups and adverse events revealed that none of the included studies alone had an obvious impact on the

Table 1. Characteristics of included studies

Author, Year, Study	Study design	Total no. (PARPis/ Placebo)	Primary treatment received	Treatment arms	Duration of maintenance (mo)	Median age (y)*	Median duration of follow up (mo)	Median PFS (mo)*
González-Martín, 2019 PRIMA	RCT	487/246	PDS/IDS + PBC	Niraparib versus Placebo, Dosage: 300 mg orally once daily	36	62 (32–85) versus 62 (33–88)	13.8	13.8 versus 8.2
Ray-Coquard, 2019 PAOLA-1	RCT	537/269	PDS/IDS + PBC + bevacizumab	Olaparib + Bevacizumab versus Placebo plus Bevacizumab, Dosage:300 mg orally twice daily	24	61 (32–87) versus 60 (26–85)	22.7 in olaparib group and 24.0 in placebo group	22.1 versus 16.6
Coleman, 2019 VELIA	RCT	382/375	PDS/IDS + PBC + Veliparib	Veliparib versus Placebo, Dosage: 400 mg orally twice daily	21	62 (30–85) 62 (33–86)	28	23.5 versus 17.3
Moore, 2018 SOLO1	RCT	260/131	PDS/IDS + PBC	Olaparib versus Placebo, Dosage: 300 mg orally twice daily	24	53 (29–82) versus 53 (31–84)	40.7 in olaparib group and 41.2 in placebo group	49.9 versus 13.8

IDS, interval debulking surgery; mo, month; PBC, platinum-based chemotherapy; PDS, primary debulking surgery; y, year.
*PARPis versus Placebo.

direction or magnitude of the outcomes. Publication bias was evaluated using funnel plots, and the shape of the funnel plot did not provide evidence of visible asymmetry (Figure S2). Therefore, the present results are statistically steady and robust.

Discussion

Main findings

This meta-analysis of four RCTs with a total of 2687 patients confirmed the effectiveness of PARPis in improving PFS of patients with newly diagnosed advanced ovarian cancer, in a first-line maintenance setting after platinum-based chemotherapy compared with standard treatment (HR = 0.53; $P < 0.0001$). The greatest magnitude of benefit was in women with BRCA mutations (HR = 0.35; $P < 0.00001$), followed by those with HRD-positive tumours (HR = 0.43; $P < 0.00001$). The PFS benefit of PARPis was also seen in patients without BRCA mutations (HR = 0.72; $P < 0.00001$) and even in the HRD-negative subgroup (HR = 0.83; $P = 0.04$).

Strengths and limitations

A meta-analysis by Shao et al.[25] demonstrated that PARPis can significantly improve PFS in ovarian cancer patients. However, they did not evaluate the efficacy in newly diagnosed patients. Ibrahim et al.[26] conducted a meta-analysis which confirmed the PFS benefit of PARPis in patients with newly diagnosed advanced ovarian cancer stratified mainly by clinical variables. However, they did not report the toxicity analyses, which are important to weigh the risk and benefit. Our meta-analysis investigated the efficacy and safety of PARPis in newly diagnosed advanced ovarian cancer and stratified results paying particular attention to the type of BRCA mutational and HRD status. Specifically, our results confirmed the PFS improvement in all subgroups, including HRD-negative patients, and thus provide the possibility of expanding the use of PARPis to the whole population.

Several limitations of our study should be considered. First of all, heterogeneity may be present because of the use of different PARPis in different populations with different intervention designs. Furthermore, although we attempted to perform an extensive literature search to obtain all published studies, there were only four relevant RCTs. For this reason, we were unable to compare the different PARPis in order to distinguish them in terms of efficacy and toxicity. What is more, the overall survival (OS) outcome is now unavailable, which is the ultimate treatment goal in ovarian cancer but is difficult to achieve. Moreover, we were not able to perform a

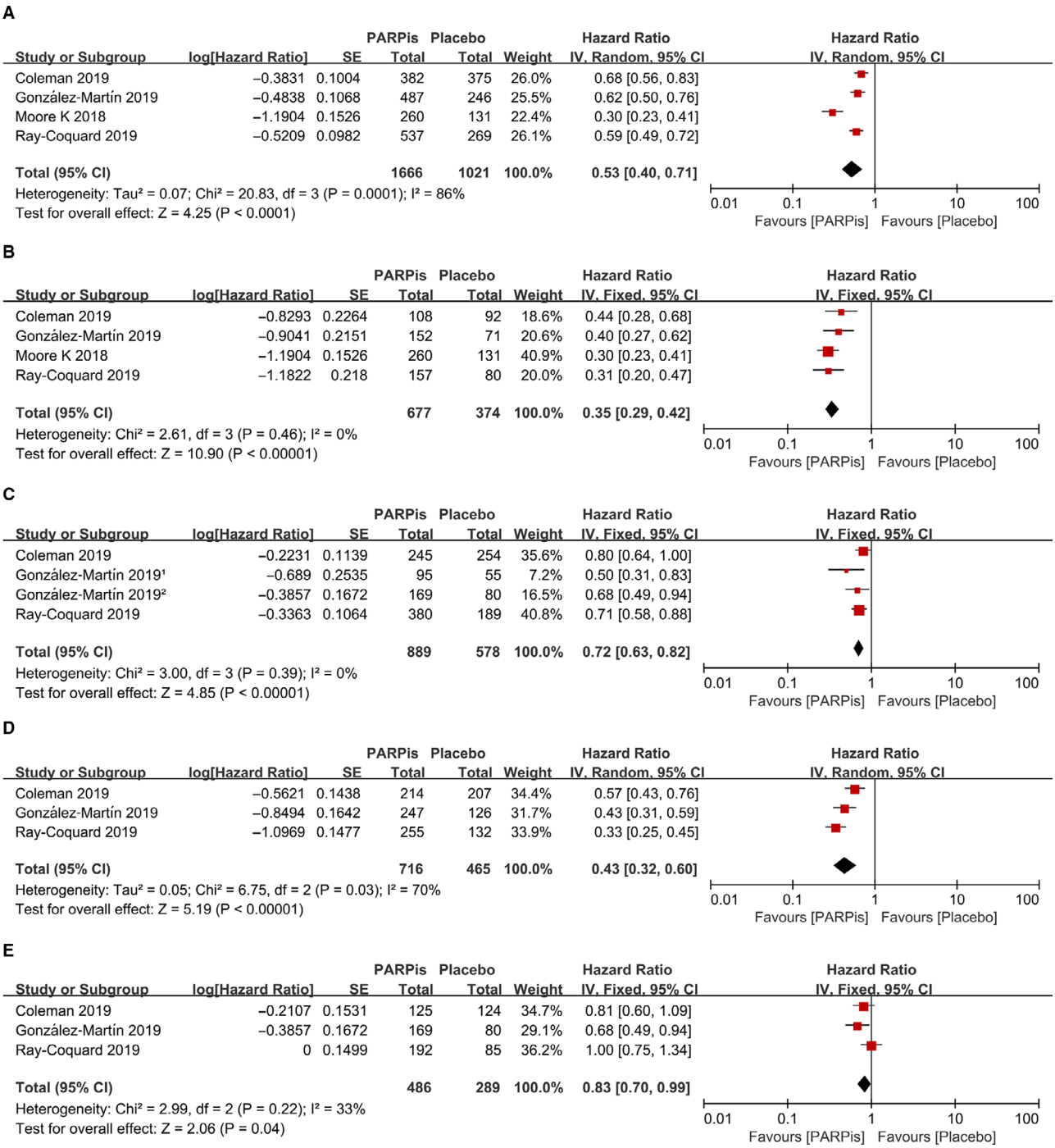

Figure 2. Forest plot for comparison of PFS between PARPis and placebo. (A) Whole population. (B) BRCA-mutated patients. (C) Patients without BRCA mutations: 1 – patients with tumours that had HRD without a BRCA mutation in González-Martín's study; 2 – HRD-negative patients in González-Martín's study. (D) HRD-positive patients. (E) HRD-negative patients.

search of unpublished studies; studies with negative results are less likely to be published and thus the results of our study were limited by the inclusion of published data only. Finally, only English-language studies were included in this meta-analysis, which may have introduced a language bias.

Interpretation

Despite a high response rate to initial cytoreductive surgery and subsequent chemotherapy, up to 70% of the patients with advanced ovarian cancer have a recurrence of the disease within 3 years.[7] After initial therapy,

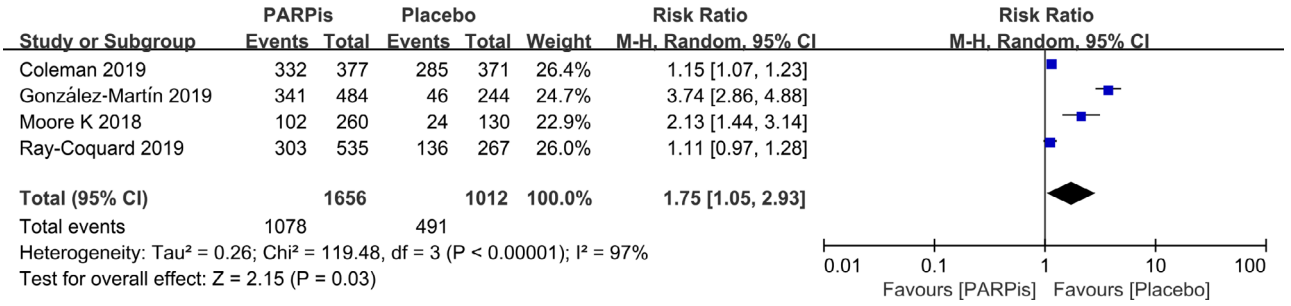

Figure 3. Forest plot for adverse events of grade 3 or higher.

management of advanced ovarian cancer may include maintenance therapy with the goal of inducing a lasting remission, or prolonging the disease-free interval before recurrence. Published medical literature indicates that PARPis are efficacious as a maintenance therapy in platinum-sensitive relapsed ovarian cancer.[13–17] Olaparib, niraparib and rucaparib have been approved for maintenance of patients with platinum-sensitive ovarian cancer who have responded to platinum in the second-line or third-line setting. The most important clinical question now is whether early treatment with PARPis will improve outcomes. Our meta-analysis suggested that among patients with newly diagnosed advanced ovarian cancer, the use of maintenance therapy with PARPis after platinum-based chemotherapy led to a significantly improvement in PFS. Thus it provides a first-line maintenance therapy option for advanced ovarian cancer

BRCA1 and BRCA2 are tumour suppressor genes involved in the repair of double-strand DNA breaks by homologous recombination (HR).[8] PARPis play a crucial role in the repair of single-strand DNA breaks.[27] PARPis induce 'synthetic lethality' in mutated BRCA1/2 cancers by simultaneous targeting of two DNA repair pathways.[28,29] For this reason, PARPis are considered particularly effective in BRCA-mutated patients. The results of this meta-analysis confirmed the substantial benefit of maintenance therapy with PARPis in the BRCA-mutated subgroup with regard to PFS among women with newly diagnosed advanced ovarian cancer. Although BRCA1 and BRCA2 are required for HR and are the most important targets for therapy, other genes involved in HR and/or associated DNA repair pathways, also cause sensitivity to PARPis in preclinical models.[11,12,30,31] It is considered that the remarkable efficacy of PARPis in ovarian cancer is not restricted to patients with BRCA1/2 mutations but extends to those with tumours positive for HRD.[31] Our meta-analysis showed significant improvement of PFS in the subgroup of HRD-positive patients, affirming the measurable effects that maintenance PARPis have on first-line HRD tumour therapy. Finally, our analysis highlights the PFS benefit of PARPi maintenance therapy in patients without BRCA mutations and even in those with HRD-negative tumours. It showed that PARPis may have mechanisms of action other than blocking the repair of damaged DNA. Recent studies have showed that PARPis may induce replication stress and subsequent DNA damage. Furthermore, PARP-regulated gene transcription, protein translation and immune activation may also explain this clinical observation.[32] Our analysis showed the possibility of expanding the use of PARPis to the whole population as first-line maintenance in newly diagnosed ovarian cancer, although the greatest magnitude of benefit was still found in women with BRCA mutation, followed by those with HRD-positive tumours. For the patients without BRCA mutations, the magnitude of benefit will depend on the HRD status. In the HRD-negative population, the efficacy of PARPis was minor; a careful risk–benefit discussion is needed in clinical practice.

In terms of safety, the most common adverse events (all grades) that occurred at a higher incidence among patients receiving PARPis compared with the control arm in our study were nausea, fatigue, anaemia, neutropenia and thrombocytopenia; these were consistent with the PARPi class-specific adverse events, which can often be managed with dose reductions or interruptions.[13–15,17,33] In addition, we have analysed grade 3 or higher adverse events, as we focused on those toxicities that might have been disadvantageous in terms of outcomes and quality of life (QoL). Although there were more grade 3 or higher adverse events in the PARPi maintenance arm, few patients discontinued therapy because of adverse events (11.5–20.4%). The safety profile appears unbalanced on different PARPis; in particular, niraparib reported a high incidence of grade 3 or higher adverse events (RR = 3.74), the majority of which were haematological toxicity. However, the discontinuation rate was relatively low (12.0%). Fatigue and nausea were the most common adverse events of olaparib;[21,24] these were usually managed by dose interruption or dose reduction. The most common adverse event leading to the discontinuation of veliparib[23] therapy was nausea (in 8% of patients). Furthermore, the overall risk of myelodysplastic syndrome and acute myeloid leukaemia, which were

considered the most troublesome PARPi class-specific potential adverse reactions, was quite low. The safety profile of PARPis appeared to be generally acceptable among patients with newly diagnosed advanced ovarian cancer receiving maintenance treatment.

Conclusion

Our results indicate the possibility of using PARPis as first-line maintenance therapy to prevent recurrence in advanced ovarian epithelial cancer. Future directions for research would be to determine when and how to sequence PARPi therapy with standard chemotherapeutic regimens, long-term outcomes and use of PARPis as the primary method along with targeted therapy in advanced epithelial ovarian cancer.

Disclosure of interests

None declared. Completed disclosure of interest forms are available to view online as supporting information.

Contributions to authorship

JYT, WCL and QQL conceived and designed the study. QQL, YLG and JL extracted and analysed data. WCL and QQL were the statisticians who confirmed the analysis of this study. QQL and SX wrote the manuscript. JYT and HKS critically revised the manuscript. All authors reviewed and approved the final manuscript.

Details of ethics approval

Not applicable.

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Acknowledgements

None.

Supporting Information

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Figure S1. The mechanism of action of PARP inhibitors.

Figure S2. Funnel plot for the detection of publication.

Table S1. Number of patients according to the BRCA mutational status and HRD status.

Table S2. Quality assessments for the included randomised controlled studies using the Cochrane Collaboration tool. ■

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