Administrative Information

Title:
Efficacy of nab-paclitaxel and effectiveness weekly paclitaxel for the treatment of recurrent, platinum resistant ovarian, fallopian tube, and peritoneal cancer: a systematic review

Registration:
Our systematic review protocol was registered with the International Prospective Register of Systematic Reviews (PROSPERO) on 30/09/2024

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Guarantors:

MF and TK

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Role of funders and sponsors:

Corcept Therapeutics Inc. and Nord-Ostdeutsche Gesellschaft für Gynäkologische Onkologie (NOGGO e.V.) conceived this project. They advised on the inclusion criteria and outcomes of this systematic review and specified the desired extraction variables. This protocol was developed in close collaboration with Nord-Ostdeutsche Gesellschaft für Gynäkologische Onkologie (NOGGO e.V.). The protocol was revised with feedback from Corcept Therapeutics Inc.

Introduction

Rationale:

Paclitaxel was approved for ovarian cancer treatment in 1992 and still remains the preferred chemotherapeutic agent for ovarian cancer at all stages.[1] Despite its standing as the standard of care, paclitaxel has notable limitations.[1,2] Paclitaxel is itself insoluble in saline and is therefore formulated with Cremophor EL (polyoxyethylated castor oil) and ethanol.[3,4] Due to the potential for adverse events, including life-threatening histamine-induced hypersensitivity reactions to cremophor, patients are required to undergo a long infusion time between three and twenty-four hours. As an additional precaution, premedication is administered prior to paclitaxel infusion.[4,5] It is imperative to emphasize that despite these precautions, the potential for fatality due to a cremophor-induced hypersensitivity reaction persists.[4]

Nab-paclitaxel is an albumin-bound formulation of paclitaxel that has emerged in response to the known adverse events caused by the cremophor additive in the conventional formulation of paclitaxel.[6] Unlike paclitaxel, nab-paclitaxel is water-soluble, avoiding the need for cremophor and the adverse events caused by this additive.[5,6] Current guidelines set forth by the National Comprehensive Cancer Network establish that nab-paclitaxel can be a substitute for paclitaxel only after patients experience a hypersensitivity reaction following paclitaxel administration.[1] If nab-paclitaxel is equally effective as paclitaxel for the treatment of ovarian cancer, then it could be a viable first-line anti-neoplastic alternative to paclitaxel for the treatment of ovarian cancer with potentially fewer side effects.

The Cochrane Library published “Taxane monotherapy regimens for the treatment of recurrent epithelial ovarian cancer” in July 2022.[7] In this systematic review and meta-analysis, randomized controlled trials that compared taxane regimens were included (until the search date of 22. March 2022). However, this study excluded trials that used nab-paclitaxel. To our knowledge, there is no evidence synthesis that investigates the effectiveness of nab-paclitaxel compared to paclitaxel for patients with recurrent ovarian cancer.

The aim of this project is to summarize the best available evidence for the efficacy and/or effectiveness of nab-paclitaxel and paclitaxel monotherapy regimens for the treatment of recurrent, platinum-resistant ovarian, fallopian tube, and peritoneal cancer. We plan to perform a systematic review that will build on the evidence available in the aforementioned Cochrane Review[7] by identifying evidence that investigates nab-paclitaxel for treatment of recurrent,

platinum-resistant ovarian, fallopian tube, and peritoneal cancer, as well as randomized controlled trials more recent than the date of the search in the Cochrane Review.

Research Questions:

Primary

1. How effective is nab-paclitaxel for progression-free survival for patients being treated for recurrent, platinum-resistant ovarian, fallopian tube, and peritoneal cancer?
2. How effective is paclitaxel for progression-free survival for patients being treated for recurrent, platinum-resistant ovarian, fallopian tube, and peritoneal cancer?
3. How effective is nab-paclitaxel for overall survival for patients being treated for recurrent, platinum-resistant ovarian, fallopian tube, and peritoneal cancer?
4. How effective is paclitaxel for overall survival for patients being treated for recurrent, platinum-resistant ovarian, fallopian tube, and peritoneal cancer?

Secondary:

5. What is the safety profile of nab-paclitaxel amongst patients being treated for recurrent, platinum-resistant ovarian, fallopian tube, and peritoneal cancer (hematological toxicities, non-hematological toxicities, allergic reactions, neuropathy)?
6. What is the safety profile of paclitaxel amongst patients being treated for recurrent, platinum-resistant ovarian, fallopian tube, and peritoneal cancer (hematological toxicities, non-hematological toxicities, allergic reactions, neuropathy)?
7. What is the quality of life for patients treated with nab-paclitaxel for recurrent, platinum-resistant ovarian cancer?
8. What is the quality of life for patients treated with paclitaxel for recurrent, platinum-resistant ovarian cancer?

Definition:

recurrent, platinum resistant cancer	The definition of platinum resistance has changed over time.[8] In this review, we will use the National Cancer Society definition: "Cancer that responds at first to treatment with drugs that contain the metal platinum, such as cisplatin and carboplatin, but then comes back within a certain period [...] ovarian cancer that comes back within 6 months after treatment is considered platinum resistant."[9]

Methods

We plan to perform systematic searches to identify records that will identify the following sample frames amongst patients diagnosed with recurrent, platinum-resistant epithelial ovarian cancer:

1. **Sample frame 1** will seek to include randomized controlled trials that include paclitaxel as an intervention drug and any taxane as the comparator drug.
2. **Sample frame 2** will seek to include any clinical trial or cohort study that includes nab-paclitaxel as the intervention.

Eligibility criteria:

Sample frame 1:

	Inclusion	**Exclusion**
P	- adult (18+) patients - diagnosis of recurrent, platinum-resistant epithelial ovarian, fallopian tube, or peritoneal cancer (International Federation of Gynecology and Obstetrics (FIGO) Stage I to IV)	- animal studies - studies with exclusively pediatric (<18) patients - ovarian cancer patients that are not being treated for recurrent, platinum-resistant disease
I	- treatment with weekly monotherapy paclitaxel - treatment is given for cancer recurrence	- treatment is not weekly - one or more treatment groups is receiving bevacizumab or carboplatin in combination with paclitaxel -
C	- any other taxane	- no comparator - drug other than a taxane
O	- progression-free survival (survival until progression of disease or death from any cause assessed from the time of enrollment in the study) - overall survival (survival until death from all causes assessed survival from the time of enrollment in the study) - adverse events (hematological toxicities, non-hematological toxicities, allergic reactions, neuropathy) - Quality of life	- none

T	- published on or after March 22, 2022	- published before March 22, 2022

S	- randomized controlled trials	- trials that are not randomized controlled trials
		- observational studies, e.g.,
		  - case reports
		  - case series
		  - cross-sectional studies
		  - cohort studies
		  - case-control studies

P = population; I = Intervention; C = Comparator; O = Outcome; T = time frame limit; S = study design limit

Sample frame 2:

	Inclusion	**Exclusion**
P	- adult (18+) patients - diagnosis of recurrent, platinum-resistant epithelial ovarian, fallopian tube, or peritoneal cancer (International Federation of Gynecology and Obstetrics (FIGO) Stage I to IV)	- animal studies - studies with exclusively pediatric (<18) patients - ovarian cancer patients that are not being treated for recurrent, platinum-resistant disease
I	- treatment with NAB-paclitaxel (monotherapy, unless paclitaxel is the comparator) - treatment is given for cancer recurrence	- one or more treatment groups is receiving bevacizumab or carboplatin in combination with NAB-paclitaxel
C	- no comparator chemotherapy - any other comparator chemotherapy	- none
O	- progression-free survival (survival until progression of disease or death from any cause assessed from the time of enrollment in the study) - overall survival (survival until death from all causes assessed survival from the time of enrollment in the study) - adverse events (hematological toxicities, non-hematological toxicities, allergic reactions, neuropathy) - Quality of life	- none

T	- any time frame	- none
S	- Randomized controlled trials, controlled non-randomized clinical trials, controlled before-after studies - cohort studies - cross-sectional studies	- case reports - case series - case-control studies

P = population; I = Intervention; C = Comparator; O = Outcome; T = time frame limit; S = study design limit

Information Sources:

- MEDLINE Ovid (1946 to date of search)
- Embase Ovid (1974 to date of search);
- Cochrane Central Register of Controlled Trials (CENTRAL; current issue) in the Cochrane Library;
- Citation searching;
- Grey literature

Search strategy:

The following search strategy was devised in MEDLINE Ovid and will be translated to Embase Ovid and CENTRAL:

MEDLINE search components:

Search component	Search Synonyms	Search Syntax
ovarian cancer	ovar* cancer* ovar* carcinoma* ovar* tumo$r ovar* neoplasm* ovar* malignan*	exp ovarian neoplasms/ (ovar* cancer*).ti,ab. (ovar* carcinoma*).ti,ab. (ovar* tumo$r).ti,ab. (ovar* neoplasm).ti,ab. (ovar* malignan*).ti,ab.
NAB-paclitaxel	nab-paclitaxel albumin-bound paclitaxel Abraxane ABI 007 component paclitaxel liposomal encapsulated paclitaxel nab-paclitaxel component paclitaxel nanoparticulate paclitaxel paclitaxel protein-bound albumin-stabilized paclitaxel paclitaxel protein-bound Nanoxel	<u>NAB-paclitaxel drug names</u> exp Albumin-Bound Paclitaxel/ (“nab-paclitaxel” or “abraxane” or “abi 007” or “abi007” or nanoxel).ti,ab. <u>Protein Bound + Paclitaxel</u> (“nanoparticulate*” or “liposomal encapsulated*” or “protein*” or “albumin*” or “ABI 007*”) adj5 ([paclitaxel search syntax]).ti,ab.
paclitaxel	taxol NSC-125973	paclitaxel/ or paclitaxel.ti,ab. or taxol.ti,ab. or nsc125973.ti,ab. or nsc 125973.ti,ab. or

	Anzatax Asotax bristaxol bris taxol onxol paxene Praxel	anzatax.ti,ab. or asotax.ti,ab. or bristaxol.ti,ab. or bris taxol.ti,ab. or paxene.ti,ab. or praxel.ti,ab. or onxol.ti,ab.
RCT	Cochrane sensitivity-maximizing search filter[10]	1. exp randomized controlled trial/ 2. controlled clinical trial.pt. 3. randomized.ab. 4. placebo.ab. 5. drug therapy.fs. 6. randomly.ab. 7. trial.ab. 8. groups.ab. 9. 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 10. animals [mh] NOT humans [mh] 11. 9 not 10

Sample frame 1:

1	Search Syntax: ovarian cancer
2	Search Syntax: paclitaxel
3	1 AND 2
4	filter: Cochrane's sensitivity-maximizing RCT filter[10]
5	filter: 22 March 2022 - date of search
6	3 AND 4 AND 5

Sample frame 2:

1	Search Syntax: ovarian cancer
2	Search Syntax: NAB-paclitaxel drug names
3	Search Syntax: (Protein-bound) AND (paclitaxel)
4	2 OR 3
5	1 AND 4

Data Management

Paperpile (RRID:SCR_014002) will be used to manage bibliographic references from all information sources. This project will have a folder, and each sample frame will have its own subfolder. For each sample frame, each information source will have its own subfolder.

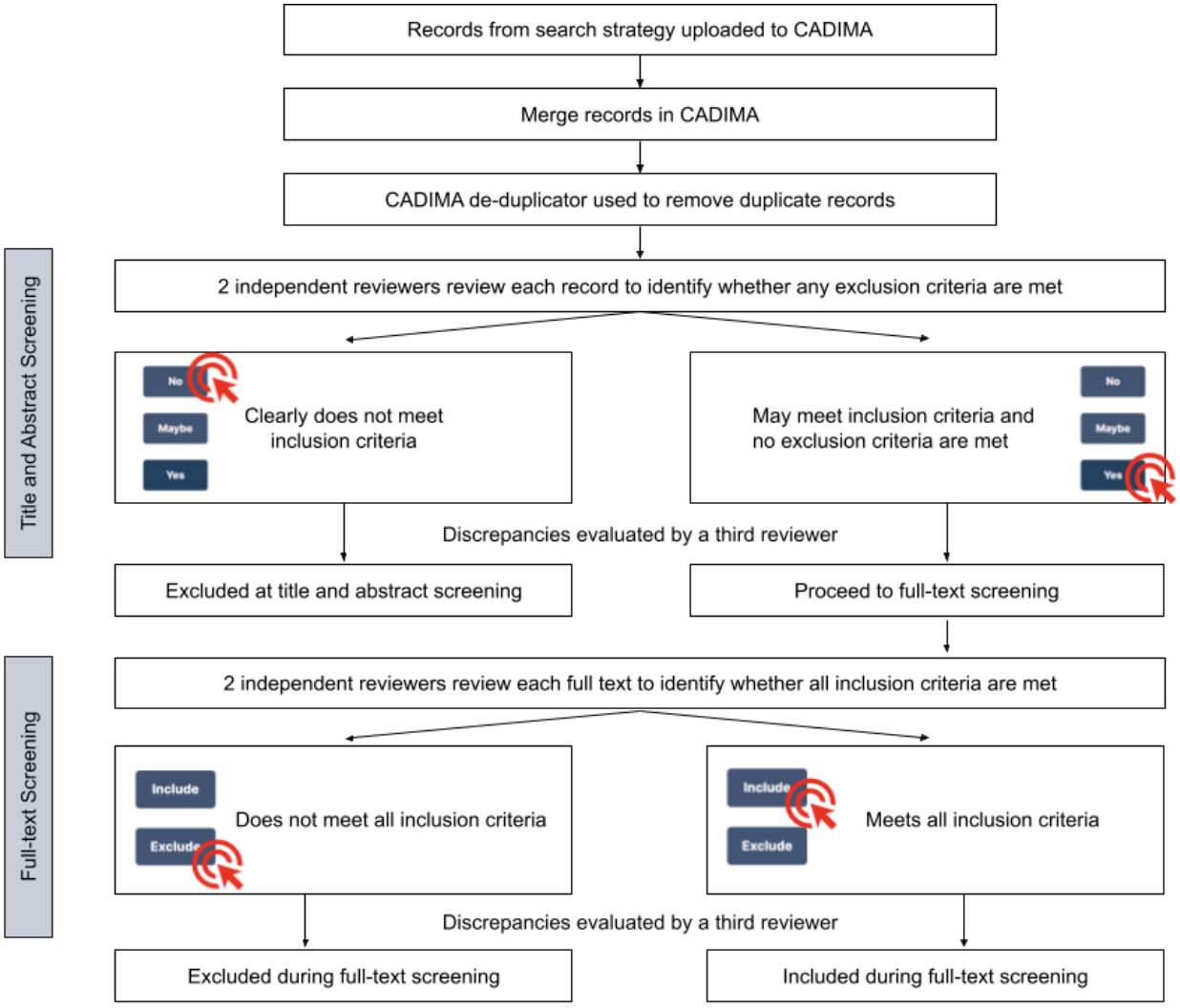
Each sample frame will have its own project in CADIMA[11] because they have differing inclusion criteria.

Screening, extraction, and risk of bias data will be stored in the CADIMA[11] systematic review manager. Upon conclusion of the project, data will be downloaded locally and ultimately uploaded to a public GitHub (RRID:SCR_002630) repository.

Selection Process:

The screening protocols will be piloted by all screeners that will initiate the review. The protocol will be refined to clarify discrepancies that arise prior to study inception.

Once the screening protocol is finalized, records will be uploaded to CADIMA[11] systematic review manager, merged, and subsequently de-duplicated with the de-duplication tool within this software. Screening of records will be performed in a two-stage process. By two independent reviewers, records will undergo title and abstract screening and then full-text screening in accordance with the following diagram:



All records that are included in the full-text screening will proceed to data extraction.

Data Extraction:

All reviewers will pilot the extraction form, which will initiate data extraction. The protocol will be refined to clarify discrepancies that arise during piloting.

Data extraction will be performed by two independent reviewers using the CADIMA[11] systematic review manager.

The following data will be extracted from each included study:

- Study details
    - sponsorship source
    - country
    - setting
    - trial registration number
- Author's contact details:
    - Name
    - Institution
    - Email
    - Address
- Study aim
- Study design
- Method of recruitment
- Recruitment period
- Total sample size with ovarian cancer
- Number of withdrawals
- Reasons for withdrawals
- Population details
    - inclusion criteria
    - exclusion criteria
    - group differences
    - baseline characteristics
        - mean age (years) ± SD
        - race or ethnic group
        - FIGO stage at first diagnosis (I, II, III, or IV)
        - BRCA status

- Relapse (first, second, ≥ third)
- Relapse-free interval
- ECOG PS
- histology
    - serous
        - high-grade, low-grade or
        - for studies planned/recruiting until 2014: Grading I, II, III, or
        - if not defined: consult with NOGGO e.V.
    - endometrioid
    - clear cell
    - mucinous
    - undifferentiated
    - other or mixed
- first-line chemotherapy (adjuvant, neoadjuvant)
- first-line chemotherapy (platinum-based, taxane-based, bevacizumab, PARP-inhibitor, no previous chemotherapy)
- first-line chemotherapy: number of cycles of
- No. of cycles of first-line platinum-doublet chemotherapy, median or mean plus range
- Previous relapse therapy (multiple answers possible)
    - Topotecan
    - Pegylated liposomal doxorubicin
    - Alkylating antineoplastic agent
    - Bevacizumab
    - PARP-Inhibitor
    - Endocrine therapy, e.g. tamoxifen
    - Paclitaxel
    - Other
    - No previous chemotherapy
- Tumor marker at baseline (prior to paclitaxel) (CA-125 level (U/mL)

- Intervention drug
    - Number of participants allocated
    - Number of participants analyzed
    - Intervention drug (nab-paclitaxel or paclitaxel)

        - Dose and dosing frequency
        - Method of administration
- Comparator drug
    - Number of participants allocated
    - Number of participants analyzed
    - Comparator drug (if applicable)
    - Dose and dosing frequency (if applicable)
    - Method of administration (if applicable)
- Outcomes
    - Progression-free survival (including outcome definition and unit of measurement)
    - Overall survival (including outcome definition and unit of measurement)
    - Adverse events
        - hematological toxicities
        - non-hematological toxicities
        - allergic reactions
        - neuropathy
    - Quality of life (as measured by EORTC questionnaires, FACT questionnairs, or Short Form (SF) questionnaires)
- Duration of follow up

Risk of Bias

Two independent reviewers (MF and NW) will evaluate risk of bias for each study at the study-level. We will employ the following checklists to evaluate risk of bias according to study design:

Randomized controlled trials	Cochrane risk-of-bias tool (RoB 2)[12]
Other trial designs	Risk Of Bias In Non-randomised Studies - of Interventions (ROBINS-I)[13]
Cohort studies	Risk Of Bias In Non-randomised Studies - of Interventions (ROBINS-I)[13]

Discrepancies will be resolved via discussion amongst reviewers (MRF and NW), and, if needed, clarified with TK.

Records will not be removed from our report based on risk of bias. However, risk of bias will be taken into consideration in the interpretation of study results.

Data synthesis

We will narratively synthesize the results of this systematic review and generate a summary table of all included studies from a clinical perspective. The variables incorporated in this table will include the intervention drug, the comparator drug(s), study design, progression-free survival data, overall survival data, reported adverse events data, population characteristics, and any other relevant extraction variables in the protocol testing phases. We plan to group these studies first by intervention drugs and then by the comparator drug.

The results of the results from Sample Frame 1 can be descriptively compared to the results that have already been synthesized in the 2022 Cochrane Review "Taxane monotherapy regimens for the treatment of recurrent epithelial ovarian cancer."[7]

We plan to compare nab-paclitaxel to paclitaxel only if we are able to identify studies that compare these two drugs directly. If we are unable to find such studies, we will narratively summarize the data for Sample Frame 1 and Sample Frame 2 separately without comparisons of treatment efficacy or effectiveness between the drugs.

Due to anticipated heterogeneity of study designs and results, a meta-analysis from the findings of this systematic review will not be conducted.

Confidence in cumulative evidence

We will evaluate the certainty of evidence for each study using the Grading of Recommendations, Assessment, Development, and Evaluations (GRADE) framework.

Acknowledgements:

This protocol was compiled following the reporting guideline "PRISMA for systematic review protocols (PRISMA-P)."[14]

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