INPLASY PROTOCOL

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None declared.

Efficacy and safety of PARP inhibitor therapy in advanced ovarian cancer: A systematic review and network meta-analysis of randomized controlled trials

Chen, JY[1]; Wu, XZ[2]; Wang, HZ[3]; Lian, XS[4]; Li, B[5]; Zhan, XB[6].

Review question / Objective: **The aim of this network meta-analysis of randomized controlled trials is to evaluate the efficacy and safety of PARP inhibitor therapy in advanced ovarian cancer. And try to find the optimal PARP inhibitor therapy choice in advanced ovarian cancer. Population: women with advanced ovarian cancer; Intervention: PARP inhibitor alone or combination with other agents; Comparison: Placebo, or chemotherapy, or antiangiogenic inhibitors, or other targeted agents; Outcome: Median progression-free survival (PFS) or overall survival (OS) or the adverse events or time to start of first subsequent therapy (TFST) or time to start of second subsequent therapy (TSST).**
Condition being studied: **Ovarian cancer is a leading cause of death from gynecologic cancers worldwide. Most of the ovarian cancer cases are diagnosed at an advanced stage of the disease, which impairs the chances of prolonged complete remission. The standard front-line treatment combines surgery with platinum-based chemotherapy. Most patients will relapse in the years following the initial treatment. Several PARP inhibitors showed substantial efficacy in ovarian cancer. This network meta-analysis of randomized controlled trials is to evaluate the efficacy and safety of PARP inhibitor therapy in advanced ovarian cancer. And try to find the optimal PARP inhibitor therapy choice in advanced ovarian cancer.**

INPLASY registration number: This protocol was registered with the International Platform of Registered Systematic Review and Meta-Analysis Protocols (INPLASY) on 16 February 2022 and was last updated on 16 February 2022 (registration number INPLASY202220059).

INTRODUCTION

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the optimal PARP inhibitor therapy choice in advanced ovarian cancer. Population: women with advanced ovarian cancer; Intervention: PARP inhibitor alone or combination with other agents; Comparison: Placebo, or chemotherapy, or antiangiogenic inhibitors, or other targeted agents; Outcome: Median progression-free survival (PFS) or overall survival (OS) or the adverse events or time to start of first subsequent therapy (TFST) or time to start of second subsequent therapy (TSST).

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METHODS

Participant or population: Patients diagnosed with advanced cancer of high-grade serous or endometrioid ovarian cancer, primary peritoneal cancer, or fallopian-tube cancer.

Intervention: Any dosage and treatment duration of any type of PARP inhibitor alone or combination with other agents on ovarian cancer.

Comparator: Placebo, or chemotherapy, or antiangiogenic inhibitors, or other targeted agents.

Study designs to be included: We will enroll all the relevant phase 2 or phase 3 randomized controlled trials (RCT) with at least two arms.

Eligibility criteria: The relevant clinical trials on the efficacy and safety of PARP inhibitors 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 advanced ovarian cancer with or without BRCA1 or BRCA2 mutations, platinum-sensitive or platinum-resistant. (2) The trial compared PARP inhibitors or PARP inhibitors combination with other interventions such as placebo or angiogenesis inhibitors or other chemotherapy drugs. (3) The study provided available data to calculate the HR of PFS or OS or TFST and RR of AEs.

Information sources: A comprehensive literature search will be conducted in PubMed, Cochrane Library, Web of Science and Embase from inception to January 2022 for all RCTs. References of the selected articles will be checked and searches will be re-run prior to the final analysis.A comprehensive literature search will be conducted in PubMed, Cochrane Library, Web of Science and Embase . References of the selected articles will be checked and searches will be re-run prior to the final analysis.

Main outcome(s): Median progression-free survival (PFS) or overall survival (OS) or the overall risk to suffer grade≥3 AEs. Measures of effect: The combination of hazard ratio (HR) and 95% credible interval (CI).

Additional outcome(s): Time to start of first subsequent therapy (TFST) or time to start of second subsequent therapy (TSST).

Quality assessment / Risk of bias analysis: Two authors will independently extract data and assess the risk of bias. Any disagreement will be resolved by discussion until consensus is reached or by consulting a third author. We will use the Cochrane Collaboration's tool for assessing risk of bias. This tool covers seven sources of bias: (1) random sequence generation; (2) allocation concealment; (3) blinding of participants

and personnel; (4) blinding of outcome assessment; (5) incomplete outcome data; (6) selective reporting; (7) other bias. For each one of the them the risk can be assessed as high risk, unclear risk or low risk depending of the information offered by the study.

Strategy of data synthesis: The network meta-analysis used Bayesian random effects models to compare the effects of interventions to explain the efficacy and safety of various PARP inhibitors alone or in combination with other agents in advanced ovarian cancer. Modeling was performed using the Markov chain Monte Carlo method, four Markov chains were run simultaneously, the annealing times were set to 20,000 times, and the modeling was completed after 50,000 simulation iterations. The deviation information criterion (DIC) will be used to compare model fit and overall consistency, and if there is a closed-loop mesh, we will use node splitting to analyze local consistency. In addition, SUCRA-based rankings were performed on each intervention for each outcome to analyze the optimal probability for each outcome, and league tables were generated to compare the effects of different outcomes across interventions. The network relationship network diagram was drawn in Stata 15.0 (Stata Corporation, College Station, TX), the network meta-analysis was performed in R software 4.0.4, and the package used was gemtc. $P<0.05$ indicated that the difference was statistically significant.

Subgroup analysis: PFS in patients with germinal or somatic BRCA mutations or other homologous recombination deficiencies (HRD) or BRCA wild-type.

Sensitivity analysis: In the sensitivity analysis, we excluded one study without changing the network structure, and conducted a complete network meta-analysis on the remaining studies to observe whether the results were significantly changed from those of all included studies.

Country(ies) involved: China.

Keywords: PARP inhibitors; Olaparib; Rucaparib; Niraparib; Veliparib; ovarian cancer; systematic review; network meta-analysis.

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