INPLASY PROTOCOL

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Corresponding author:
Zhang Yao

hulunbeier0223@aliyun.com

Author Affiliation:
First Teaching Hospital of Tianjin University of Traditional Chinese Medicine.

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None declared.

Traditional Chinese medicine combined with EGFR-TKIs in the treatment of advanced non-small cell lung cancer with classical EGFR mutations

Zhang, Y[1].

Review question / Objective: **Traditional Chinese medicine (TCM) has been used for NSCLC patients receiving EGFR-TKIs for more than 10 years as an adjuvant treatment. Studies were searched from Chinese National Knowledge Infrastructure, Wanfang Database, MEDLINE (PubMed), and Cochrane Library from January 2003 and January 2023. Randomized controlled clinical trials and retrospective cohort studies comparing EGFR-TKIs + TCM versus EGFR-TKIs with/without placebo in participants with advanced NSCLC harboring EGFR sensitizing mutation were included in this study. Two authors screened all references, assessed the risk of bias and extracted data independently. Data were summarized using hazard ratio (HR) and risk ratios (RR), with 95% confidence intervals (CI) for binary outcomes. Overall quality of evidence was assessed using GRADE.**

INPLASY registration number: This protocol was registered with the International Platform of Registered Systematic Review and Meta-Analysis Protocols (INPLASY) on 10 February 2023 and was last updated on 10 February 2023 (registration number INPLASY202320042).

INTRODUCTION

Review question / Objective: **Traditional Chinese medicine (TCM) has been used for NSCLC patients receiving EGFR-TKIs for more than 10 years as an adjuvant treatment. Studies were searched from Chinese National Knowledge Infrastructure, Wanfang Database, MEDLINE (PubMed), and Cochrane Library from January 2003 and January 2023. Randomized controlled clinical trials and retrospective cohort studies comparing EGFR-TKIs + TCM versus EGFR-TKIs with/without placebo in participants with advanced NSCLC harboring EGFR sensitizing mutation were included in this study. Two authors screened all references,**

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Condition being studied: Non-small cell lung cancer (NSCLC) is the leading cause of cancer-related deaths worldwide. Lung cancer caused 1.8 million deaths worldwide in 2020, accounting for nearly one-fifth of the total deaths from malignant tumors. Most of NSCLC cases are diagnosed at inoperable advanced stage. Discovery of driving genes such as EGFR mutation (mainly exon 19 Del and exon 21L858R), and development of epidermal growth factor receptor (EGFR) tyrosine kinase inhibitors (EGFR-TKIs), such as gefitinib, erlotinib, icotinib and osimertinib have significantly improved prognosis of advanced NSCLC patients harboring EGFR sensitizing mutation. Despite initial therapeutic responses, most patients acquire resistance to EGFR-TKIs and report significant disease progress within 9–11 months, and although Osimertinib was designed for "secondary resistance", it can develop again after 10 months of treatment. The mechanism of resistance has many similarities with the first and second generations drugs, but it is not the same. TCM treatment is characterized by multi-level and comprehensive regulation. Combining the holistic regulation of TCM with the precise targeting characteristics of EGFR-TKIs can produce complementarity at the macro and micro levels. Therefore, various study on traditional Chinese medicine and targeted combination therapy are increasing day by day, becoming an important direction in the exploration of traditional Chinese medicine and combination therapy mode.

METHODS

Participant or population: The participants with advanced NSCLC harboring EGFR sensitizing mutation were included in this study.

Intervention: Epidermal growth factor receptor tyrosine kinase inhibitors （EGFR-TKIs） + traditional Chinese medicine (TCM).

Comparator: Comparing EGFR-TKIs + TCM versus EGFR-TKIs with/without placebo.

Study designs to be included: Randomized controlled clinical trials and retrospective cohort studies.

Eligibility criteria: ①Type of studies: all randomized controlled trials and retrospective cohort studies published in English or Chinese between January 2003 and January 2023. were considered, regardless of blinding. ②Type of Participants: participants with pathologically or cytologically confirmed with inoperable stage III-IV NSCLC, harboring sensitive EGFR mutation and with Eastern Cooperative Oncology Group (ECOG) performance status (PS) scores of 0–3 or Karnofsky Performance Status (KPS) scores above 60 without major organ dysfunction were included in the study. ③Type of Intervention: EGFR-TKIs + TCM. TCM was either administered orally, externally or intravenously. EGFR-TKIs include all first-line recommended drugs recommended in the NCCN guidelines, such as gefitinib, erlotinib, icotinib, osimertinib, etc. ④ Types of controls: TKIs ± placebo group received the same EGFR-TKIs as intervention group, with or without placebo. ⑤Types of outcome measures: primary outcomes were PFS, which was measured with the date of videography from a random assignment to the date of objective progression or death by the researcher. Secondary endpoints included a comparison of overall survival (OS), ORR, disease control rate (DCR), 1- and/or 2-years survival rate, KPS, QoL and safety. QoL was evaluated with the Functional Assessment of Cancer Therapy–Lung (FACT-L) questionnaire. Safety was evaluated based on common terminology criteria for adverse events (CTCAE) version 3.0 guidelines.

Information sources: Articles were searched in Chinese National Knowledge Infrastructure (CNKI), Wanfang database, MEDLINE (PubMed), and Cochrane Library from January 2003 to January 2023.Search terms included "non-small cell lung cancer", "NSCLC", "epidermal growth factor receptor", "EGFR TKI", "traditional Chinese medicine", "Chinese herbal medicine" and "randomized controlled trial"," retrospective cohort study".

Main outcome(s): Outcome measurements: primary outcomes: PFS; secondary outcomes: OS, ORR, DCR, 1- and/or 2-years survival rate, QoL, KPS, and toxicity (overall AE, rash, diarrhea, hepatic dysfunction and dental ulcer).

Quality assessment / Risk of bias analysis: Cochrane Risk Bias Assessment Tool 5.1.0 was used to evaluate the design and methods of included papers, and risk of bias and applicability. Methodological issues related to quality of randomized controlled trials and retrospective cohort studies were generation of treatment allocation, concealment of treatment, blinding, completeness of the resulting data, selective reporting of findings, and other potential risks of bias. Presence of potential biases within the studies was reported descriptively.

Strategy of data synthesis: Meta-analysis was performed using Review Manager 5.4 software. Statistical analysis was performed following the statistical guidelines cited in the latest Cochrane Handbook for Systematic Reviews of Interventions. Chi-squared test for heterogeneity was performed, and heterogeneity might not be important when I2 was 0–40%. Moderate heterogeneity was present when I2 was 30–60%. Substantial heterogeneity was present when I2 was 50–90%. Considerable heterogeneity was present when I2 was 75–100%, in which case, meta-analysis was not performed and the source of heterogeneity was explored. Random-effect model was used for meta-analysis. Effectiveness on PFS was presented with hazard ratio (HR) and 95% confidential interval (CI). Effectiveness on ORR, DCR and AE were presented with risk ratio (RR) and 95% CI. Description analysis was performed when quantitative data could not be pooled. Funnel plots were generated to analyze potential publication bias. GRADE was used to assess overall quality of evidence.

Subgroup analysis: Subgroup data based on sex (male vs female), age (<65vs≥65), ECOG PS (0 vs 1 vs 2), staging (IIIb vs IV), smoking status (yes vs no), EGFR mutation status (19 Del vs 21L858R vs other rare mutations), TKIs (different types of targeted drugs) and CHM prescriptions.

Sensitivity analysis: Random-effect model was used for meta-analysis. Effectiveness on PFS was presented with hazard ratio (HR) and 95% confidential interval (CI). Effectiveness on ORR, DCR and AE were presented with risk ratio (RR) and 95% CI.Chi-squared test for heterogeneity was performed, and heterogeneity might not be important when I2 was 0–40%. Moderate heterogeneity was present when I2 was 30–60%. Substantial heterogeneity was present when I2 was 50–90%. Considerable heterogeneity was present when I2 was 75–100%, in which case, meta-analysis was not performed and the source of heterogeneity was explored.

Country(ies) involved: China.

Keywords: Non-small cell lung cancer; Traditional Chinese Medicine; EGFR-TKIs; Effectiveness; Safety

Contributions of each author:
Author 1 - Zhang yao.