INPLASY PROTOCOL

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Corresponding author:
Qing Zhang

zhangqing@ccmu.edu.cn

Author Affiliation:
Beijing Hospital of Traditional Chinese Medicine, Capital Medical University, Dongcheng District, Beijing, China.

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Conflicts of interest:
None declared.

The Efficacy and Safety of Apatinib Combined with Chemotherapy in the Treatment of Advanced Breast Cancer：A protocol for systematic review and meta-analysis

Li, KX[1]; Chen, XJ[2]; Liu, M[3]; Zhang, Q[4].

Review question / Objective: **To evaluate the efficacy and safety of apatinib combined with chemotherapy in the treatment of advanced breast cancer in randomized controlled trials and restospective studies.**
Eligibility criteria: **1. The study type was RCTs or retrospective case-control studies. Case reports, reviews, and animal studies will be excluded. 2. Participants. Advanced breast cancer patients (diagnosed by pathology or imaging and identified by the 8th edition of TNM staging system) of any race, age or nationality. 3. Interventions. The control group was treated with chemotherapy, while the experimental group was treated with apatinib on the basis of the control group. The dosage and treatment time of the 2 groups are not considered in this study. 4. At least one of ORR, DCR, OS, PFS is reported.**

INPLASY registration number: This protocol was registered with the International Platform of Registered Systematic Review and Meta-Analysis Protocols (INPLASY) on 20 June 2021 and was last updated on 23 June 2021 (registration number INPLASY202160066).

INTRODUCTION

Review question / Objective: **To evaluate the efficacy and safety of apatinib combined with chemotherapy in the treatment of advanced breast cancer in randomized controlled trials and restospective studies.**

Rationale: **Breast cancer is a common malignant tumor, especially in women, which seriously endangers human health. Apatinib is a kind of targeted drug inhibiting angiogenesis, which has preventive and therapeutic effects on a variety of cancers. In recent years, more and more studies have shown the efficacy**

of apatinib on remedying advanced breast cancer. Therefore, our study aims to evaluate the efficacy and safety of apatinib combined with chemotherapy in the treatment of ABCBreast cancer is a common malignant tumor, especially in women, which seriously endangers human health. Clinical benefit and prolonged are the main treatment goals of advanced breast cancer. Targeted therapies have shown promising potentials in HER2(Human epidermal growth factor receptor-2) positive breast cancer, but with uncertain effects in HER2-negative breast cancer, especially when disease is progressing rapidly. The regimen of antiangiogenic therapy combined with chemotherapy had been studied for years. Apatinib is an oral, highly potent tyrosine kinase inhibitor targeting vascular endothelial growth factor receptor 2 (VEGF-2), which has preventive and therapeutic effects on a variety of cancers. In recent years, more and more studies have shown the efficacy of apatinib on remedying advanced breast cancer.

Condition being studied: Advanced Breast Cancer. 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.

METHODS

Search strategy: ((((apatinib[Title/Abstract]) AND ((chemotherapy[Title/Abstract]) OR (drug therapy[Title/Abstract]))) 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 (controlled clinical trial[Publication Type])) OR (randomized[Title/Abstract])) OR (randomly[Title/Abstract])) OR (retrospective[Title/Abstract])).

Participant or population: Advanced breast cancer patients.

Intervention: The experimental group was treated with apatinib combined with chemotherapy. The dosage and treatment time of the 2 groups are not considered in this study.

Comparator: The control group was treated with chemotherapy. The dosage and treatment time of the 2 groups are not considered in this study.

Study designs to be included: Randomized controlled trials and retrospective case-control studies.

Eligibility criteria: 1. The study type was RCTs or retrospective case-control studies. Case reports, reviews, and animal studies will be excluded. 2. Participants. Advanced breast cancer patients (diagnosed by pathology or imaging and identified by the 8th edition of TNM staging system) of any race, age or nationality. 3. Interventions. The control group was treated with chemotherapy, while the experimental group was treated with apatinib on the basis of the control group. The dosage and treatment time of the 2 groups are not considered in this study. 4. At least one of ORR, DCR, OS, PFS is reported.

Information sources: PubMed, Cochrane Library, Embase, Web of Science, Clinical Trials, China National Knowledge Infrastructure, Chinese biomedical literature service system and WanFang Database. We will also trace the references of relevant studies to ensure that any potential eligible studies will not be missed.

Main outcome(s): Objective response rate or disease control rate or progression-free survival or overall survival or all.

Additional outcome(s): Adverse events.

Data management: The search results will be imported into EndNote software. After the elimination of duplicates, 2 independent researchers will screen the literatures that do not meet the established inclusion criteria of the study by reading the title and abstract. Then, download the included literatures and read the full text carefully to

further decide whether to be include or not. For cases of any disagreement, the two researchers discussed or seek a third party's opinion until consensus. Data will be extracted from the eligible studies by 2 researchers independently with same pre-designed data extraction table and the results will be managed with Excel.

Quality assessment / Risk of bias analysis: Two researchers will evaluate the quality of the randomized controlled trials separately using the Risk of Bias Assessment Tool recommended by Cochrane and evaluate the retrospective studies using the Newcastle-Ottawa Scale. If the two researchers have different opinions, they will discuss or seek a third party's opinion to reach agreement.

Strategy of data synthesis: Stata and RevMan software will be performed for data analysis. Heterogeneity will be assessed by Chi-Squared test and I2 test. I2 < 50% and P > 0.05 indicate that there is no statistical heterogeneity between each studies, then a fixed effect model will be used to estimate the combined effect size. I2 ≥ 50% or P < 0.05 indicates the existence of statistical heterogeneity, a random effect model should be used to estimate the combined effect size. In addition, due to the existence of heterogeneity, we will conduct subgroup analysis to look for the potential causes.

Subgroup analysis: If there is a significant heterogeneity in the studies, we will conduct a subgroup analysis according to different factors such as the treatment cycle, the type of intervention in the control group, etc.

Sensitivity analysis: Sensitivity analysis will be conducted by removing the study one by one and then merge the data to assess the impact of different literatures.

Language: Language limits will not be imposed on the search.

Country(ies) involved: China.

Keywords: advanced breast cancer, apatinib, efficacy and safety, meta-analysis, protocol.

Contributions of each author:

Author 1 - Kexin Li.
Email: 970075833@qq.com
Author 2 - XJ Chen.
Author 3 - M Liu.
Author 4 - Qing Zhang.
Email: zhangqing@ccmu.edu.cn