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Effectiveness and safety of weekly therapy versus 3-weekly therapy of paclitaxel plus carboplatin in women with ovarian cancer: a protocol of systematic review and meta-analysis

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ABSTRACT

Introduction Network meta-analyses have confirmed that paclitaxel plus carboplatin could improve progression-free survival (PFS) and overall survival (OS) compared with platinum alone. However, detailed implementation schedule (weekly or 3-weekly therapy) was not specified in clinical practice guidelines. Evidence from studies is also inconsistent. We will conduct a systematic review and meta-analysis to evaluate the benefits and harms of weekly therapy and 3-weekly therapy of paclitaxel combined with carboplatin in women with ovarian cancer.

Methods We will search PubMed, EMBASE and the Cochrane Library databases to include relevant randomised controlled trials comparing weekly therapy versus 3-weekly therapy of paclitaxel combined with carboplatin for women with ovarian cancer. Random-effects model will be used to pool data for patient-reported outcomes including survival rate, OS, PFS and adverse events. Grading of Recommendation, Assessment, Development and Evaluation approach will be used to rate the quality of evidence.

Ethics and dissemination This systematic review and meta-analysis will be based on published data and does not therefore require specific ethical approval or consent for participation. The results will be published in a peer-reviewed journal.

OSF registration number 10.17605/OSF.IO/GJUMA.

Strengths and limitations of this study

- Detailed subgroup analysis (eg, dose-dense vs metronomic dosing schedule in patients who underwent completely tumour resection, optimally and suboptimally resection debulking surgery, different mean follow-up duration) will be undertaken.
- We will use the Grading of Recommendation, Assessment, Development and Evaluation system to calculate absolute effects for each outcome and rate the certainty of evidence.
- We will only include studies in English, which may increase the risk of bias.
- Studies might selectively report data regarding adverse events in their full publications, which could lead to risk of reporting bias.

INTRODUCTION

Paclitaxel combined with carboplatin was recommended as a first-line chemotherapy strategy for ovarian cancer by National Institute for Health and Care Excellence, Scottish Intercollegiate Guidelines Network and National Comprehensive Cancer Network guidelines.[1–3] Network meta-analyses have confirmed that paclitaxel plus carboplatin could improve progression-free survival (PFS) and overall survival (OS) compared with platinum alone.[4 5] However, detailed implementation schedule (weekly or 3-weekly therapy) was not specified in these guidelines.

It is the most common first-line chemotherapeutic approach for women with advanced epithelial ovarian cancer to combine treatment 3-weekly paclitaxel plus carboplatin.[6 7] One randomised controlled trial (RCT) with 631 patients found that, at long-term follow-up, weekly (80 mg/m^2) versus 3-weekly (180 mg/m^2) regimens of paclitaxel plus carboplatin at an area under the curve of 6 mg/mL/min significantly improved PFS (HR 0.76, 95% CI 0.62 to 0.91) and OS (100.5 months vs 62.2 months, HR 0.79, 95% CI 0.63 to 0.99).[8]

However, other trials showed inconsistent results. The Gynecologic Oncology Group (GOG)-0252 trial with 692 patients found that weekly paclitaxel versus paclitaxel administered every 3 weeks, did not prolong PFS. But subgroup analysis found that weekly paclitaxel improved PFS that was 3.9 months longer than that observed with paclitaxel administered every 3 weeks (HR 0.62, 95% CI

0.40 to 0.95) among patients who were not treated with bevacizumab.[9]

Another trial concluded significant improvement in PFS but no difference in OS.[10] Evidence from observational studies is also inconsistent.[10–13] Thus, it is necessary to conduct this meta-analysis to clarify the effectiveness and safety of weekly paclitaxel plus carboplatin regimen compared with 3-weekly paclitaxel plus carboplatin regimen for women with ovarian cancer.

MATERIAL AND METHODS

Study registration

The protocol and registration information is available at OSF REGISTRIES (10.17605/OSF.IO/GJUMA) international prospective register. The study will be performed in accordance with the Preferred Reporting Items for Systematic reviews and Meta-Analysis Protocols guidelines (online supplemental file 1).[14–16] The systematic review and meta-analysis will be conducted and reported in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses 2020 statement.[17]

Search terms for retrieval of studies

We will systematically search PubMed, EMBASE and the Cochrane Library database to collect RCTs on weekly and 3 weekly of paclitaxel and carboplatin chemotherapy for women with ovarian cancer, and the retrieval time is from inception to May 2021. There will be no restriction on the publication date and language. Search terms will combine Medical Subject Headings (MeSH) termsand full-text terms related to “Paclitaxel”, “taxol”, “anzatax”, “paxene”, “onxol”, “abraxane”, “praxel”, “Ovarian Neoplasms”, “ovarian cancer”, “ovarian adenocarcinoma”, “Drug Administration Schedule”, “dose-dense” and “weekly”. Details of search strategy in each database could be found in online supplemental file 2. In addition, we will check the reference lists of the included studies, so as to identify potentially relevant literature.

Inclusion criteria

Studies

We will include RCTs.

Participants

Adult women, 18 years or older, newly diagnosed with ovarian cancer confirmed by pathology, the expected survival time is at least 6 months, the living condition score (Kamofsky score) >60, without intracranial and bone metastases, and the function of heart, liver, kidney and bone marrow is normal.

Intervention

Weekly therapy of paclitaxel including dose-dense (increased cumulative dosage) or metronomic (similar cumulative dosage) in combination with carboplatin, without limitation on drug regimen, dosage and course of treatment.

Comparison

Three-weekly therapy of paclitaxel combined with carboplatin, without limitation on drug regimen, dosage and course of treatment.

Types of outcome measures

We will include patient-reported outcomes to compare the effectiveness and safety of weekly and 3-weekly therapy of paclitaxel combined with carboplatin for ovarian cancer in the analysis, which included:

- PFS.
- OS.
- Survival rate.
- Adverse events.

Exclusion criteria

- Patients accompanied with other primary malignant tumours.
- Studies not published in English.
- Similar studies were reported without additional data to analyse and extract.
- Articles published as abstracts or with incomplete data, or valid original data were unable to obtain even after contacting the author(s).
- Studies without the relevant outcome indicators.

Data collection and analysis

Selection process

We will use Covidence[18] to store and manage records. Two independent reviewers will select titles and abstracts of the studies according to inclusion criteria. If disagreements between the reviewers cannot be resolved through discussion, a third reviewer will arbitrate the final decision. We will acquire the full text of potentially relevant studies for further assessment. Records will be downloaded into Covidence and screened. The process of screening the studies was shown in online supplemental file 3.[17]

Data extraction

We will use Microsoft Excel V.2019 software to extract relevant information, which included:

- Characteristics of research (the title of the study, first author name, year of publication, journal, population location, funding source, study design).
- Characteristics of study population (total sample size, average age, mean follow-up duration, grade, histotype, comorbidities).
- Characteristics of interventions and comparators (types, dosage forms, frequency, and duration in the intervention and comparison groups, the number of events and the number of people assessed in the intervention and comparison groups).
- Required outcome indicators (PFS, OS, survival rate and adverse events).
- Quality assessment items.

A standard form will be used to extract data from the included studies. Two reviewers will independently extract the related data and any dispute will be discussed and resolved by the third reviewer. When the required data

are incomplete or not reported in a study, the reviewer will contact the corresponding author or other authors by telephone or email to obtain the missing data.

Risk of bias assessment

Two reviewers will independently assess potential risks of bias for all included studies using the Cochrane's Risk of Bias tool.[19] The tool contains six different domains: sequence generation; allocation concealment; blinding of participants, personnel and outcome assessors; incomplete outcome data; selective outcome reporting; and other sources of bias. Each domain receives a high, low or unclear bias depending on reviewers' judgement. We will summarise results in both a 'risk of bias' graph and a 'risk of bias' summary. Where doubt existed as to a potential risk of bias, we will contact authors of the included studies for clarification.

Sum statistical analysis

Data synthesis

We will present risk ratio (RR) and 95% CI as the effect size for dichotomous outcomes. For time-to-event data, we will pool HRs. Forest plots will be produced to visually assess the RR and corresponding 95% CI using random-effects models. Statistical heterogeneity between studies will be assessed via the forest plot, while I^2[22] values described the total variation between studies. I^2 values of <25%, 25%–50%, and>50% indicated low, moderate, and high heterogeneity, respectively. We will use STATA software V.15.0 (StataCorp, College Station, Texas, USA) to synthesise all the obtained data.

Subgroup analysis and investigation of heterogeneity

We will conduct subgroup analyses to investigate potential source of heterogeneity on treatment effect size, including clinical heterogeneity or methodological heterogeneity. We will perform subgroup analyses for dose-dense (increased cumulative dosage) versus metronomic (similar cumulative dosage) dosing schedule in patients who underwent completely tumour resection, optimally and suboptimally resection debulking surgery, timing of cytoreductive surgery (primary debulking surgery or interval debulking surgery), studies conducted in Asia or with a majority of Asian patients versus studies conducted in Western countries, the survival rate at different mean follow-up duration.

Sensitivity analysis

Sensitivity analysis will be performed to test the stability of the indexed meta-analysis results by the elimination method and explore and interpret the sources of high heterogeneity.[20] We will delete one single study from the overall pooled analysis each time to check the influence of the removed data set to the overall estimates.

Assessment of the publication bias

We will adopt funnel plot and Egger's test[21] to detect publication bias only when there are at least 10 studies included in the meta-analysis; because when there are fewer studies, the power of the tests is too low to distinguish chance from real asymmetry.[19]

Summary of findings

We will use the Grading of Recommendation, Assessment, Development and Evaluation (GRADE) system[22] to assess the quality of evidence associated with specific outcomes and constructed a 'summary of findings' table. The GRADE approach will be used to assess the quality of evidence based on the extent to which one can be confident that an estimate of effect or association reflects the item being assessed. Assessment of the quality of evidence considers study methodological quality, directness of the evidence, heterogeneity of the data, precision of the effect estimates and risk of publication bias.

Patient and public involvement

Patients and the public will not participate directly in this review study as we only use secondary data provided in the literature and other sources.

DISCUSSION

In our study, we will comprehensively search and include available RCTs to investigate the effectiveness and safety of weekly and 3-weekly therapy of paclitaxel with carboplatin for ovarian cancer.

The PFS has been regarded as a patient-important outcome in clinical studies of ovarian cancer for a long time, while the OS is normally regarded as a surrogate outcome.[23] Compared with OS, the advantages of PFS include assessing antitumour efficacy earlier and more sensitively, a lower likelihood of influence by competing risks and a lesser chance of confounding due to treatments received after progression.

Among patients with ovarian cancer in a Japanese GOG (JGOG) trial, dose-dense weekly paclitaxel was associated with longer OS than treatment as conventionally administered 3 weekly.[8] Nonetheless, JGOG data were limited to the Japanese population, so we will conduct a subgroup analysis according to the Asian and Europeans and Americans in PFS, OS and survival rate.

In addition, a meta-analysis had combined the results of three trials to compare the efficacy of weekly versus 3-week chemotherapy regimes, in term of survival outcomes and toxic effects.[9 24 25] However, the results of ICON8 trial had been published.[26 27] Another study conducted reported that dose-dense weekly paclitaxel and carboplatin treatment improves survival compared with conventional paclitaxel and carboplatin treatment.[28] Therefore, it seems that an updated comprehensive meta-analysis is required to shed light on the effectiveness and safety of weekly paclitaxel with carboplatin regimen compared with 3-weekly paclitaxel with carboplatin regimen for women with ovarian cancer. Our review will include a systematic and rigorous approach to the identification of RCTs investigating the impact of effectiveness and safety of weekly and 3-weekly therapy of paclitaxel plus carboplatin for ovarian

cancer. This is an updated systematic review and meta-analysis protocol focused on this topic[29] and we design a number of preplanned subgroup analyses to explore the differences in PFS, OS and survival rate. Besides, we will use the GRADE approach to assess the quality of evidence, allowing us to better interpret the results for patient-reported outcomes.

Our study also has limitations. First, studies might selectively report data regarding adverse events in their full publications, which could lead to risk of reporting bias. Second, publication bias will not be conducted to by Egger's test because few studies could lead to insufficient power of statistical tests.

ETHICS AND DISSEMINATION

This systematic review and meta-analysis will be based on published data and does not therefore require specific ethical approval or consent for participation. The results will be published in a peer-reviewed journal.

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Contributors WQ and YF conceived the study, developed the search strategy and drafted the protocol. Both authors critically revised the manuscript for methodological and intellectual content, and have read and approved the final manuscript. YL was involved in conception and generation of the study protocol. ST, BM, RL and QL were involved in study design. YD, BC, ST, BM, RL, QL and YL contributed to and approved the final manuscript of the protocol review.

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Competing interests None declared.

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