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Unveiling the Power of PARP Inhibitors: A Meta-Analysis on Newly Diagnosed Advanced Ovarian Cancer Maintenance Therapy

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ADMINISTRATIVE INFORMATION

Support - No.

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Conflicts of interest - None declared.

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Amendments - This protocol was registered with the International Platform of Registered Systematic Review and Meta-Analysis Protocols (INPLASY) on 23 March 2025 and was last updated on 23 March 2025.

INTRODUCTION

Review question / Objective This meta-analysis sought to assess the efficacy and safety of poly (adenosine diphosphate-ribose) polymerase inhibitors as maintenance therapy for patients with newly diagnosed advanced ovarian cancer.

Condition being studied Ovarian cancer (OC) is recognized as the most lethal form of gynecological malignancy and is the eighth leading cause of cancer-related mortality among women worldwide. Annually, approximately 324,398 new cases and 206,839 deaths are attributed to OC globally. Importantly, nearly 75% of OC cases are diagnosed at an advanced stage. The current standard treatment for newly diagnosed advanced OC involves cytoreductive surgery followed by platinum-based chemotherapy. Despite the implementation of advanced surgical techniques and the development of improved chemotherapeutic protocols, the majority of patients with advanced OC experience disease recurrence within three years.

Approximately 13% of OC patients possess mutations in the BRCA1 or BRCA2 genes, while 50% exhibit somatic homologous recombination deficiency (HRD)[5]. Additionally, genomic alterations and/or epigenetic silencing of other pathway genes, including ATR, ATM, CHK1/2, RAD51/54, NBS1, PALB2, and PTEN, have been associated with HRD. Poly (adenosine diphosphate-ribose) polymerase (PARP) is an enzyme in eukaryotic cells that acts as a substrate for caspase, a critical component in the process of apoptosis. PARP inhibitors (PARPi) can hinder the repair of DNA single-strand breaks (SSB), leading to the formation of double-strand breaks (DSB) that are not accurately repairable in tumors exhibiting HRD, ultimately resulting in cell death. Recently, the advent of PARP inhibitors has significantly transformed the therapeutic landscape for OC.

Key PARPi include olaparib, niraparib, rucaparib, fluzoparib, senaparib, veliparib, talazoparib, and pamiparib, among others[10, 11]. Currently, three PARPi have received approval from the U.S. Food and Drug Administration (FDA) for the treatment of OC: olaparib and niraparib are approved as monotherapies for maintenance therapy following primary and recurrent chemotherapy. Prior RCTs have demonstrated that PARPi significantly enhance progression-free survival (PFS) when administered as maintenance therapy in patients with platinum-sensitive recurrent OC, irrespective of biomarker status such as BRCAm or HRD. More recent randomized controlled trials (RCTs) have further established that PARPi maintenance therapy significantly improves PFS in patients with newly diagnosed advanced OC, regardless of the presence of BRCA mutations (BRCAm) or HRD. Moreover, two recent RCTs have reported a survival benefit associated with PARPi, specifically in terms of overall survival (OS), for newly diagnosed advanced OC patients with BRCAm or HRD.

The various treatment strategies involving PARPi have resulted in clinical uncertainty regarding which approach may offer optimal survival benefits for patients. It is crucial to synthesize these findings to furnish clinicians with an evidence-based reference. Consequently, we conducted this meta-analysis, incorporating all eligible and pertinent RCTs, to evaluate the efficacy and safety of PARPi as a maintenance therapy following platinum-based chemotherapy in patients with newly diagnosed advanced OC. Additionally, we performed subgroup analysis to determine the most advantageous treatment regimen for advanced OC.

METHODS

Participant or population Patients with newly diagnosed high-grade serous or endometrioid ovarian cancer of FIGO stage III or IV.

Intervention PARP inhibitors were used as first-line maintenance therapy (for participants who had complete response (CR) or partial response (PR) after chemotherapy).

Comparator Placebo was used as first-line maintenance therapy (for participants who had complete response (CR) or partial response (PR) after chemotherapy).

Study designs to be included Randomized controlled trials.

Eligibility criteria (1) patients with newly diagnosed high-grade serous or endometrioid ovarian cancer of FIGO (International Federation of Gynecology and Obstetrics) stage III or IV; (2) the comparison was PARPi versus placebo, of which, PARP inhibitors were used as first-line maintenance therapy (for participants who had complete response (CR) or partial response (PR) after chemotherapy); (3) Data of PFS, OS, or related adverse reactions were reported in the literature; (4) RCTs.

Information sources PubMed, Medline, EMBASE, Cochrane Library, and Web of Science databases.

Main outcome(s) The primary outcomes assessed were progression-free survival (PFS), overall survival (OS), and adverse events (AEs).

Quality assessment / Risk of bias analysis Each domain of risk of bias was independently assessed by two reviewers utilizing the Cochrane Risk of Bias Tool for RCTs. This assessment encompassed sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective outcome reporting, and other potential sources of bias. Studies receiving scores between 0 and 3 points were classified as low quality, whereas those with scores ranging from 4 to 7 points were categorized as high quality.

Strategy of data synthesis For PFS and OS, pooled hazard ratios (HR) with 95% confidence intervals (CI) were computed. In assessing the incidence of grade 3 or higher AEs, pooled risk ratios (RR) with 95% CI were determined.

Subgroup analysis The subgroup analysis was performed in HRD, HRP, BRCAm, BRCAwt, age, Eastern Cooperative Oncology Group (ECOG) performance status, CA125 levels, FIGO stage, receipt of neoadjuvant therapy, or response to chemotherapy.

Sensitivity analysis A chi-squared (χ^2) test for heterogeneity was employed to evaluate statistical heterogeneity among the studies. A fixed-effects model was applied when the I^2 statistic was ≤ 50%; otherwise, a random-effects model was utilized.

Country(ies) involved Chins.

Keywords newly diagnosed, advanced ovarian cancer, PARP inhibitors, maintenance therapy, meta-analysis.

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