INPLASY PROTOCOL

To cite: Yu et al. The efficacy and safety of Tyrosine kinase inhibitors in HER-2 positive breast cancer with brain metastases: A systematic review and Meta-analysis. Inplasy protocol 202170064. doi: 10.37766/inplasy2021.7.0064

Received: 20 July 2021

Published: 20 July 2021

Corresponding author:
Chuangui Song

Songcg1971@hotmail.com

Author Affiliation:
Fujian Medical University Union Hospital

Support: **None.**

Review Stage at time of this submission: **The review has not yet started.**

Conflicts of interest:
None declared.

The efficacy and safety of Tyrosine kinase inhibitors in HER-2 positive breast cancer with brain metastases: A systematic review and Meta-analysis

Yu, Y[1]; Zhang, J[2]; Huang, K[3]; Lin, Y[4]; Song, C[5].

Review question / Objective: **We conducted this meta-analysis to explore the efficacy and safety of Tyrosine kinase inhibitors(TKIs) compared with non-TKIs regimens in HER-2 positive breast cancer with brain metastases.**
Condition being studied: **The survival of breast cancer brain metastasis (BCBM) patients is extremely poor. The cornerstone of treatment modalities for BCBM include whole brain radiation therapy (WBRT), stereotactic radiosurgery (SRS), and surgery. However, those therapies do not provide a favorable outcome. The TKIs bind the extracellular domains of HER-2, block tyrosine phosphorylation, and downstream signal events of ligand binding, and contend with ATP at the cytoplasmic catalytic kinase domain. They also have a high blood-brain barrier penetrability that may better control intracranial lesions and produce less neurotoxicity. The efficacy and safety of TKIs for treatment of HER-2 positive breast cancer brain metastasis patients still remain unconfirmed and there was no meta-analysis exists to the best of our team's knowledge. Therefore, we performed a meta-analysis using latest data to provide a comprehensive overview of TKIs in HER-2 positive breast cancer brain metastasis.**

INPLASY registration number: This protocol was registered with the International Platform of Registered Systematic Review and Meta-Analysis Protocols (INPLASY) on 20 July 2021 and was last updated on 20 July 2021 (registration number INPLASY202170064).

INTRODUCTION

Review question / Objective: **We conducted this meta-analysis to explore the efficacy and safety of Tyrosine kinase inhibitors (TKIs) compared with non-TKIs regimens in HER-2 positive breast cancer with brain metastases.**

Condition being studied: **The survival of breast cancer brain metastasis (BCBM) patients is extremely poor. The cornerstone**

of treatment modalities for BCBM include whole brain radiation therapy (WBRT), stereotactic radiosurgery (SRS), and surgery. However, those therapies do not provide a favorable outcome. The TKIs bind the extracellular domains of HER-2, block tyrosine phosphorylation, and downstream signal events of ligand binding, and contend with ATP at the cytoplasmic catalytic kinase domain. They also have a high blood-brain barrier penetrability that may better control intracranial lesions and produce less neurotoxicity. The efficacy and safety of TKIs for treatment of HER-2 positive breast cancer brain metastasis patients still remain unconfirmed and there was no meta-analysis exists to the best of our team's knowledge. Therefore, we performed a meta-analysis using latest data to provide a comprehensive overview of TKIs in HER-2 positive breast cancer brain metastasis.

METHODS

Participant or population: HER-2 positive breast cancer with brain metastases.

Intervention: HER-2 positive breast cancer with brain metastases patients treated with Tyrosine kinase inhibitors comtaining regimens.

Comparator: HER-2 positive breast cancer with brain metastases patients treated with non-TKIs comtaining regimens.HER-2 positive breast cancer with brain metastases patients treated with Tyrosine kinase inhibitors

Study designs to be included: All TKIs for treatment of HER-2 positive BCBM patients.

Eligibility criteria: All clinical trials that investigating TKIs for treating HER-2 positive BCBM patients were included. Phase II or III clinical trials published in the form of full papers or abstracts if full papers were not available (especially those from ASCO, ESMO, and SABCS) were included in the analysis. Case reports, systemic reviews, and retrospective studies were excluded. If there were multiple publications of the same trial, only the latest was included.

Information sources: We followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines to perform this meta-analysis. Searches were performed on PubMed, Embase, and Cochrane Central Register of Clinical Trials, utilizing the following keywords: "(breast OR mammary) AND (cancer OR carcinoma OR malignant OR neoplasm OR tumor) AND (HER-2 OR HER2 OR HER2/neu OR ERBB2 OR human epidermal growth factor receptor 2) AND (positive OR +) AND (brain OR central nervous system) AND (metastasis OR metastases OR metastatic) AND (small-molecule tyrosine kinase inhibitors OR lapatinib OR neratinib OR afatinib OR tucatinib OR pyrotinib)", only in English, without any limits such as time, race, etc. We also went through the American Society of Clinical Oncology (ASCO) and ESMO annual meetings and San Antonio Breast Cancer Symposiums (SABCS) online articles and included articles published before November 01, 2020. The reference of all studies complying with the eligibility criteria was examined for other relevant studies, especially relevant meta-analysis.

Main outcome(s): The outcomes analysis including PFS, CNS ORR, OS, TTP, 6-month PFS rate, 6-month OS rate, 12-month OS rate, median PFS and median OS were conducted based on the investigator-assessed response by RECIST 1.1. The data was also corrected and indicated in the characteristics of inclusive trials. Anemia, neutropenia, thrombocytopenia, vomiting/nausea, diarrhea, stomatitis mucositis, skin and subcutaneous tissue disorders, sensory neuropathy, and hepatic toxicity were considered as the most crucial side effects. The adverse events grade ≥ 3 AEs were calculate with the National Cancer Institute Common Terminology Criteria (NCI-CTC) version 4.0.

Quality assessment / Risk of bias analysis: Study quality of seven included RCTs was accessed by the Cochrane risk of bias tool. Eight single-arm studies were assessed

using the MINORS index scored. We included clinical trials which can ensured their high quality and integrity owing to high heterogeneity may appear in single-arm meta-analysis, and randomized effect model was applied to minimize the bias.

Strategy of data synthesis: The Cochrane Q chi-square test and I2 statistic were used to examine the heterogeneity across studies. The fixed-effects model was used for pooled results with low heterogeneity (I2 ≤ 50 %). If not, the random-effects model was used for analysis. The Begg's and Egger's tests were applied to examine potential publication bias of included clinical trials.

Subgroup analysis: (1) To explore the treatment effect of TKIs with different combinations of drugs across subgroups, subgroup analysis was performed using the following classification variables: TKIs were used alone TKI (Monotherapy), TKIs were combined with capecitabine (TKI+Cap), TKIs were combined with other drugs except capecitabine (TKI+Others); (2) To explore the treatment effect of different type TKI drugs.

Sensitivity analysis: The sensitivity analysis was performed by excluding each study one by one if the pooled values with high heterogeneity.

Country(ies) involved: China.

Keywords: The small-molecule tyrosine kinase inhibitors; HER-2 positive; Breast cancer; Brain metastases; Meta-analysis.

Contributions of each author:

Author 1 - Yushuai Yu.
Email: 1248698628@hotmail.com
Author 2 - Jie Zhang.
Author 3 - Kaiyan Huang.
Author 4 - Yuxiang Lin.
Author 5 - Chuangui Song.
Email: Songcg1971@hotmail.com