INPLASY PROTOCOL

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Conflicts of interest:
None declared.

Comparative efficacy and safety of metronomic chemotherapy in breast cancer：A network meta-analysis protocol

Xie, Y[1]; Chen, X[2]; Wang, X[3].

Review question / Objective: **Evaluation of the efficacy and safety of metronic versus conventional treatment in randomized controlled clinical trials of breast cancer.**
Condition being studied: **The objective is important for clinical treatment There has been a certain amount of studies published and other studies registered on Clinical Trials website. The authors mastered the method of meta analysis and network meta analysis.**
Information sources: **PubMed, EMBASE, Web of Science, and the Cochrane Central Register of Controlled Trials.**

INPLASY registration number: This protocol was registered with the International Platform of Registered Systematic Review and Meta-Analysis Protocols (INPLASY) on 29 April 2021 and was last updated on 19 May 2021 (registration number INPLASY202140142).

INTRODUCTION

Review question / Objective: **Evaluation of the efficacy and safety of metronic versus conventional treatment in randomized controlled clinical trials of breast cancer.**

Rationale: **A recent clinical trial testing the effect of capecitabine in lower dosage and higher frequency versus Observation after surgery has demonstrated an extension of progression-free survival. As early as 2000, animal experiments have shown that low doses of chemotherapeutic agents can**

inhibit angiogenesis and thus reduce tumor growth and metastasis. In recent years, there have been clinical trials in a number of cancer types that have tested the efficacy of metronomic therapy over conventional treatment. In clinical trials of metronomic therapy for breast cancer, a variety of drugs and administration regiments have been mentioned, including chemotherapy drugs, antiangiogenic targeting drugs and small molecule inhibitors, etc. Currently, there is a lack of unified understanding on which therapeutic strategy is more effective and how safe it is.

Condition being studied: The objective is important for clinical treatment There has been a certain amount of studies published and other studies registered on Clinical Trials website. The authors mastered the method of meta analysis and network meta analysis.

METHODS

Search strategy: ((((Capecitabine Maintenance Therapy[Title/Abstract]) OR (((((((((metronomic schedule[Title/Abstract]) OR (antiangiogenic scheduling[Title/Abstract])) OR (metronomic Etoposide[Title/Abstract])) OR (metronomic cisplatin[Title/Abstract])) OR (metronomic gemcitabine[Title/Abstract])) OR (metronomic Vinorelbine[Title/Abstract])) OR (metronomic cyclophosphamide[Title/Abstract])) OR (Antiangiogenic scheduling of chemotherapy[Title/Abstract])) OR (Continuous low-dose therapy[Title/Abstract])) OR (Metronomic chemotherapy[Title/Abstract]) AND (humans[Filter])) AND ((((cancer[Title/Abstract]) OR (tumor[Title/Abstract])) OR (carcinoma[Title/Abstract])) OR (neoplasm[Title/Abstract]))) AND (((breast[Title/Abstract]) OR (mammary[Title/Abstract])))) AND (((randomized controlled trial[Publication Type]) OR (randomized[Title/Abstract])) OR (placebo[Title/Abstract])).

Participant or population: Breast cancer.

Intervention: Metronomic therapy.

Comparator: Conventional therapy.

Study designs to be included: RCT.

Eligibility criteria: 1. Pathologically confirmed primary breast cancer or recurrence of breast cancer; 2. Intervention is the mentronomic schedule of anti-tumor drugs comparing to the routine dosing strategy of the same drug; 3. The study type was RCT; 5. At least one of OS and DFS is reported.

Information sources: PubMed, EMBASE, Web of Science, and the Cochrane Central Register of Controlled Trials.

Main outcome(s): Disease free survival or overall survival or both.

Additional outcome(s): Adverse events.

Data management: We will use the Excel software to manage data.

Quality assessment / Risk of bias analysis: Quality assessment will be conducted according to the Cochrane risk-of-bias assessment tool.

Strategy of data synthesis: A Bayesian multiple treatment network meta-analysis with random effects and uninformative priors will be performed with both placebo- and active-controlled trials be considered. The Glass Δ will be used as the standardized mean difference (SMD) measure with a 95% credibility interval (CrI). An SMD of 0.20 is considered a small difference between the experimental and the control group; 0.50, a moderate difference; and 0.80, a large difference. Besides, Random-effect model and Der-Simonain-Laird method were used for cases with high heterogeneity, otherwise fixed-effect model and Inverse-variance method were undertaken for ordinary meta-analysis.

Subgroup analysis: We will conduct subgroup analysis based on the molecular subtypes of breast cancer contains HER2 positive breast cancer. HER2 negative and

hormone receptor positive breast cancer and triple negative breast cancer.

Sensitivity analysis: One study will be eliminated at a time, and the rest will be synthesized to detect the sensitive individual study that significantly changes the combination results.

Language: English.

Country(ies) involved: China.

Keywords: Metronmic therapy, anti-tumor strategy, breast cancer, network meta-analysis, angiogenesis.

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