INPLASY

First-Line Therapies in EGFR-Mutated Non-Small Cell Lung Cancer with Brain Metastases: A Systematic Review and Meta-Analysis

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ADMINISTRATIVE INFORMATION

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Review Stage at time of this submission - Formal screening of search results against eligibility criteria.

Conflicts of interest - None declared.

INPLASY registration number: INPLASY202460015

Amendments - This protocol was registered with the International Platform of Registered Systematic Review and Meta-Analysis Protocols (INPLASY) on 05 June 2024 and was last updated on 05 June 2024.

INTRODUCTION

Review question / Objective Which first-line treatment regimens provide the best outcomes for patients with epidermal growth factor receptor (EGFR)-mutant non-small cell lung cancer (NSCLC) with brain metastases? Epidermal growth factor receptor (EGFR) mutant non-small cell lung cancer (NSCLC) patients with brain metastases have an extremely poor prognosis. Optimal first-line treatment regimens, whether EGFR tyrosine kinase inhibitors (TKIs) alone, in combination with chemotherapy, vascular endothelial growth factor or its receptor (VEGF/VEGFR) monoclonal antibodies (mAbs) or EGFR-MET bispecific antibodies, remain uncertain.

Rationale The quest to optimize first-line therapeutic strategies for patients with EGFR-mutant NSCLC complicated by BM remains at the forefront of oncology research. Our comprehensive NMA, which pooled data from related RCTs involving EGFR-mutant B patients, provides important insights into the relative efficacy of different therapeutic regimens.

Condition being studied Lung cancer is a leading cause of cancer-related death worldwide, and NSCLC is the predominant type. Approximately 30% to 40% of patients with advanced NSCLC experience brain metastases (BM), which not only has a significant impact on prognosis, but also complicates the selection of treatment strategies. In recent years, the therapeutic armamentarium for EGFR-mutant NSCLC with BM has expanded to include not only generations of EGFR-TKIs with varying degrees of BBB penetration and intracranial antitumor activity but also novel combinations of EGFR-TKIs with chemotherapy, anti-angiogenic agents such as VEGF or VEGFR

mAbs, or EGFR-MET BsAb. These developments of combination therapies have the potential to increase intracranial antitumor efficacy and prolong survival in this high-risk patient population. This study aims to address this critical knowledge gap by conducting a comprehensive network meta-analysis (NMA) that integrates data from multiple RCTs to compare the efficacy of different first-line treatment strategies in EGFR-mutant NSCLC patients with BM. Ultimately, our findings are intended to guide clinical practice by providing clinicians with suggestions for developing individualized treatments for patients with BM and contribute to improved survival in this challenging patient cohort.

METHODS

Search strategy (EGFR-TKIs OR gefitinib OR icotinib OR erlotinib OR afatinib OR dacomitinib OR osimertinib OR aumolertinib OR almonertinib OR furmonertinib OR lazertinib OR amivantamab OR zorifertinib OR AZD3759) AND (NSCLC OR lung cancer) NOT adjuvant NOT neoadjuvant.

Participant or population Patients: untreated NSCLC patients with BM harboring EGFR activating mutations in exon 19 deletion or L858R.

Intervention Interventions: including different generations of EGFR-TKIs or combination regimens based on EGFR-TKI in combination with chemotherapy, anti-angiogenic inhibitors (e.g., VEGFR mAb or TKIs), or EGFR-Met BsAb.

Comparator Comparisons: comparisons between different generations of EGFR-TKIs or their combination therapies.

Study designs to be included Study design: prospective RCTs only, excluding observational studies, case reports, or retrospective analyses.

Eligibility criteria (1) Patients: untreated NSCLC patients with BM harboring EGFR activating mutations in exon 19 deletion or L858R; (2) Interventions: including different generations of EGFR-TKIs or combination regimens based on EGFR-TKI in combination with chemotherapy, anti-angiogenic inhibitors (e.g., VEGFR mAb or TKIs), or EGFR-Met BsAb; (3) Comparisons: comparisons between different generations of EGFR-TKIs or their combination therapies; (4) Outcomes: reporting at least one or more of the following outcomes in NSCLC patients with BM: progression-free survival (PFS), overall survival (OS), objective response rate (ORR), iPFS, intracranial ORR (iORR), intracranial disease control rate (iDCR), or intracranial duration of response (iDOR), with a focus on statistically reported and analyzable data; (5) study design: prospective RCTs only, excluding observational studies, case reports, or retrospective analyses.

Information sources The search covered databases including PubMed, EMBASE and the Cochrane Library.

Main outcome(s) Primary outcomes included OS, PFS, and intracranial PFS. The secondary outcomes included iORR, iDCR and iDOR.

Data management Two investigators independently extracted data from the main text, tables, and figures of each included study into a standardized Microsoft Excel spreadsheet. Extracted data included, but were not limited to, lead author, year of publication, geographic region, total number of patients, number of patients with BM, study design, patient age, gender, treatment regimen, follow-up duration, and PFS, OS, ORR, along with their intracranial equivalents and corresponding HR values. Any disagreements encountered during the data extraction process were resolved through iterative discussions between the reviewers. If consensus could not be reached, a third investigator was consulted to arbitrate and finalize the data entry.

Quality assessment / Risk of bias analysis Study quality was assessed using methods recommended by the Cochrane Collaboration, focusing on random sequence generation, allocation concealment, blinding of participants and personnel, outcome assessment blinding, incomplete outcome data, selective reporting, and other biases. Each criterion was categorized as high, low, or unclear risk.

Strategy of data synthesis Direct comparisons were statistically analyzed using Stata 12.0 software. Primary outcomes for the BM population (ORR, PFS, OS, and HR values) were summarized, with the I^2 statistic used to evaluate heterogeneity between studies. If $p \leq 0.05$ or $I^2 > 50\%$, a random-effects model (DerSimonian-Laird method) was used; otherwise, a fixed-effects model (inverse variance method) was used. Network meta-analyses were performed using R software (version 4.3.2) and the netmeta package (version 2.9.0) to generate network graphs, forest plots, adjusted funnel plots, node split analysis comparing direct and indirect methods, and SUCRA rankings between interventions.

Subgroup analysis Node split analysis comparing direct and indirect methods, and SUCRA rankings between interventions.

Sensitivity analysis Leave-one-out sensitivity analyses will be conducted if necessary.

Language restriction English.

Country(ies) involved China.

Keywords NSCLC；EGFR；Brain Metastases；Network Meta-Analysis.

Contributions of each author

Author 1 - Jietao Ma - Author 1 drafted the manuscript.
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Author 6 - Xiaoxue Pang - The author contributed to the development of the selection criteria, and the risk of bias assessment strategy.