INPLASY PROTOCOL

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Conflicts of interest:
None declared.

The efficacy and safety of vascular endothelial growth factor receptor (VEGFR) inhibitors for recurrent ovarian cancer: a systematic review and meta-analysis

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Review question / Objective: **The aim of this systematic review is to evaluate the efficacy and safety of targeting VEGFR drugs for recurrent ovarian cancer.**
Condition being studied: **Ovarian cancer causes the most fatalities from gynecological carcinoma. Among malignant ovarian neoplasms, epithelial ovarian cancers are more than 90% of cases . The 5-year survival is lower than 50%, with a median age at diagnosis of 63 years.Annually worldwide, 295,000 women will be diagnosed and 184,000 will die. The combination of cytoreductive surgery with complete resection of all macroscopic disease and platinum-based chemotherapy is the existing standard of treatment for ovarian cancer. Many women with ovarian cancer eventually develop resistance to conventional chemotherapy drugs, and so novel agents are being developed to target specific molecular pathways. One such class of drugs inhibits angiogenesis (the development of new blood vessels), which is essential for tumour growth. Angiogenesis plays a pivotal role in normal ovarian physiology as well as in the progression of ovarian cancer through ascites formation and metastatic spread. Vascular endothelial growth factor receptor (VEGFR) inhibitors showed activity in ovarian cancer, but preliminary data could not accurately reflect the survival benefit. We thus will do a systematic review and meta-analysis of randomized controlled trials to assess the efficacy and safety of VEGFR inhibitors combined with chemotherapy for ovarian cancer.**

INPLASY registration number: This protocol was registered with the International Platform of Registered Systematic Review and Meta-Analysis Protocols (INPLASY) on 05 February 2021 and was last updated on 05 February 2021 (registration number INPLASY202120019).

INTRODUCTION

Review question / Objective: **The aim of this systematic review is to evaluate the efficacy and safety of targeting VEGFR drugs for recurrent ovarian cancer.**

Rationale: Angiogenesis requires signaling between tumour cells and nearby endothelial (lining) cells of normal blood vessels, stimulating them to sprout, multiply and invade the growing tumour. The process involves release of agents by cancer cells, stimulated by low oxygen levels or low pH. These agents bind to receptors on endo-thelial cells, which then trigger downstream intracellular signalling, leading to growth and migration of endothelial cells. This process can be inhibited at each of these stages. Because angiogenesis is normally inactive in adults, its inhibition is an attractive candidate for selective anti-tumour therapies. Another advantage is that tumour endothelial cells are not themselves malignant and so, unlike cancer cells themselves, do not have pre-existing mutations that favour the development of further mutations, which could lead to drug resistance. In addition, anti-angiogenic agents may work synergistically with conventional chemotherapeutic agents or other novel systemic agents, due to their different mechanisms of action.

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METHODS

Search strategy: We will search the following databases for relevant literature: Cochrane Library, Web of Science (WOS), PubMed, Excerpt Medica Database (EMBASE), China National Knowledge Infrastructure (CNKI) and Wanfang Database, VIP, SinoMed from their inception to 31st January 2021. The search strategy: (ovarian cancer OR ovarian carcinoma OR ovarian neoplasm OR ovarian tumor OR ovarian tumour OR ovarian malignan) AND (vascular endothelial growth factor receptor inhibitors OR VEGFR OR VEGF-R OR monoclonal antibodies OR anti-VEGFR OR VEGFR-target OR Antiangiogen) AND (sorafenib OR sunitinib OR Axitinib OR pazopanib OR Ramucirumab OR Apatinib). The electronic database search will be supplemented by a manual search of the reference lists of included articles.

Participant or population: Adults with recurrent ovarian cancer (as diagnosed by a clinician, or using any recognized diagnostic criteria) will be included. No age or race limitation.

Intervention: Vascular endothelial growth factor receptor inhibitors (such as apatinib, ramucirumab, bevacizumab, pazopanib, Axitinib, sorafenib ,Sunitinib).

Comparator: Placebo, conventional chemotherapy drugs.

Study designs to be included: Randomized clinical trials will be included irrespective of blinding, publication status or language.

Eligibility criteria: 1.Types of studies:Randomised controlled trials (RCTs) of VEGFR inhibitors plus

conventional chemotherapy versus conventional chemo-therapy alone, and VEGFR inhibitors versus no treatment. 2.Types of participants:Adult women with histologically proven ovarian cancer. Women with other concurrent malignancies were excluded. 3.Types of interventions: VEGFR inhibitors + conventional chemotherapy versus conventional chemotherapy. VEGFR inhibitors versus no treatment. 4.Types of outcome measures: Overall survival (OS); Progression-free survival (PFS); Quality of life (QOL); immune function evaluation; Safety assessment.

Information sources: Cochrane Library, Web of Science (WOS), PubMed, Excerpt Medica Database (EMBASE), China National Knowledge Infrastructure (CNKI) and Wanfang Database.

Main outcome(s): The primary outcomes will be the therapeutic effects of treatment according to Response Evaluation Criteria in Solid Tumors 1.1 (RECIST Criteria 1.1). (a) Overall response rate (ORR) and disease control rate (DCR); (b) Overall survival (OS, which is defined as the time from the date of randomization to death from any cause); (c) Progression-free survival (PFS, which is defined as the time from the date of randomization until disease progression or death). * Measures of effect Early and durable response will be recorded among included studies. All time points will be considered due to the anticipated variability in follow-up. The details of the follow-up period will also be recorded for all studies.

Additional outcome(s): Secondary outcomes will include: (a) immune function evaluation; (b) quality of life (QOL) as evaluated by Karnofsky score and (c) treatment–related adverse effects assessment. * Measures of effect Early and durable response will be recorded among included studies. All time points will be considered due to the anticipated variability in follow-up. The details of the follow-up period will also be recorded for all studies.

Data management: Two reviewers will be responsible for the data extraction independently according to the Cochrane Handbook for Systematic Reviews of Intervention. The following data will be extracted from eligible literatures: the first author, year of publication, country of study, participants (sample size, TNM stage, age, gender, inclusion and exclusion criteria, etc.), details of all experimental and control interventions regimen (dosage of drugs, administration route, duration of treatment, follow-up time, etc.), outcomes (ORR, DCR, OS, PFS, QOL, immune function and adverse effects). For survival outcomes, Hazard ratios (HRs) with corresponding 95% confidence intervals (CIs) will be extracted from trials or be estimated from Kaplan–Meier survival curves by established methods. Any disagreements will be resolved by discussion, and a third reviewer will make the final decision. Excluded studies and the reasons for exclusion will be listed in a table.

Quality assessment / Risk of bias analysis: The risk of bias tool presented in the Cochrane Handbook 5.3.0 will be used to assess the methodological quality of the included studies by two independent reviewers. Any disagreements will be resolved by discussion with a third reviewer. Seven items are included in the Cochrane Collaboration's tool: random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective reporting and other sources of bias. Judgments for each item are divided into three levels: low risk of bias, high risk of bias and unclear risk of bias.

Strategy of data synthesis: Statistical analyses will be performed using Review Manager 5.3 (Nordic Cochran Centre, Copenhagen, Denmark) and Stata 14.0 (Stata Corp, College Station, TX, USA) statistical software. Because it belongs to the time survival variables, mainly OS and PFS data merge analysis, including OS HR (hazard ratio)[95%CI] and PFS HR[95%CI], also, the review analyse the safety of this

kind of drugs including the number of adverse events of speacial interest such as Hypertension, proteriuria, bleeding/ haemorrhage, hand-foot syndrome.

Subgroup analysis: If the data are available and sufficient, subgroup and meta-regression analysis will be conducted to explore the source of heterogeneity with respect to age, gender, region, tumor stage, sample sizes, follow-up period, chemotherapy regimens and types of involved studies.

Sensitivity analysis: If sufficient data is available a sensitivity analysis will be conducted to detect the stability of our findings.

Language: English.

Country(ies) involved: China.

Keywords: Vascular endothelial growth factor receptor Inhibitors; Ovarian cancer; Progression-free survival; Overall survival; Toxicity.

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