INPLASY

Evaluating the Synergistic Impact of PD-1/PD-L1 Blockade and Platinum-Based Chemotherapy in Modulating the Tumor Microenvironment for Enhanced T Cell-Mediated Immune Responses in Advanced Endometrial Cancer: A Meta-Analysis

INPLASY202490121
doi: 10.37766/inplasy2024.9.0121
Received: 26 September 2024
Published: 27 September 2024

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ADMINISTRATIVE INFORMATION

Support - This work was supported by the National Natural Science Foundation of China (grant nos. 82074487, 81903998).

Review Stage at time of this submission - Preliminary searches.

Conflicts of interest - None declared.

INPLASY registration number: INPLASY202490121

Amendments - This protocol was registered with the International Platform of Registered Systematic Review and Meta-Analysis Protocols (INPLASY) on 27 September 2024 and was last updated on 27 September 2024.

INTRODUCTION

Review question / Objective In this systematic review and meta-analysis, the primary objective is to assess the efficacy and safety of combining PD-1/PD-L1 immune checkpoint inhibitors with platinum-based chemotherapy as a first-line treatment for advanced endometrial cancer.

Condition being studied The condition being studied is advanced or metastatic endometrial cancer, a common malignancy of the female reproductive system. This study focuses on evaluating treatment strategies for patients with advanced stages of the disease, where current therapeutic options are limited, and prognosis is poor. Specifically, the study investigates the efficacy and safety of combining PD-1/PD-L1 immune checkpoint inhibitors with platinum-based chemotherapy as a first-line treatment.

METHODS

Search strategy A comprehensive literature search was performed using the following electronic databases: PubMed, Embase, Cochrane Central Register of Controlled Trials (CENTRAL), and ClinicalTrials.gov. The search period covered all published studies from database inception up to 10th August 2024. The search strategy included a combination of medical subject headings (MeSH) and free-text terms related to "endometrial cancer," "PD-1," "PD-L1," "immune checkpoint inhibitors," "platinum-based chemotherapy," and "first-line treatment." Additionally, references of retrieved articles were manually checked to identify any additional relevant studies.A comprehensive search of relevant literature was conducted in PubMed, EMBASE, Cochrane Library, and Scopus databases. The search was restricted to articles published between January 2000 and September 2024. The following keywords were used in various combinations: "Premature Ovarian Failure," "POF,"

"Gonadotropin Releasing Hormone Analogs," "GnRH analogs," "Ovarian Cancer," "Cancer Prevention," and "Ovarian Function." No language restrictions were applied, and the search also included grey literature such as conference abstracts and unpublished studies, where applicable.

Participant or population Patients with advanced or metastatic endometrial cancer, including those with mismatch repair deficient (dMMR) and mismatch repair proficient (pMMR) tumors.

Intervention Combination of PD-1/PD-L1 immune checkpoint inhibitors (e.g., pembrolizumab, dostarlimab, avelumab) with platinum-based chemotherapy (e.g., carboplatin-paclitaxel).

Comparator Platinum-based chemotherapy alone or other standard treatments.

Study designs to be included Randomized controlled trials (RCTs), non-randomized controlled trials, and observational studies.

Eligibility criteria Studies were included in the meta-analysis if they met the following criteria:
(1)Patients with histologically confirmed advanced or metastatic endometrial cancer.
(2)Treatment with a combination of anti-PD-1 or anti-PD-L1 agents and platinum-based chemotherapy as first-line therapy.
(3) Studies with either a comparison arm using chemotherapy alone or with other treatment regimens were considered.
(4)Reported at least one of the following outcomes: progression-free survival (PFS), overall survival (OS), objective response rate (ORR), and treatment-related adverse events (AEs).
(5)Randomized controlled trials (RCTs), non-randomized controlled trials, and observational studies.
While this study adhered to strict inclusion criteria, we acknowledge that the exclusion of non-English publications and studies with insufficient data may introduce some bias. The primary reason for excluding non-English studies is the language limitations of the research team, which could lead to potential inaccuracies in translation. Moreover, studies with insufficient data were excluded to ensure the robustness of the meta-analysis and to avoid the risk of misinterpreting incomplete or unclear results. However, we recognize that these exclusions may limit the generalizability of our findings. Future research could address this limitation by incorporating a broader range of languages and including studies with additional data sources.

Information sources PubMed, Embase, Cochrane Central Register of Controlled Trials (CENTRAL), and ClinicalTrials.govPubMed, EMBASE, Cochrane Library, and Scopus databases.

Main outcome(s) Primary outcomes include progression-free survival (PFS) and overall survival (OS).

Additional outcome(s) Secondary outcomes include objective response rate (ORR) and treatment-related adverse events (AEs), particularly immune-related adverse events(irAEs).

Data management Two independent reviewers screened the titles and abstracts of all identified studies. Full texts of potentially eligible studies were retrieved for further evaluation. Discrepancies between reviewers were resolved through discussion or consultation with a third reviewer.

Quality assessment / Risk of bias analysis The quality of included studies was assessed using the Cochrane Risk of Bias Tool for randomized controlled trials and the Newcastle-Ottawa Scale (NOS) for observational studies. The Cochrane tool evaluates the risk of bias in seven domains: sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective outcome reporting, and other sources of bias. The NOS assesses the quality of non-randomized studies in three domains: selection of study groups, comparability of groups, and ascertainment of outcomes. Studies were rated as having low, moderate, or high risk of bias based on these criteria.

Strategy of data synthesis Meta-analyses were performed using the Review Manager (RevMan) software version 5.5 and Stata version 15.5E. The primary outcomes were PFS and OS, and the secondary outcomes included ORR and AEs. Hazard ratios (HRs) with 95% confidence intervals (CIs) were used to assess PFS and OS. For dichotomous outcomes like ORR and AEs, odds ratios (ORs) with 95% CIs were calculated. Heterogeneity among studies was assessed using the I^2 statistic and Chi-square test. An I^2 value of 0–40% was considered low heterogeneity, 41–60% moderate heterogeneity, and above 60% high heterogeneity. A random-effects model was used if significant heterogeneity was detected ($I^2 > 50\%$); otherwise, a fixed-effects model was applied. Sensitivity analyses were conducted by excluding studies with a high risk of bias or those with outlying results to evaluate the robustness of the findings.

Subgroup analysis Subgroup analyses were conducted to investigate the effects of certain patient and treatment characteristics on the outcomes of interest.

Sensitivity analysis Sensitivity analyses were performed to evaluate the stability of the results. This included re-analyzing the data after excluding studies with a high risk of bias, using alternative statistical models (fixed-effect versus random-effect models), and excluding outliers or studies with extreme results.

Country(ies) involved China/ Nanjing University of Chinese Medicine.

Keywords Endometrial cancer, Platinum-based chemotherapy, Immune checkpoint inhibitors, Anti-PD-1, Meta-analysis.

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