Living Evidence Syntesis Protocol
Servei d'Epidemiologia Clínica i Salut Pública
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Title

Effectiveness and safety of targeted therapy in patients with advanced ovarian cancer: An overview. (Protocol)

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On behalf of the Living Evidence to inform health decisions research group

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Abstract

Several primary studies and systematic reviews (SRs) are being published in the last years to assess the safety and effectiveness of targeted therapy (bevacizumab, olaparib, niraparib, rucaparib) as a treatment for advanced ovarian cancer.

Objective

To evaluate the efficacy and safety of targeted therapy (bevacizumab, olaparib, niraparib, rucaparib) for patients with advanced ovarian cancer.

Methods

We will carry out a living overview of systematic reviews including only systematic reviews (SR). To prioritize interventions, comparisons, and outcomes more relevant for the decision-making and define the final PICO questions we will perform a Delphi process. Searches will be performed in Epistemonikos database and results will be incorporated into the L·OVE platform identified as "Targeted therapy for ovarian cancer". We will assess the certainty of evidence using the GRADE approach.

We will monitor the L.OVE platform every two months searching for relevant trials that could imply changes in the available evidence. The living process will end after 12 months of surveillance.

Background

Condition or domain being studied

Ovarian cancer is the leading cause of death among all gynaecological cancers in developed countries, and more than two-thirds of patients have advanced-stage tumours (FIGO stages III and IV). Globally, it represents 3% of tumours in women and is the fourth leading cause of cancer death in women after lung, breast, and colorectal cancer. The estimated number of new cases of ovarian cancer in Europe in 2012 was 65,538 with 42,704 deaths (1).

Why it is important to do this review

Targeted therapy is a type of cancer treatment that uses drugs to identify and attack cancer cells with little damage to normal cells. Each type of targeted therapy works differently, although they all change the way a cancer cell grows, divides, repairs itself, or interacts with other cells.

Bevacizumab (Avastin) is in a class of drugs called angiogenesis inhibitors. Bevacizumab has been shown to shrink or slow the growth of advanced-stage epithelial ovarian cancers. This drug seems to work best when given along with chemotherapy, working well in terms of shrinking tumours (or stopping them from growing). However, it does not appear to help women live longer. Bevacizumab can also be given together with olaparib as a maintenance treatment in women whose cancers have the BRCA gene mutation.

Olaparib (Lynparza), rucaparib (Rubraca), and niraparib (Zejula) are drugs known as

PARP (poly (ADP) -ribose polymerase) inhibitors. By blocking the PARP process, these drugs make it very difficult for tumor cells with an abnormal BRCA gene to repair damaged DNA, which often results in the death of these cells. Olaparib (Lynparza) and rucaparib (Rubraca) are used to treat advanced ovarian cancer, usually, after chemotherapy has been tried. These drugs can be used in patients with or without mutations in one of the BRCA genes.

The number of studies and systematic reviews evaluating the efficacy of biological or targeted therapy for the management of advanced ovarian cancer has increased in recent years with the incorporation of new drugs.

We initially performed a tiered search strategy, beginning with the identification of SRs included in the Epistemonikos Database (2). We identified more than 90 SRs conducted during 2014 and 2021, to assess the effect of targeted therapy in ovarian cancer. When reviewing the primary studies, we found that there is great variability in type and dose targeted therapy, target population, and outcomes of interest.

Considering the characteristics of the available evidence, the width variability of the SRs currently published and taking into account that the evidence on this therapy is on
the rise (i.e. new studies have been published and other studies are going to be published in the near future), we propose to carry out a living overview of SRs with the aim of updating the estimates of the effect of this intervention on the patients with advanced ovarian cancer once new evidence emerges.

This overview of SRs will be developed as part of the *Living Evidence to Inform Health Decisions* project, which supports health system organizations in the implementation of the living evidence model for the development of evidence synthesis to inform health decisions (3).

Objective

To evaluate the efficacy and safety of targeted therapy (bevacizumab, olaparib, niraparib, rucaparib) for patients with advanced ovarian cancer.

Types of studies to be included

We will include systematic reviews (SRs) published since 2015, including any type of primary study. The selection will be restricted to Spanish and English.

We consider systematic reviews those that summarize primary studies (any study design) according to the definition provided by the Cochrane Collaboration and the PRISMA Statement: “A systematic review attempts to collect all empirical evidence that fits the pre-specified eligibility criteria in order to answer a specific research question. It uses explicit, systematic methods that are selected with a view to minimizing bias, thus providing more reliable findings from which conclusions can be drawn and decisions made”. An eligible review must meet all of the following criteria: reports searching at least one electronic database; reports of at least one

criterion for the inclusion of studies.

Types of participants

Adult patients (>18 years old) diagnosed with advanced ovarian cancer (stages III and IV).

PICO question

To better support clinical decision-making, a two-round modified Delphi panel (4) with online questionnaires will be conducted to prioritize the intervention, comparisons, and outcomes to select those considered more relevant for the decision-making.

For the Delphi process, we will elaborate a comprehensive list of the general interventions, comparisons, and outcomes described below to be assessed by the panel. We will ask them to rate each intervention, comparison, and outcome from 1 to 9 points as follows: low importance (score: 1–3), important but non-critical (score: 4–6), and critical (score: 7–9).
To define the final PICO questions for the proposed review will be only considered the PICO components rated as critical.

Intervention

Treatment with targeted therapy including bevacizumab, olaparib, niraparib, or rucaparib for advanced ovarian cancer in any administration route, frequency of administration, or treatment duration.

Comparator

Placebo, or control.

Types of outcome measures

Main outcomes

-Overall survival (OS) (defined as the time that passes from the date of diagnosis or the start of treatment for a disease, during which patients with the disease are still alive) at 3, 6, 9, 12, 24 months and time until the event.

-Progression-free survival (PFS) (defined as the time that passes between the beginning of treatment for a disease, and after treatment, during which a patient lives with the disease, but it does not get worse) at 3, 6, 9, 12, 24 months and time until the event.

-Functional status (FS), measured by Karnofsky or ECOG scale.

-Toxicity, measured as moderate or severe adverse events, according to the standardized classification.

Additional outcomes

-Symptom related with the disease, measured with validated scales that assess one or more symptoms.

-Health related quality of life, measured by a specific questionnaire or by a non-specific questionnaire (e.g. EuroQoL 5D, SF-36 and Cleveland Global Quality of Life Score (CGQoL)).

Methods for identification of studies

The main search source will be the Epistemonikos database (https://www.epistemonikos.org), a comprehensive database of systematic reviews and other types of evidence, maintained by screening multiple information sources to identify systematic reviews and their included primary studies, including Cochrane Database of Systematic Reviews, MEDLINE, EMBASE, CINAHL, PsycINFO, LILACS, DARE, HTA Database, Campbell database, JBI Database of Systematic Reviews and Implementation Reports, EPPI-Centre Evidence Library (2).

An additional search will be performed on MEDLINE in order to identify randomized trials/primary studies not included in reviews. The searches will cover from the inception date of each database. No publication status or language restriction will be applied to the searches in Epistemonikos. We will apply validated filters to identify clinical trials in MEDLINE database.

Results from these searches will be automatically included in the L.OVE platform of the Epistemonikos Foundation (5). This platform has been validated as a repository for the COVID-19 showing to be a highly comprehensive source of evidence (6, 7).

Our literature search will be devised by the team maintaining the Epistemonikos-L·OVE platform (https://app.iloveevidence.com), using the following approach:

1. Identification of terms relevant to the population and intervention components of the search strategy, using Word2vec technology (3) to the corpus of documents available in Epistemonikos Database.
2. Discussion of terms with content and methods experts to identify relevant, irrelevant, and missing terms.
3. Creation of a sensitive boolean strategy encompassing all the relevant terms. **Boolean search strategy**

Epistemonikos

(ovar* AND (cancer* OR neoplas* OR tumor* OR tumour* OR malignan* OR metasta* OR nodul* OR polyp* OR cyst* OR adenocarcinoma* OR carcinoma* OR oncolog* OR dysplasia*)) AND (Olaparib* OR Lynparza* OR AZD2281* OR "AZD 2281" OR "AZD-2281" OR MK7339* OR "MK 7339" OR "MK-7339")

(ovar* AND (cancer* OR neoplas* OR tumor* OR tumour* OR malignan* OR metasta* OR nodul* OR polyp* OR cyst* OR adenocarcinoma* OR carcinoma* OR oncolog* OR dysplasia*)) AND (niraparib* OR Zejula* OR "MK-4827" OR "MK 4827" OR MK4827*)

(ovar* AND (cancer* OR neoplas* OR tumor* OR tumour* OR malignan* OR metasta* OR nodul* OR polyp* OR cyst* OR adenocarcinoma* OR carcinoma* OR oncolog* OR dysplasia*)) AND (rucaparib* OR rubraca* OR "AG0 14699" OR "AG0-14699" OR AG014699*)

(ovar* AND (cancer* OR neoplas* OR tumor* OR tumour* OR malignan* OR metasta* OR nodul* OR polyp* OR cyst* OR adenocarcinoma* OR carcinoma* OR oncolog* OR dysplasia*)) AND (bevacizumab* OR avastin)

Other sources

In order to identify articles that might have been missed in the electronic searches, and to keep monitoring for the new evidence that arise, we will do manual search for reviewing the reference list of included studies and will run additionally searches in WHO International Clinical Trials Registry Platform and clinicaltrials.gov.

Selection of studies

The results of the literature searches will be automatically incorporated into the L·OVE platform (automated retrieval) identified as "Targeted therapy for ovarian cancer" Firstly, titles and abstracts will be independently screened by at least two reviewers against the inclusion criteria. We will resolve disagreements by consensus or by a discussion with a third review author. Secondly, we will obtain the full reports for all records that appear to meet the inclusion criteria (according to the Delphi results). We will record the reasons for excluding studies and show the study selection process in a PRISMA flow diagram.

Data extraction and management

We will use an excel spreadsheet to extract information about studies characteristics (characteristics of participants; inclusion-exclusion criteria; intervention and comparison description, outcomes, and results). Data extraction will be performed by two authors.

Assessment of risk of bias of included studies

We will evaluate the risk of bias of the included SRs using the AMSTAR-2 tool (8). Two independent review authors will do this assessment. Discrepancies will be resolved by consensus.

Overlap Assessment

We will construct a table to assess the possible overlap of primary studies. In this table, the columns will represent all included reviews, and the rows, the primary studies included by previous reviews. From this, we will calculate the corrected covered area, and we will interpret that the overlap of primary studies will not be important if it is <5%, it will be moderate if it is> 5% and <10%, high if it is> 10% and <15%. , and very high if it is> 15% (37).

Measures of treatment effect

We will make a description of the general characteristics of the included reviews and their main synthesized results. Then, we will extract the data from each primary study, as reported in each SR. If the same primary study is included in more than one review, we will extract the data only once from the SR with the lowest risk of bias, to avoid an overestimation of the effects due to the double-counting of the same study.

For each comparison, we will carry out a de novo meta-analysis based on the data from the primary studies, extracted from the SR. We will analyze dichotomous outcomes with an odds ratio (OR), continuous outcomes with a mean difference or standardized mean difference, and time-event outcomes with a hazard ratio (HR), all with a 95% confidence interval.

Data synthesis

We will evaluate the heterogeneity of the included studies with I^2 as follows: I2 < 50% as low, heterogeneity, I2 > 50% and < 90% as high, and > 90% as very high. When heterogeneity is below 90%, we will perform a meta-analysis using a random-effects model in RevMan 5.4.

Subgroup analysis

We will perform the following subgroup analyses if data is available:

•Patients with BRCA gene mutation versus without BRCA gene

mutation

•In recurrent cancer: platinum-sensitive / resistant patients (defined by the time elapsed from the end of initial treatment to recurrence)

•Concomitant administration with chemotherapy/maintenance.

Sensitivity analysis

We will perform a sensitivity analysis excluding the studies with a high risk of

bias. **Certainty of evidence**

We will assess the certainty of evidence using the GRADE approach (9), both for the evidence found as part of the initial or baseline review, and for the updates resulting from the living evidence process.

Two reviewers will independently define the certainty of evidence and discuss any disagreement to reach a consensus. We will present the results using a summary of findings tables.

Evidence monitoring and surveillance plan

In order to maintain the living evidence process for this review, the Epistemonikos-L.OVE platform (5) will be used as a technological enable to support the evidence identification, screening, and selection. We will keep a living search in

the L·OVE platform to detect systematic reviews and randomized controlled trials. Additionally, every three months, we will manually search for ongoing studies in the WHO International Clinical Trials Registry Platform and the clinicaltrials.gov.

One reviewer will be in charge of assessing the evidence that has entered the L.OVE of this question every month and applying the selection criteria presented above. If a potentially eligible study is found, a second reviewer will confirm its eligibility by reading the full text. Results of evidence surveillance will be collected and kept as part of the study records. Information on PRISMA will be updated accordingly. Criteria for selecting studies will be revised and changed accordingly during the LE processes every 4 months.

All new eligible studies will undergo to data extraction process. The data synthesis will be updated immediately after that taking into account the predefined subgroups of interest, and the body of evidence for the outcomes of interest will be assessed
following the GRADE approach accordingly looking for changes on the certainty assessment results.

The living process for this question will end after 12 months of surveillance updating the evidence synthesis report.

Statistical considerations for the living evidence synthesis

The inclusion of new studies identified as part of evidence surveillance and reporting on the outcomes of interest will follow this approach: We will perform a meta-analysis for each of the outcomes of interest reported by the new studies using a fixed-effect model in order to evaluate the statistical heterogeneity among included studies by using the I^2statistics. If new heterogeneity is detected (i.e. increase the heterogeneity previously identified or new heterogeneity arises where it was previously undetected), we will explore its potential sources by reviewing the new studies against previously included studies in order to identify reasons that may explain inconsistent results among studies. In presence of unexplained heterogeneity (I2> 70%), we will consider not to Meta-analyze them and explain the evidence synthesis narratively. If the $I^2$is below 90%, we will perform a meta-analysis by using the fixed effects of the random-effects model, whichever is pertinent.

Dissemination plan

We plan to communicate our overview results as publication in a scientific journal.

If during the living process, new relevant results that imply changes in the current clinical practice are identified, we will update the report of this review and disseminate the update among potential users.

We will elaborate evidence technical reports to the hospital Health Assessment Committee. We will share the results through our social media channels. All periodical updates will be available on the LE_IHD project website

(https://livingevidenceframework.com/en/).

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