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Corresponding author:
Xueyan Wang

1406960652@qq.com

Author Affiliation:
Guizhou University of Traditional Chinese Medicine.

A meta-analysis of the clinical efficacy and safety of Traditional Chinese Medicine in combination with PD-1/PD-L1 inhibitors in patients with non-small cell lung cancer

Wang, XY[1]; Pan, LJ[2]; Wang, FQ[3]; Yang, B[4]; Tang, DX[5].

ADMINISTRATIVE INFORMATION

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Review Stage at time of this submission - Data analysis.

Conflicts of interest - None declared.

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Amendments - This protocol was registered with the International Platform of Registered Systematic Review and Meta-Analysis Protocols (INPLASY) on 16 June 2023 and was last updated on 16 June 2023.

INTRODUCTION

Review question / Objective The inclusion criteria, based on the PICOS acronym, were as follows: Participants (P): Patients with a diagnosis of NSCLC by pathology, diagnostics, and imaging in accordance with the Clinical Practice Guidelines for Molecular Pathology Testing of Non-Small Cell Lung Cancer and the NCCN Clinical Guidelines for the Management of Non-Small Cell Lung Cancer . There were no gender, race, or country restrictions. Patients were fully informed about the study and voluntarily signed a written informed consent. The study was approved by the hospital ethics committee. Patients with other malignant neoplasms, infectious diseases, hypersensitivity to the test drug, severe underlying diseases, combined congenital or acquired cellular immune dysfunction, immune system disorders, psychiatric or psychological disorders, or non-compliance with the study were excluded.
Intervention (I): Randomised clinical trials (RCTs) of traditional Chinese medicine in combination with PD-1/PD-L1 inhibitors were included. There was no restriction on the type of Chinese medicine and

no restriction on whether it was combined with chemotherapy.
Comparison (C): In the control group, patients with NSCLC received PD-1/PD-L1 inhibitor regimens, with no restriction on whether they were combined with chemotherapy.
Outcome (O): Clinical efficacy and safety of the herbal combination.
Study design(s): randomised controlled clinical trial.
Outcome measures include short-term clinical efficacy ORR and DCR, adverse drug reactions (ADRs), tumour markers and associated factors CA125 and CYFRA21-1, T-lymphocyte subsets CD3+, CD4+, CD4+/CD8+ and post-treatment Karnofsky Performance Status (KPS) scores.

Condition being studied Lung cancer has the highest incidence and mortality rate of any malignancy worldwide.It is estimated that 80-85% of lung cancer patients have non-small cell lung cancer, the main types of which are adenosquamous, large cell, adenocarcinoma and squamous cell carcinoma, and non-small cell lung cancer lacks typical symptoms in its early stages, and most patients have advanced disease by the time they are diagnosed. The National Comprehensive Cancer Network (NCCN) has published the 2nd edition of the NCCN Clinical Practice Guidelines in Oncology: Non-Small Cell Lung Cancer, in February 2023 , which focuses on diagnostic principles, diagnosis and treatment of various lung cancers, and immunotherapy, etc. In immunotherapy, immune checkpoint inhibitors are one of the modalities widely used in the clinical treatment of NSCLC, and immune checkpoint inhibitors, such as programmed cell death receptor 1/programmed cell death receptor ligand 1 (PD-1/PD-L1) monoclonal antibodies, have been shown to improve the survival of lung cancer patients. At the same time, however, immune checkpoint inhibitors can cause serious side effects such as endocrine dysregulation, Immune pneumonia, hypothyroidism and skin damage , and a large proportion of patients still have poor outcomes with ICIs. How to further improve the efficacy of ICIs for the benefit of patients has become the focus of current research.

METHODS

Search strategy Keywords searched included non-small cell lung cancer, PD-1/PD-L1 inhibitors, immune checkpoint inhibitors, soups/dispersions/pills/granules/capsules/injections, Traditional Chinese Medicine/Chinese patent medicine, combination therapy. The search formula is as follows (((Traditional Chinese medicine) OR (Chinese medicine combined)) AND (PD-1 or PD-L1 inhibitors)) AND (Non-small cell lung cancer), (((Traditional Chinese medicine) OR (Chinese medicine combined)) AND (Non-small cell lung cancer)) AND (Pabrolizumab), (((Traditional Chinese medicine) OR (Chinese medicine combined)) AND (Non-small cell lung cancer)) AND (Navulizumab) , etc. The title and abstract were screened independently and then the full text of the relevant literature was read to determine eligibility.

Participant or population A total of 14 randomised controlled clinical trials were included in this study, with a total of 514 patients in the TCM combination treatment group and 506 patients in the control group.

Intervention The test group was a combination of Traditional Chinese Medicine (oral and injectable) combined with PD-1/PD-L1 inhibitors with or without chemotherapy; the control group was PD-1/PD-L1 inhibitors with or without chemotherapy. A subgroup analysis was performed for the effect of chemotherapy.

Comparator TCM combined with PD-1/PD-L1 inhibitor with or without chemotherapy in the trial group; PD-1/PD-L1 inhibitor with or without chemotherapy in the control group.

Study designs to be included Randomized controlled clinical trial.

Eligibility criteria Exclusion criteria: Studies with (i) non-randomised controlled trials, (ii) incomplete outcomes, and (iii) insufficient data were excluded. Primary outcomes included three efficacy indicators: short-term and long-term clinical outcomes and adverse drug reactions (ADRs) according to World Health Organization (WHO) criteria and Response Evaluation Criteria in Solid Tumours (RECIST). (1) Short-term clinical outcomes: Short-term tumour remission includes complete remission (CR), partial remission (PR), stable remission (SD), progressive remission (PD), ORR and disease control rate (DCR).

Information sources The seven electronic databases including PubMed, Cochrane Library, Excerpt Medica Database (Embase), Web of Science (WOS), Chinese Biomedical Literature Database (CBM), China National Knowledge Infrastructure (CNKI), and Wan-fang Database were systematically searched for eligible studies from 2000 to June 2023.

Main outcome(s) Clinical efficacy and safety of the herbal combination.Outcome measures include short-term clinical efficacy ORR and DCR, adverse drug reactions (ADRs), tumour markers and associated factors CA125 and CYFRA21-1, T-lymphocyte subsets CD3+, CD4+, CD4+/CD8+ and post-treatment Karnofsky Performance Status (KPS) scores.

Quality assessment / Risk of bias analysis The Cochrane risk of bias tool Review Manager 5.4 was used to assess the quality of the trials. The review criteria covered seven areas, including random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessments, incomplete outcome data, selective reporting and other sources of bias. The included studies were assessed at three levels: low, unclear and high risk of bias.

Strategy of data synthesis Literature searches in both international (Cochrane Library, PubMed, EMBASE and Web of Science) and Chinese (CBM, CNKI and Wan-fang Database) databases will be systematically searched for eligible studies from 2000 to June 2023, were conducted independently by two researchers (Wang Xue-yan and Pan Li-jun). Keywords searched included non-small cell lung cancer, PD-1/PD-L1 inhibitors, immune checkpoint inhibitors, soups/dispersions/pills/granules/capsules/injections, Traditional Chinese Medicine/Chinese patent medicine, combination therapy. The search formula is as follows (((Traditional Chinese medicine) OR (Chinese medicine combined)) AND (PD-1 or PD-L1 inhibitors)) AND (Non-small cell lung cancer), (((Traditional Chinese medicine) OR (Chinese medicine combined)) AND (Non-small cell lung cancer)) AND (Pabrolizumab), (((Traditional Chinese medicine) OR (Chinese medicine combined)) AND (Non-small cell lung cancer)) AND (Navulizumab) , etc. The title and abstract were screened independently and then the full text of the relevant literature was read to determine eligibility. Any discrepancies were discussed with a third researcher (Dongxin Tang). In addition, the original report and references listed in previous reviews were checked.

Subgroup analysis We divided ORR and DCR into two subgroups for meta-analysis: combination chemotherapy group and non-combination chemotherapy group.
We further performed subgroup analysis for CD3+,CD4+ and CD4+/CD8+ in the oral herbal medicine combined with PD-1/PD-L1 inhibitors and chemotherapy group and the oral herbal medicine combined with PD-1/PD-L1 inhibitors non-chemotherapy group.

Sensitivity analysis: To assess the stability of the results. The meta-analysis of the remaining literature was combined after sequentially excluding one literature, and the changes in the combined results were observed to assess whether the results of the original meta-analysis were significantly changed by certain studies.

Country(ies) involved China.

Keywords Traditional Chinese Medicine; PD-1/PD-L1 inhibitors ;non-small cell lung cancer; Chemotherapy; Combination therapy; meta-analysis.

Contributions of each author

Author 1 - Xueyan Wang.
Email: 1406960652@qq.com
Author 2 - Lijun Pan.
Email: 13025640@qq.com
Author 3 - Feiqing Wang.
Email: kele190615@163.com
Author 4 - Bing Yang.
Author 5 - Dongxin Tang.
Email: tangdongxin1204@sina.com