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

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Effectiveness and safety of weekly therapy versus three-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 three-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 three-weekly therapy of paclitaxel combined with carboplatin in women with ovarian cancer.

Methods We will search PubMed, EMBASE, the Cochrane Library databases to include relevant randomized controlled trials (RCTs) comparing weekly therapy versus three-weekly therapy of paclitaxel combined with carboplatin for women with ovarian cancer. Random model will be used to pool data for patient reported outcomes including survival rate, OS, PFS and adverse events. GRADE 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 therefore not 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

Keywords paclitaxel, carboplatin, ovarian cancer, weekly therapy, three-weekly therapy

Strengths and limitations of this study
• The review will provide a meticulous overview of the existing evidence on the effectiveness and safety of a weekly paclitaxel with carboplatin regimen compared to a three-weekly paclitaxel with carboplatin regimen for women with ovarian cancer.
• Detailed subgroup analysis (eg, dose-dense versus metronomic dosing schedule, different mean follow-up duration) will be undertaken.
• We will use the GRADE 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.\textsuperscript{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.\textsuperscript{4,5} However, detailed implementation schedule (weekly or three-weekly therapy) was not specified in these guidelines. Combination treatment with paclitaxel and carboplatin, given on a three-weekly basis, is the most common first line chemotherapeutic approach for women with advanced epithelial ovarian cancer.\textsuperscript{6,7} Interest in a three-weekly paclitaxel regimen was inspired by the Japanese Gynaecologic Oncology Group (JGOG) 3016 trial, which found that weekly paclitaxel was associated with an improvement in PFS (28.2 months versus 17.5 months, hazard ratio (HR) = 0.76, P value < 0.01) and OS (100.5 months versus 62.2 months, HR = 0.79, P = 0.04), even at long-term follow-up.\textsuperscript{8}

However, other trials showed inconsistent results. The GOG 262 trial found that there was no difference in PFS or OS between the weekly and three-weekly regimens, but subgroup analysis showed that, in women not treated with bevacizumab, a weekly paclitaxel regimen improved PFS compared with a three-weekly regimen.\textsuperscript{9} Another trial concluded significant improvement in PFS but no difference in OS.\textsuperscript{10} Evidence from observational studies is also inconsistent.\textsuperscript{10-13} Thus, it is necessary to conduct this meta-analysis to clarify the effectiveness and safety of a weekly paclitaxel with carboplatin regimen compared to a three-weekly paclitaxel with carboplatin regimen for women with ovarian cancer.

Material and Methods

Study registration

The protocol and registration information are 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 (PRISMA-P) guidelines (online supplemental 1).

Search terms for retrieval of studies

We will systematically search PubMed, EMBASE, the Cochrane Library database to collect randomized controlled trials (RCTs) on weekly and three-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 MeSH and full text terms related to “Paclitaxel”, “taxol”, “anzatax”, and “paxene”, “onxol”, “abraxane”, “praxel” and “Ovarian Neoplasms”. Details of searching 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 literatures.

Inclusion criteria

Studies

We will include RCTs.

Participants
Patients with ovarian cancer confirmed by pathology, the expected survival time is at least six months, the living condition score (Kamofsky score, KPS) >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 three-weekly therapy of paclitaxel combined with carboplatin for ovarian cancer in the analysis, which included:

- Progression free survival (PFS).
- Overall survival (OS).
- Survival rate.
- Adverse events.

**Exclusion criteria**
- Patients accompanied with other primary malignant tumors.
- Studies not published in English.
- Similar studies were reported without additional data to analyze 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 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, co-morbidities).
- 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 (ROB) tool. 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’ judgment. We will summarize 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% confidence interval (CI) as the effect size for dichotomous outcomes. For time-to-event data, we will pool hazard ratios (HR). 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 $I^2$ 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 version 15.0 (StataCorp, College Station, TX) to synthesis 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, studies conducted in Asia or with a majority of Asian patients versus studies conducted in Western countries and 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. 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\textsuperscript{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.\textsuperscript{19}

**Summary of findings**

We will use the Grades of Recommendation, Assessment, Development and Evaluation (GRADE) system\textsuperscript{22} to assess the quality of evidence associated with specific outcomes and constructed a ‘Summary of findings’ (SoF) 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 three-weekly therapy of paclitaxel with carboplatin for ovarian cancer.

The debate on the role of PFS as primary endpoint in ovarian cancer clinical trials has been discussed in long time and in the last years, it has become to be considered as a surrogate endpoint of OS.\textsuperscript{23} The advantages of this endpoint are an earlier and more sensitive assessment of antitumor efficacy, a lower likelihood of influence by competing risks (especially in elderly subjects), and a lesser chance of confounding because of treatments received after progression.

Among patients with ovarian cancer in a Japanese Gynecologic Oncologic Group trial, dose-dense weekly paclitaxel was associated with longer OS than treatment as conventionally administered three-weekly.\textsuperscript{8} Nonetheless, JGOG data was 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.

Our review will include a systematic and rigorous approach to the identification of RCTs investigating the impact of effectiveness and safety of weekly and three-weekly therapy of paclitaxel plus carboplatin for ovarian cancer. This is a update systematic review and meta-analysis protocol focused on this topic\textsuperscript{24} 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 patients-reported outcomes.

Our study also has limitations. Firstly, studies might selectively report data regarding adverse events in their full publications, which could lead to risk of reporting bias. Secondly, 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 therefore not require specific ethical approval or consent for participation. The results will be published in a peer-reviewed journal.

Footnotes

Authors’ contribution Weitao Qiu and Yu Fu conceived of 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.

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Competing interests All authors declare no conflict of interest.

Patient consent for publication Not required.

Provenance and peer review Not commissioned; externally peer reviewed.

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Supplemental file 2. Search strategy

**MEDLINE OVID**

1 exp Ovarian Neoplasms/
2 (ovar* adj5 (cancer* or tumor* or tumour* or neoplas* or carcinoma* or adenocarcinoma* or malignan*)).mp.
3 1 or 2
4 Paclitaxel/
5 (paclitaxel or taxol or praxel or anzatax or nsc125973 or nsc 125973 or paxene or onxol or abraxane).mp.
6 4 or 5
7 exp Drug Administration Schedule/
8 ad.fs.
9 (dose or dosage or dosing or dose-dense or PcW or Pc3W or week or weekly or schedule*).mp.
10 7 or 8 or 9
11 randomised controlled trial.pt.
12 controlled clinical trial.pt.
13 randomized.ab.
14 placebo.ab.
15 drug therapy.fs.
16 randomly.ab.
17 trial.ab.
18 groups.ab.
19 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18
20 3 and 6 and 10 and 19

**Embase OVID**

1 exp Ovarian Neoplasms/
2 (ovar* adj5 (cancer* or tumor* or tumour* or neoplas* or carcinoma* or adenocarcinoma* or malignan*)).mp.
3 1 or 2
4 Paclitaxel/
5 (paclitaxel or taxol or praxel or anzatax or nsc125973 or nsc 125973 or paxene or onxol or abraxane).mp.
6 4 or 5
7 exp Drug Administration Schedule/
8 ad.fs.
9 (dose or dosage or dosing or dose-dense or PcW or Pc3W or week or weekly or schedule*).mp.
10 7 or 8 or 9
11 randomised controlled trial.pt.
12 controlled clinical trial.pt.
13 randomized.ab.
14 placebo.ab.
15 drug therapy.fs.
16 randomly.ab.
17 trial.ab.
18 groups.ab.
19 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18
20 3 and 6 and 10 and 19

Cochrane library
1 MeSH descriptor: [Ovarian Neoplasms] explode all trees
2 Ovarian cancer:ti,ab,kw
3 1 or 2
4 MeSH descriptor: [Drug Administration Schedule] explode all trees
5 dose or dosage or dosing or dose-dense or PcW or Pc3W or week or weekly or schedule*:ti,ab,kw
6 4 or 5
7 MeSH descriptor: [Paclitaxel] explode all trees
8 (paclitaxel or taxol or praxel or anzatax or nsc125973 or nsc 125973 or paxene or onxol or abraxane): ti,ab,kw
9 7 or 8
10 3 and 6 and 9
Supplemental file 3.

Figure Flow diagram.

Records identified from databases (n = )
  PubMed (n = )
  EMBASE (n = )
  Cochrane (n = )

Records removed before screening:
  Duplicate records (n = )

Records excluded (n =)
  Unrelated interventions (n=)
  Unrelated comparison (n=)
  Not RCT (n=)
  Animal studies (n=)
  Repeat published (n=)

Reports screened (n =)

Reports not retrieved (n = )

Reports assessed for eligibility (n = )

Reports excluded (n = )
  Unrelated interventions (n=)
  Unrelated comparison (n=)
  Unrelated disease(n=)
  Not RCT (n = )
  Incomplete data (n = )

Studies included in review (n = )

Records screened (n = )
  Reports assessed for eligibility (n = )
  Reports not retrieved (n = )

Records identified from databases (n = )
  PubMed (n = )
  EMBASE (n = )
  Cochrane (n = )

Records removed before screening:
  Duplicate records (n = )

Records excluded (n =)
  Unrelated interventions (n=)
  Unrelated comparison (n=)
  Not RCT (n=)
  Animal studies (n=)
  Repeat published (n=)

Reports screened (n =)

Reports not retrieved (n = )

Reports assessed for eligibility (n = )

Reports excluded (n = )
  Unrelated interventions (n=)
  Unrelated comparison (n=)
  Unrelated disease(n=)
  Not RCT (n = )
  Incomplete data (n = )

Studies included in review (n = )
Supplemental file 1

**PRISMA-P (Preferred Reporting Items for Systematic review and Meta-Analysis Protocols) 2015 checklist: recommended items to address in a systematic review protocol***

| Section and topic | Item No | Checklist item                                                                 | Page No. |
|-------------------|---------|---------------------------------------------------------------------------------|----------|
| **ADMINISTRATIVE INFORMATION** |         |                                                                                |          |
| Title:            | 1a      | Identify the report as a protocol of a systematic review                        | 1        |
|                   | 1b      | If the protocol is for an update of a previous systematic review, identify as such |          |
| Registration      | 2       | If registered, provide the name of the registry (such as PROSPERO) and registration number | 1        |
| Authors:          | 3a      | Provide name, institutional affiliation, e-mail address of all protocol authors; provide physical mailing address of corresponding author | 1        |
| Contributions     | 3b      | Describe contributions of protocol authors and identify the guarantor of the review | 6        |
| Amendments        | 4       | If the protocol represents an amendment of a previously completed or published protocol, identify as such and list changes; otherwise, state plan for documenting important protocol amendments | 6        |
| Support:          | 5a      | Indicate sources of financial or other support for the review                   | 6        |
| Sources           | 5b      | Provide name for the review funder and/or sponsor                              |          |
| Sponsor           | 5c      | Describe roles of funder(s), sponsor(s), and/or institution(s), if any, in developing the protocol |          |
| Role of sponsor   |         |                                                                                |          |
| or funder         |         |                                                                                |          |
| **INTRODUCTION**  |         |                                                                                |          |
| Rationale         | 6       | Describe the rationale for the review in the context of what is already known   | 1        |
| Objectives        | 7       | Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO) | 2        |
| **METHODS**       |         |                                                                                |          |
| Eligibility criteria | 8     | Specify the study characteristics (such as PICO, study design, setting, time frame) and report characteristics (such as years considered, language, publication status) to be used as criteria for eligibility for the review | 2        |
| Information sources | 9     | Describe all intended information sources (such as electronic databases, contact with study authors, trial registers or other grey literature sources) with planned dates of coverage | 2        |
| Search strategy   | 10      | Present draft of search strategy to be used for at least one electronic database, including planned limits, such that it could be repeated | 2        |

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| Study records:                                                                 |   |
|------------------------------------------------------------------------------|---|
| Data management                                                              |   |
| 11a Describe the mechanism(s) that will be used to manage records and data  | 3 |
| throughout the review                                                        |   |
| Selection process                                                            |   |
| 11b State the process that will be used for selecting studies (such as two  | 3 |
| independent reviewers) through each phase of the review (that is,          |   |
| screening, eligibility and inclusion in meta-analysis)                       |   |
| Data collection process                                                      |   |
| 11c Describe planned method of extracting data from reports (such as        | 3 |
| piloting forms, done independently, in duplicate), any processes for       |   |
| obtaining and confirming data from investigators                            |   |
| Data items                                                                    |   |
| 12 List and define all variables for which data will be sought (such as     | 3 |
| PICO items, funding sources), any pre-planned data assumptions and          |   |
| simplifications                                                              |   |
| Outcomes and prioritization                                                  |   |
| 13 List and define all outcomes for which data will be sought, including    | 3 |
| prioritization of main and additional outcomes, with rationale               |   |
| Risk of bias in individual studies                                           |   |
| 14 Describe anticipated methods for assessing risk of bias of individual     | 4 |
| studies, including whether this will be done at the outcome or study level, |   |
| or both; state how this information will be used in data synthesis           |   |
| Data synthesis                                                               |   |
| 15a Describe criteria under which study data will be quantitatively          | 4 |
| synthesised                                                                  |   |
| 15b If data are appropriate for quantitative synthesis, describe planned     | 4 |
| summary measures, methods of handling data and methods of combining data     |   |
| from studies, including any planned exploration of consistency (such as     |   |
| I², Kendall’s τ)                                                            |   |
| 15c Describe any proposed additional analyses (such as sensitivity or       | 4 |
| subgroup analyses, meta-regression)                                         |   |
| 15d If quantitative synthesis is not appropriate, describe the type of      | 4 |
| summary planned                                                              |   |
| Meta-bias(es)                                                                |   |
| 16 Specify any planned assessment of meta-bias(es) (such as publication      | 4 |
| bias across studies, selective reporting within studies)                     |   |
| Confidence in cumulative evidence                                            |   |
| 17 Describe how the strength of the body of evidence will be assessed (such  | 5 |
| as GRADE)                                                                    |   |

*It is strongly recommended that this checklist be read in conjunction with the PRISMA-P Explanation and Elaboration (cite when available) for important clarification on the items. Amendments to a review protocol should be tracked and dated. The copyright for PRISMA-P (including checklist) is held by the PRISMA-P Group and is distributed under a Creative Commons Attribution Licence 4.0.

From: Shamseer L, Moher D, Clarke M, Ghersi D, Liberati A, Petticrew M, Shekelle P, Stewart L, PRISMA-P Group. Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015: elaboration and explanation. BMJ. 2015 Jan 2;349(jan02 1):g7647.
**Effectiveness and safety of weekly therapy versus three-weekly therapy of paclitaxel plus carboplatin in women with ovarian cancer: a protocol of systematic review and meta-analysis**

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| Keywords         | Gynaecological oncology < ONCOLOGY, GYNAECOLOGY, ONCOLOGY |
Effectiveness and safety of weekly therapy versus three-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 three-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 three-weekly therapy of paclitaxel combined with carboplatin in women with ovarian cancer.

Methods We will search PubMed, EMBASE, the Cochrane Library databases to include relevant randomized controlled trials (RCTs) comparing weekly therapy versus three-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. GRADE 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 therefore not 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

Keywords paclitaxel, carboplatin, ovarian cancer, weekly therapy, three-weekly therapy

Strengths and limitations of this study

- The review will provide a meticulous overview of the existing evidence on the effectiveness and safety of a weekly paclitaxel with carboplatin regimen compared to a three-weekly paclitaxel with carboplatin regimen for women with ovarian cancer.
- Detailed subgroup analysis (eg, dose-dense versus metronomic dosing schedule, different mean follow-up duration) will be undertaken.
- We will use the GRADE 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.\textsuperscript{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.\textsuperscript{4,5} However, detailed implementation schedule (weekly or three-weekly therapy) was not specified in these guidelines. Combination treatment with paclitaxel and carboplatin, given on a three-weekly basis, is the most common first line chemotherapeutic approach for women with advanced epithelial ovarian cancer.\textsuperscript{6,7} Interest in a three-weekly paclitaxel regimen was inspired by the Japanese Gynaecologic Oncology Group (JGOG) 3016 trial, which found that weekly paclitaxel was associated with an improvement in PFS (28.2 months versus 17.5 months, hazard ratio (HR) = 0.76, P value < 0.01) and OS (100.5 months versus 62.2 months, HR = 0.79, P = 0.04), even at long-term follow-up.\textsuperscript{8}

However, other trials showed inconsistent results. The GOG 262 trial found that there was no difference in PFS or OS between the weekly and three-weekly regimens, but subgroup analysis showed that, in women not treated with bevacizumab, a weekly paclitaxel regimen improved PFS compared with a three-weekly regimen.\textsuperscript{9} Another trial concluded significant improvement in PFS but no difference in OS.\textsuperscript{10} Evidence from observational studies is also inconsistent.\textsuperscript{10-13} Thus, it is necessary to conduct this meta-analysis to clarify the effectiveness and safety of a weekly paclitaxel with carboplatin regimen compared to a three-weekly paclitaxel with carboplatin regimen for women with ovarian cancer.

Material and Methods

Study registration

The protocol and registration information are 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 (PRISMA-P) guidelines (online supplemental 1).\textsuperscript{14-16} The systematic review and meta-analysis will be conducted and reported in accordance with the PRISMA 2020 statement.\textsuperscript{17}

Search terms for retrieval of studies

We will systematically search PubMed, EMBASE, the Cochrane Library database to collect randomized controlled trials (RCTs) on weekly and three-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 MeSH and 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 searching 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 literatures.

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 six months, the living condition score (Kamofsky score, KPS) >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 three-weekly therapy of paclitaxel combined with carboplatin for ovarian cancer in the analysis, which included:
- Progression free survival (PFS).
- Overall survival (OS).
- Survival rate.
- Adverse events.

**Exclusion criteria**
- Patients accompanied with other primary malignant tumors.
- Studies not published in English.
- Similar studies were reported without additional data to analyze 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\(^\text{18}\) 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.\(^\text{17}\)

**Data extraction**
We will use Microsoft Excel 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, co-morbidities).
- 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 (ROB) tool. 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’ judgment. We will summarize 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% confidence interval (CI) as the effect size for dichotomous outcomes. For time-to-event data, we will pool hazard ratios (HR). 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 $I^2$ 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 version 15.0 (StataCorp, College Station, TX) to synthesis 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, chemotherapy regimens (cytoreductive (or debulking) surgery to remove malignant tissue versus no cytoreductive surgery), timing of cytoreductive surgery (primary surgery or interval cytoreduction), studies conducted in Asia or with a majority of Asian patients versus studies conducted in Western countries and 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. 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\textsuperscript{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.\textsuperscript{19}

Summary of findings
We will use the Grades of Recommendation, Assessment, Development and Evaluation (GRADE) system\textsuperscript{22} to assess the quality of evidence associated with specific outcomes and constructed a ‘Summary of findings’ (SoF) 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 three-weekly therapy of paclitaxel with carboplatin for ovarian cancer.

The debate on the role of PFS as primary endpoint in ovarian cancer clinical trials has been discussed in long time and in the last years, it has become to be considered as a surrogate endpoint of OS.\textsuperscript{23} The advantages of this endpoint are an earlier and more sensitive assessment of antitumor efficacy, a lower likelihood of influence by competing risks (especially in elderly subjects), and a lesser chance of confounding because of treatments received after progression.

Among patients with ovarian cancer in a Japanese Gynecologic Oncologic Group trial, dose-dense weekly paclitaxel was associated with longer OS than treatment as conventionally administered three-weekly.\textsuperscript{8} Nonetheless, JGOG data was 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.

Our review will include a systematic and rigorous approach to the identification of RCTs investigating the impact of effectiveness and safety of weekly and three-weekly therapy of paclitaxel plus carboplatin for ovarian cancer. This is a update systematic review and meta-analysis protocol focused on this topic\textsuperscript{24} 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 patients-reported outcomes.

Our study also has limitations. Firstly, studies might selectively report data regarding adverse events in their full publications, which could lead to risk of reporting bias. Secondly, 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 therefore not require specific ethical approval or consent for participation. The results will be published in a peer-reviewed journal.

Footnotes

Authors’ contribution WQ and YF conceived of 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, QL were involved in study design. YD, BC, ST, BM, RL, QL, YL contributed to and approved the final manuscript of the protocol review.

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Competing interests All authors declare no conflict of interest.

Patient consent for publication Not required.

Provenance and peer review Not commissioned; externally peer reviewed.

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Supplemental file 2. Search strategy

**MEDLINE OVID**

1 exp Ovarian Neoplasms/
2 (ovar* adj5 (cancer* or tumor* or tumour* or neoplas* or carcinoma* or adenocarcinoma* or malignan*)).mp.
3 1 or 2
4 Paclitaxel/
5 (paclitaxel or taxol or praxel or anzatax or nsc125973 or nsc 125973 or paxene or onxol or abraxane or "abi 007" or asotax or bristaxol or xytotax).mp.
6 4 or 5
7 exp Drug Administration Schedule/  
8 ad.fs.
9 (dose or dosage or dosing or dose-dense or PcW or Pc3W or week or weekly or schedule*).mp.
10 7 or 8 or 9
11 randomised controlled trial.pt.
12 controlled clinical trial.pt.
13 randomized.ab.
14 placebo.ab.
15 drug therapy.fs.
16 randomly.ab.
17 trial.ab.
18 groups.ab.
19 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18
20 3 and 6 and 10 and 19

**Embase OVID**

1 exp Ovarian Neoplasms/
2 (ovar* adj5 (cancer* or tumor* or tumour* or neoplas* or carcinoma* or adenocarcinoma* or malignan*)).mp.
3 1 or 2
4 Paclitaxel/
5 (paclitaxel or taxol or praxel or anzatax or nsc125973 or nsc 125973 or paxene or onxol or abraxane or "abi 007" or asotax or bristaxol or xytotax).mp.
6 4 or 5
7 exp Drug Administration Schedule/
8 ad.fs.
9 (dose or dosage or dosing or dose-dense or PcW or Pc3W or week or weekly or schedule*).mp.
10 7 or 8 or 9
11 randomised controlled trial.pt.
12 controlled clinical trial.pt.
13 randomized.ab.
14 placebo.ab.
15 drug therapy.fs.
16 randomly.ab.
17 trial.ab.
18 groups.ab.
19 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18
20 3 and 6 and 10 and 19

Cochrane library
1 MeSH descriptor: [Ovarian Neoplasms] explode all trees
2 Ovarian cancer:ti,ab,kw
3 1 or 2
4 MeSH descriptor: [Drug Administration Schedule] explode all trees
5 dose or dosage or dosing or dose-dense or PcW or Pe3W or week or weekly or schedule*:ti,ab,kw
6 4 or 5
7 MeSH descriptor: [Paclitaxel] explode all trees
8 (paclitaxel or taxol or praxel or anzatax or nsc125973 or nsc 125973 or paxene or onxol or abraxane or "abi 007" or asotax or bristaxol or xytotax): ti,ab,kw
9 7 or 8
10 3 and 6 and 9
Supplemental file 3.

Figure Flow diagram.

- Records identified from databases (n = )
  - PubMed (n = )
  - EMBASE (n = )
  - Cochrane (n = )

- Records removed before screening:
  - Duplicate records (n = )

- Records excluded (n = )
  - Unrelated interventions (n=)
  - Unrelated comparison (n=)
  - Not RCT (n=)
  - Animal studies (n=)
  - Repeat published (n=)

- Records screened (n = )

- Reports sought for retrieval (n = )

- Reports assessed for eligibility (n = )

- Reports not retrieved (n = )

- Reports excluded (n = )
  - Unrelated interventions (n=)
  - Unrelated comparison (n=)
  - Unrelated disease(n=)
  - Not RCT (n = )
  - Incomplete data (n = )

- Studies included in review (n = )
**Supplemental file 1**

**PRISMA-P (Preferred Reporting Items for Systematic review and Meta-Analysis Protocols) 2015 checklist: recommended items to address in a systematic review protocol**

| Section and topic       | Item No   | Checklist item                                                                 |
|-------------------------|-----------|---------------------------------------------------------------------------------|
| **ADMINISTRATIVE INFORMATION** |           |                                                                                  |
| Title:                  | 1a        | Identify the report as a protocol of a systematic review                        |
| Identification          |           |                                                                                  |
| Update                  | 1b        | If the protocol is for an update of a previous systematic review, identify as such|
| Registration            | 2         | If registered, provide the name of the registry (such as PROSPERO) and registration number |
| Authors:                |           |                                                                                  |
| Contact                 | 3a        | Provide name, institutional affiliation, e-mail address of all protocol authors; provide physical mailing address of corresponding author |
| Contributions           | 3b        | Describe contributions of protocol authors and identify the guarantor of the review |
| Amendments              | 4         | If the protocol represents an amendment of a previously completed or published protocol, identify as such and list changes; otherwise, state plan for documenting important protocol amendments |
| Support:                |           |                                                                                  |
| Sources                 | 5a        | Indicate sources of financial or other support for the review                   |
| Sponsor                 | 5b        | Provide name for the review funder and/or sponsor                               |
| Role of sponsor         | 5c        | Describe roles of funder(s), sponsor(s), and/or institution(s), if any, in developing the protocol |
| or funder               |           |                                                                                  |
| **INTRODUCTION**        |           |                                                                                  |
| Rationale               | 6         | Describe the rationale for the review in the context of what is already known   |
| Objectives              | 7         | Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO) |
| **METHODS**             |           |                                                                                  |
| Eligibility criteria    | 8         | Specify the study characteristics (such as PICO, study design, setting, time frame) and report characteristics (such as years considered, language, publication status) to be used as criteria for eligibility for the review |
| Information sources     | 9         | Describe all intended information sources (such as electronic databases, contact with study authors, trial registers or other grey literature sources) with planned dates of coverage |
| Search strategy         | 10        | Present draft of search strategy to be used for at least one electronic database, including planned limits, such that it could be repeated |

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml
| Study records:                                      |  |
|---------------------------------------------------|---|
| **Data management**                               | 11a | Describe the mechanism(s) that will be used to manage records and data throughout the review | 3 |
| **Selection process**                             | 11b | State the process that will be used for selecting studies (such as two independent reviewers) through each phase of the review (that is, screening, eligibility and inclusion in meta-analysis) | 3 |
| **Data collection process**                       | 11c | Describe planned method of extracting data from reports (such as piloting forms, done independently, in duplicate), any processes for obtaining and confirming data from investigators | 3 |
| **Data items**                                     | 12  | List and define all variables for which data will be sought (such as PICO items, funding sources), any pre-planned data assumptions and simplifications | 3 |
| **Outcomes and prioritization**                   | 13  | List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale | 3 |
| **Risk of bias in individual studies**            | 14  | Describe anticipated methods for assessing risk of bias of individual studies, including whether this will be done at the outcome or study level, or both; state how this information will be used in data synthesis | 4 |
| **Data synthesis**                                | 15a | Describe criteria under which study data will be quantitatively synthesised | 4 |
| **Data synthesis**                                | 15b | If data are appropriate for quantitative synthesis, describe planned summary measures, methods of handling data and methods of combining data from studies, including any planned exploration of consistency (such as I^2, Kendall’s τ) | 4 |
| **Data synthesis**                                | 15c | Describe any proposed additional analyses (such as sensitivity or subgroup analyses, meta-regression) | 4 |
| **Data synthesis**                                | 15d | If quantitative synthesis is not appropriate, describe the type of summary planned | 4 |
| **Meta-bias(es)**                                 | 16  | Specify any planned assessment of meta-bias(es) (such as publication bias across studies, selective reporting within studies) | 4 |
| **Confidence in cumulative evidence**             | 17  | Describe how the strength of the body of evidence will be assessed (such as GRADE) | 5 |

*It is strongly recommended that this checklist be read in conjunction with the PRISMA-P Explanation and Elaboration (cite when available) for important clarification on the items. Amendments to a review protocol should be tracked and dated. The copyright for PRISMA-P (including checklist) is held by the PRISMA-P Group and is distributed under a Creative Commons Attribution Licence 4.0.

From: Shamseer L, Moher D, Clarke M, Ghersi D, Liberati A, Petticrew M, Shekelle P, Stewart L, PRISMA-P Group. Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015: elaboration and explanation. BMJ. 2015 Jan 2;349(jan02 1):g7647.
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| Primary Subject Heading: | Oncology |
| Secondary Subject Heading: | Obstetrics and gynaecology |
| Keywords: | Gynaecological oncology < ONCOLOGY, GYNAECOLOGY, ONCOLOGY |
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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 three-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 three-weekly therapy of paclitaxel combined with carboplatin in women with ovarian cancer.

Methods We will search PubMed, EMBASE, the Cochrane Library databases to include relevant randomized controlled trials (RCTs) comparing weekly therapy versus three-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. GRADE 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 therefore not 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

Keywords paclitaxel, carboplatin, ovarian cancer, weekly therapy, three-weekly therapy

Strengths and limitations of this study

- Detailed subgroup analysis (eg, dose-dense versus metronomic dosing schedule in patients that underwent completely tumour resection, optimally and suboptimally resection debulked surgery, different mean follow-up duration) will be undertaken.
- We will use the GRADE 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.
survival (PFS) and overall survival (OS) compared with platinum alone.\textsuperscript{4,5} However, detailed implementation schedule (weekly or three-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 three-weekly paclitaxel plus carboplatin.\textsuperscript{6,7} One randomized controlled trial (RCT) with 631 patients found that, at long-term follow-up, weekly (80 mg/m\(^2\)) versus three-weekly (180 mg/m\(^2\)) regimens of paclitaxel plus carboplatin at an area under the curve (AUC) of 6 mg/ml/min significantly improved PFS (hazard ratio (HR) 0.76, 95%CI 0.62-0.91), and OS (100.5 months versus 62.2 months, HR 0.79, 95%CI 0.63-0.99).\textsuperscript{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 0.40-0.95) among patients who did not treated with bevacizumab.\textsuperscript{9} Another trial concluded significant improvement in PFS but no difference in OS.\textsuperscript{10} Evidence from observational studies is also inconsistent.\textsuperscript{10-13} Thus, it is necessary to conduct this meta-analysis to clarify the effectiveness and safety of weekly paclitaxel plus carboplatin regimen compared to three-weekly paclitaxel plus carboplatin regimen for women with ovarian cancer.

### Material and Methods

#### Study registration

The protocol and registration information are 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 (PRISMA-P) guidelines (online supplemental 1).\textsuperscript{14-16} The systematic review and meta-analysis will be conducted and reported in accordance with the PRISMA 2020 statement.\textsuperscript{17}

#### Search terms for retrieval of studies

We will systematically search PubMed, EMBASE, the Cochrane Library database to collect randomized controlled trials (RCTs) on weekly and three-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 MeSH and 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 searching 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 literatures.

#### 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 six months, the living condition score (Kamofsky score,
KPS) >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 three-weekly therapy of paclitaxel combined with carboplatin for ovarian cancer in the analysis, which included:
- Progression free survival (PFS).
- Overall survival (OS).
- Survival rate.
- Adverse events.

**Exclusion criteria**
- Patients accompanied with other primary malignant tumors.
- Studies not published in English.
- Similar studies were reported without additional data to analyze 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 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.

**Data extraction**
We will use Microsoft Excel 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, co-morbidities).
- 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 (ROB) tool. 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’ judgment. We will summarize 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% confidence interval (CI) as the effect size for dichotomous outcomes. For time-to-event data, we will pool hazard ratios (HR). 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 $I^2$ 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 version 15.0 (StataCorp, College Station, TX) to synthesis 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 that underwent completely tumour resection, optimally and suboptimally resection debulked surgery, timing of cytoreductive surgery (primary debulking surgery (PDS) or Interval debulking surgery (IDS)), 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. 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 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.

**Summary of findings**

We will use the Grades of Recommendation, Assessment, Development and Evaluation (GRADE) system to assess the quality of evidence associated with specific outcomes and constructed a ‘Summary of findings’ (SoF) 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 three-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 are normally regarded as a surrogate outcome. Compared with OS, the advantages of PFS include assessing antitumor 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 Gynecologic Oncologic Group trial, dose-dense weekly paclitaxel was associated with longer OS than treatment as conventionally administered three-weekly. Nonetheless, JGOG data was 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 for compare the efficacy of weekly versus 3 weeks chemotherapy regimes, in term of survival outcomes and toxic effects. However, the results of ICON8 trial had published. And another study conducted dose-dense weekly paclitaxel and carboplatin treatment improves survival compared with conventional paclitaxel and carboplatin treatment. 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 to three-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 three-weekly therapy of paclitaxel plus carboplatin for ovarian cancer. This is a update systematic review and meta-analysis protocol focused on this topic 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 patients-reported outcomes.

Our study also has limitations. Firstly, studies might selectively report data regarding adverse events in their full publications, which could lead to risk of reporting bias. Secondly, 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 therefore not require specific ethical approval or consent for participation. The results will be published in a peer-reviewed journal.

Footnotes
Authors' contribution WQ and YF conceived of 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, QL were involved in study design. YD, BC, ST, BM, RL, QL, YL contributed to and approved the final manuscript of the protocol review.

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Competing interests All authors declare no conflict of interest.

Patient consent for publication Not required.

Provenance and peer review Not commissioned; externally peer reviewed.

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Supplemental file 1

PRISMA-P (Preferred Reporting Items for Systematic review and Meta-Analysis Protocols) 2015 checklist: recommended items to address in a systematic review protocol*

| Section and topic | Item No | Checklist item                                                                 | Page No. |
|-------------------|---------|---------------------------------------------------------------------------------|----------|
| ADMINISTRATIVE INFORMATION | | | |
| Title: | | | |
| Identification | 1a | Identify the report as a protocol of a systematic review | 1 |
| Update | 1b | If the protocol is for an update of a previous systematic review, identify as such | 1 |
| Registration | 2 | If registered, provide the name of the registry (such as PROSPERO) and registration number | 1 |
| Authors: | | | |
| Contact | 3a | Provide name, institutional affiliation, e-mail address of all protocol authors; provide physical mailing address of corresponding author | 1 |
| Contributions | 3b | Describe contributions of protocol authors and identify the guarantor of the review | 6 |
| Amendments | 4 | If the protocol represents an amendment of a previously completed or published protocol, identify as such and list changes; otherwise, state plan for documenting important protocol amendments | |
| Support: | | | |
| Sources | 5a | Indicate sources of financial or other support for the review | 6 |
| Sponsor | 5b | Provide name for the review funder and/or sponsor | |
| Role of sponsor or funder | 5c | Describe roles of funder(s), sponsor(s), and/or institution(s), if any, in developing the protocol | |
| INTRODUCTION | | | |
| Rationale | 6 | Describe the rationale for the review in the context of what is already known | 1 |
| Objectives | 7 | Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO) | 2 |
| METHODS | | | |
| Eligibility criteria | 8 | Specify the study characteristics (such as PICO, study design, setting, time frame) and report characteristics (such as years considered, language, publication status) to be used as criteria for eligibility for the review | 2 |
| Information sources | 9 | Describe all intended information sources (such as electronic databases, contact with study authors, trial registers or other grey literature sources) with planned dates of coverage | 2 |
| Search strategy | 10 | Present draft of search strategy to be used for at least one electronic database, including planned limits, such that it could be repeated | 2 |
| Study records: |  |
|---|---|
| Data management | 11a | Describe the mechanism(s) that will be used to manage records and data throughout the review | 3 |
| Selection process | 11b | State the process that will be used for selecting studies (such as two independent reviewers) through each phase of the review (that is, screening, eligibility and inclusion in meta-analysis) | 3 |
| Data collection process | 11c | Describe planned method of extracting data from reports (such as piloting forms, done independently, in duplicate), any processes for obtaining and confirming data from investigators | 3 |
| Data items | 12 | List and define all variables for which data will be sought (such as PICO items, funding sources), any pre-planned data assumptions and simplifications | 3 |
| Outcomes and prioritization | 13 | List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale | 3 |
| Risk of bias in individual studies | 14 | Describe anticipated methods for assessing risk of bias of individual studies, including whether this will be done at the outcome or study level, or both; state how this information will be used in data synthesis | 4 |
| Data synthesis | 15a | Describe criteria under which study data will be quantitatively synthesised | 4 |
| 15b | If data are appropriate for quantitative synthesis, describe planned summary measures, methods of handling data and methods of combining data from studies, including any planned exploration of consistency (such as I², Kendall’s τ) | 4 |
| 15c | Describe any proposed additional analyses (such as sensitivity or subgroup analyses, meta-regression) | 4 |
| 15d | If quantitative synthesis is not appropriate, describe the type of summary planned | 4 |
| Meta-bias(es) | 16 | Specify any planned assessment of meta-bias(es) (such as publication bias across studies, selective reporting within studies) | 4 |
| Confidence in cumulative evidence | 17 | Describe how the strength of the body of evidence will be assessed (such as GRADE) | 5 |

*It is strongly recommended that this checklist be read in conjunction with the PRISMA-P Explanation and Elaboration (cite when available) for important clarification on the items. Amendments to a review protocol should be tracked and dated. The copyright for PRISMA-P (including checklist) is held by the PRISMA-P Group and is distributed under a Creative Commons Attribution Licence 4.0.*

From: Shamseer L, Moher D, Clarke M, Ghersi D, Liberati A, Petticrew M, Shekelle P, Stewart L, PRISMA-P Group. Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015: elaboration and explanation. BMJ. 2015 Jan 2;349(jan02 1):g7647.
Supplemental file 2. Search strategy

**MEDLINE OVID**
1 exp Ovarian Neoplasms/
2 (ovar* adj5 (cancer* or tumor* or tumour* or neoplas* or carcinoma* or adenocarcinoma* or malignan*)).mp.
3 1 or 2
4 Paclitaxel/
5 (paclitaxel or taxol or praxel or anzatax or nsc125973 or nsc 125973 or paxene or onxol or abraxane or "abi 007" or asotax or brixtaxol or xytotax).mp.
6 4 or 5
7 exp Drug Administration Schedule/
8 ad.fs.
9 (dose or dosage or dosing or dose-dense or PcW or Pc3W or week or weekly or schedule*).mp.
10 7 or 8 or 9
11 randomised controlled trial.pt.
12 controlled clinical trial.pt.
13 randomized.ab.
14 placebo.ab.
15 drug therapy.fs.
16 randomly.ab.
17 trial.ab.
18 groups.ab.
19 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18
20 3 and 6 and 10 and 19

**Embase OVID**
1 exp Ovarian Neoplasms/
2 (ovar* adj5 (cancer* or tumor* or tumour* or neoplas* or carcinoma* or adenocarcinoma* or malignan*)).mp.
3 1 or 2
4 Paclitaxel/
5 (paclitaxel or taxol or praxel or anzatax or nsc125973 or nsc 125973 or paxene or onxol or abraxane or "abi 007" or asotax or brixtaxol or xytotax).mp.
6 4 or 5
7 exp Drug Administration Schedule/
8 ad.fs.
9 (dose or dosage or dosing or dose-dense or PcW or Pc3W or week or weekly or schedule*).mp.
10 7 or 8 or 9
11 randomised controlled trial.pt.
12 controlled clinical trial.pt.
13 randomized.ab.
14 placebo.ab.
15 drug therapy.fs.
16 randomly.ab.
17 trial.ab.
18 groups.ab.
19 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18
20 3 and 6 and 10 and 19

Cochrane library
1 MeSH descriptor: [Ovarian Neoplasms] explode all trees
2 Ovarian cancer:ti,ab,kw
3 1 or 2
4 MeSH descriptor: [Drug Administration Schedule] explode all trees
5 dose or dosage or dosing or dose-dense or PcW or Pc3W or week or weekly or schedule*:ti,ab,kw
6 4 or 5
7 MeSH descriptor: [Paclitaxel] explode all trees
8 (paclitaxel or taxol or praxel or anzatax or nsc125973 or nsc 125973 or paxene or onxol or abraxane or "abi 007" or asotax or bristaxol or xytotax): ti,ab,kw
9 7 or 8
10 3 and 6 and 9
Supplemental file 3.

Records identified from databases (n = )
- PubMed (n = )
- EMBASE (n = )
- Cochrane (n = )

Records removed before screening:
- Duplicate records (n = )

Records excluded (n = )
- Unrelated interventions (n = )
- Unrelated comparison (n = )
- Not RCT (n = )
- Animal studies (n = )
- Repeat published (n = )

Reports sought for retrieval (n = )

Reports not retrieved (n = )

Reports assessed for eligibility (n = )

Reports excluded (n = )
- Unrelated interventions (n = )
- Unrelated comparison (n = )
- Unrelated disease (n = )
- Not RCT (n = )
- Incomplete data (n = )

Studies included in review (n = )

**Figure** Flow diagram.