INPLASY PROTOCOL

To cite: Wei et al. Efficacy and safety of traditional Chinese medicine combined with immune checkpoint inhibitors in the treatment of primary liver cancer: A protocol for systematic review and meta-analysis. Inplasy protocol 202230010. doi: 10.37766/inplasy2022.3.0010

Received: 02 March 2022

Published: 02 March 2022

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Support: **None.**

Review Stage at time of this submission: **Preliminary searches.**

Conflicts of interest:
None declared.

Efficacy and safety of traditional Chinese medicine combined with immune checkpoint inhibitors in the treatment of primary liver cancer: A protocol for systematic review and meta-analysis

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Review question / Objective: **This study aimed to comprehensively and systematically analyze the safety and efficacy of immune checkpoint inhibitors (ICIs) combined with traditional Chinese medicine (TCM) in the treatment of patients with primary liver cancer (PLC). This systematic review will solve the following questions: Whether TCM can improve the quality of life of patients by alleviating immune-related adverse events (irAEs), and whether TCM combined with ICIs can prolong the survival time of patients with PLC.**
Condition being studied: **Primary liver cancer is currently the third most lethal cancer, and the morbidity and mortality are increasing year by year. Immunotherapy (specifically ICIs) offers new opportunities for patients with PLC. However, with the use of ICIs, irAEs have become a thorny problem in clinical practice. The main clinical manifestations are skin toxicity, hepatotoxicity and gastrointestinal toxicity, and for some patients, severe irAEs will lead to termination of treatment or death. Studies have found that TCM, as an auxiliary method for the treatment of PLC, can bidirectional regulate immune function and alleviate the occurrence of irAEs related symptoms while treating PLC. However, no systematic review has been conducted for this objective. Therefore, we need a meta-analysis to evaluate the efficacy and safety of TCM combined with ICIs.**

INPLASY registration number: This protocol was registered with the International Platform of Registered Systematic Review and Meta-Analysis Protocols (INPLASY) on 02 March 2022 and was last updated on 02 March 2022 (registration number INPLASY202230010).

INTRODUCTION

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medicine (TCM) in the treatment of patients with primary liver cancer (PLC). This systematic review will solve the following questions: Whether TCM can improve the quality of life of patients by alleviating immune-related adverse events (irAEs), and whether TCM combined with ICIs can prolong the survival time of patients with PLC.

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METHODS

Participant or population: All participants had been diagnosed with PLC, regardless of gender, race and age.All participants were diagnosed with PLC, regardless of gender, race and age.

Intervention: The intervention method of the treatment group is the combination of ICIs and TCM. ICIs include anti-CTLA4, anti-PD1 and anti-PDL1.

Comparator: The control group can use ICIs only, placebo or conventional treatment.

Study designs to be included: Clinical randomized controlled trials (RCT) published before March 2022 will be selected without any geographical and language restrictions. Basic experiments, case reports, retrospective studies and reviews are excluded.

Eligibility criteria: The inclusion criteria are as follows: (1) the patients meet the internationally recognized staging and diagnostic criteria for PLC, regardless of race, age and gender; (2) the experimental research type is RCT; (3) the experimental group uses TCM combine with ICIs for the treatment of PLC, and the control group could be ICIs only, placebo or conventional treatment; The exclusion criteria are as follows: (1) the participants did not meet the diagnostic criteria of PLC. (2) study on metastatic liver cancer; (3) study on treatment of PLC without ICIs; (4) non-RCT study; (5) research with incomplete data; (6) basic experiments, case reports, retrospective studies, reviews.

Information sources: We will search the following electronic databases in this study: PubMed, Web of Science, Embase, Cochrane Library, China National Knowledge Infrastructure, China Science and Technology Journal Database, Chinese BioMedical Literature Database and Wanfang databases. Since the establishment of the database until March 1, 2022, there are no restrictions on search language, publication time, and publication status. The following medical keywords to search, including “Traditional Chinese medicine”, “Immune checkpoint inhibitor” and “primary liver cancer” of all synonyms and derivatives for all search fields. At the same time, we will manually search all reference lists from relevant systematic reviews to find other eligible studies. The purpose is to find RCT studies on ICIs and their combination with TCM in the treatment of PLC.

Main outcome(s): Overall survival, progression-free survival.

Additional outcome(s): Remission rate of irAEs, Karnofsky performance score (KPS).

Quality assessment / Risk of bias analysis: The two researchers will use the Cochrane risk bias assessment tool to evaluate the

quality of the included RCTs. The contents of evaluation include random allocation method; the distribution method is hidden; blind method; results data integrity; selective reporting of research results; other sources of bias. Through the evaluation of the above contents, the two researchers will designate each study as low risk of bias, uncertain risk of bias or high risk of bias. When two researchers disagree on the evaluation of the study, they can discuss and solve it, and the third researcher can participate in the evaluation if necessary. We will use funnel plots to publish bias.

Strategy of data synthesis: We will use RevMan 5.3 software for data analysis. The combined effect size of each study is calculated, that the binary variables are expressed by hazard ratio, and the continuous variables are expressed by standardized or weighted mean difference. The heterogeneity of the results is represented by P value and I2. When I2< 50% and P > 0.05, it indicates that the level of heterogeneity is low, and the fixed effect model will be used for data synthesis; When I2 ≥ 50% and P ≤ 0.05, it indicates significant heterogeneity, then the random effect model will be used for data synthesis. Subgroup analysis and sensitivity analysis are performed according to possible heterogeneity source factors.

Subgroup analysis: If necessary, we will conduct subgroup analysis on the factors that may lead to the source of heterogeneity, such as the number of cases, age, intervention measures and treatment time.

Sensitivity analysis: By excluding low-quality studies or different statistical methods, the combined effect size was re-estimated and compared with the previous meta-analysis results to explore the robustness of the results.

Country(ies) involved: China.

Keywords: primary liver cancer, immune checkpoint inhibitors, traditional Chinese medicine, protocol, meta-analysis.

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