INPLASY PROTOCOL

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None declared.

Efficacy and safety of Chinese herbal medicine combined with chemotherapeutics in the treatment of hepatocellular carcinoma: A systematic review and meta-analysis protocol

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Review question / Objective: **Chemotherapeutics combined with Chinese herbal medicines are a common treatment in China. However, we did not find a meta-analysis on the synergistic effects of Chinese herbal medicines combined with chemotherapeutics. Therefore, this systematic review and meta-analysis aimed to evaluate the efficacy and safety of chemotherapeutics and Chinese herbal medicine in the treatment of hepatocellular carcinoma.This study provides evidence-based medical evidence for chemotherapeutics combined with Chinese herbal medicine in the treatment of hepatocellular carcinoma and provides new ideas and methods.**
Information sources: **PubMed, Web of Science, Embase, AMED, Cochrane Library, CNKI, VIP, CBM, and Wanfang databases.**

INPLASY registration number: This protocol was registered with the International Platform of Registered Systematic Review and Meta-Analysis Protocols (INPLASY) on 11 January 2022 and was last updated on 11 January 2022 (registration number INPLASY202210050).

INTRODUCTION

Review question / Objective: **Chemotherapeutics combined with Chinese herbal medicines are a common treatment in China. However, we did not find a meta-analysis on the synergistic effects of Chinese herbal medicines combined with chemotherapeutics. Therefore, this systematic review and meta-analysis aimed to evaluate the efficacy and safety of chemotherapeutics and Chinese herbal medicine in the treatment of hepatocellular carcinoma.This study provides evidence-based medical evidence for chemotherapeutics combined**

with Chinese herbal medicine in the treatment of hepatocellular carcinoma and provides new ideas and methods.

Condition being studied: Hepatocellular carcinoma is a common malignant tumor. Chemotherapeutics combined with traditional Chinese medicine to treat tumors have gradually become the focus of complementary and alternative treatments for HCC. This therapy can not only reduce the clinical symptoms of patients but also inhibit the progression of tumors17. Chemotherapeutics combined with Chinese herbal medicine in the treatment of hepatocellular carcinoma emphasize the overall efficacy and play an important role in inhibiting tumor cell proliferation, regulating immune function, improving clinical symptoms, and reducing the damage from radiotherapy and chemotherapy. Therefore, the combination of chemotherapeutics and Chinese herbal medicine in the treatment of hepatocellular carcinoma has broad prospects for development.This study provides evidence-based medical evidence for chemotherapeutics combined with Chinese herbal medicine in the treatment of hepatocellular carcinoma and provides new ideas and methods.

METHODS

Search strategy: As of January 5th, 2022, we had searched the PubMed, Web of Science, Embase, AMED, Cochrane Library, CNKI, VIP, CBM, and Wanfang databases. The search time and language were not limited. We used a combination of medical keywords to search, including "chemotherapeutics", "Chinese herbal medicine", and "hepatocellular carcinoma". At the same time, we manually searched all reference lists from related systematic reviews to identify other eligible studies. We used Review Manager 5.3 software provided by the Cochrane Collaboration Network to perform statistical analysis. This study included clinical randomized controlled trials that studied chemotherapeutics combined with Chinese herbal medicine in the treatment of hepatocellular carcinoma. The study selection, data extraction and research quality evaluation were independently completed by two researchers. Then, we assessed the quality and risk of the included studies and observed the outcome indicators.

Participant or population: The inclusion criteria were as follows: (1) the study population included patients aged ≥ 18 years, sex was not limited, and HCC was clearly diagnosed;The exclusion criteria were as follows: (1) patients with nonhepatocellular carcinoma; (2) the experimental group was given treatments other than chemotherapeutics combined with Chinese herbal medicines.

Intervention: The experimental group was treated with chemotherapeutics combined with Chinese herbal medicine. Outcome measuresSerological indicators: The main observation indicators were AFP, ALT, TBIL and ALP levels. The secondary observation indices mainly included CD3+, CD4+, CD8+, CD4+/CD8+, and NK cell levels.Physical strength score, quality of life QOL score and quantitative score of TCM syndromes: All patients received KPS stamina scores, quality of life (QOL) scores and TCM syndrome quantitative scores before treatment and 4 months after treatment. The KPS physical strength score adopts the Koofsky score method. The quality of life (QOL) score is based on the quality of life score of cancer patients and was established in 1990. The quantitative TCM syndrome scores are formulated with reference to the main clinical manifestations of each syndrome of liver cancer.Clinical efficacy evaluation: According to the WHO's unified standards for the evaluation of the efficacy of solid tumors, all patients should be re-examined with upper abdominal CT after 4 months of treatment, and are divided into complete remission (CR), partial remission (PR), stable (NC) and progression (PD), and the sum of CR and PR is the total effective rate. Toxic side effects: During treatment, gastrointestinal reactions, decreased blood.

Comparator: The control group was treated with chemotherapeutics.

Study designs to be included: This research was conducted based on the first choice report project of a systematic review and meta-analysis (PRISMA-P). Two researchers used the Cochrane risk of bias assessment tool to separately assess the quality of the randomized studies. This study was a retrospective study and meta-analysis, the results were reported according to the PRISMA guidelines.

Eligibility criteria: Inclusion and exclusion criteria: The inclusion criteria were as follows: (1) the study population included patients aged ≥ 18 years, sex was not limited, and HCC was clearly diagnosed; (2) the study was a randomized controlled trial (RCT); and (3) the experimental group was treated with chemotherapeutics combined with Chinese herbal medicine. The control group was treated with chemotherapeutics. The exclusion criteria were as follows: (1) patients with nonhepatocellular carcinoma; (2) the experimental group was given treatments other than chemotherapeutics combined with Chinese herbal medicines; (3) the control group did not receive a placebo; and (4) The study was not a randomized controlled trial (RCT). The two researchers independently performed a literature search, screening and data extraction based on predetermined search strategies, literature inclusion and exclusion criteria, and data extraction tables. We did not include conference records, reviews, meta-analyses, newspapers, guides, letters or other documents. The research selection process is represented by the PRISMA flowchart. When the required information was missing for analysis, the author of the study was contacted for data. The two authors independently evaluated the methodological quality of the included studies according to the Cochrane manual guidelines and the results were reported according to the PRISMA guidelines. During the research period, any differences between the researchers were resolved through discussion or negotiation with another researcher until a consensus was reached, Two researchers used the Cochrane risk of bias assessment tool to separately assess the quality of the randomized studies. The evaluated content included whether the random method was correct; whether allocation concealment was achieved; whether a blinding method was implemented; whether the result data were complete; whether there was selective reporting bias; and whether there were other biases. We used Begg's and Egger's tests, a $P<0.1$ was considered statistically significant, and a funnel chart was used to evaluate publication bias. When the evaluation quality of the research was inconsistent, it was resolved by consensus of all authors.

Information sources: PubMed, Web of Science, Embase, AMED, Cochrane Library, CNKI, VIP, CBM, and Wanfang databases.

Main outcome(s): Outcome measures. Serological indicators: The main observation indicators were AFP, ALT, TBIL and ALP levels. The secondary observation indices mainly included CD3+, CD4+, CD8+, CD4+/CD8+, and NK cell levels. Physical strength score, quality of life QOL score and quantitative score of TCM syndromes: All patients received KPS stamina scores, quality of life (QOL) scores and TCM syndrome quantitative scores before treatment and 4 months after treatment. The KPS physical strength score adopts the Koofsky score method. The quality of life (QOL) score is based on the quality of life score of cancer patients and was established in 1990. The quantitative TCM syndrome scores are formulated with reference to the main clinical manifestations of each syndrome of liver cancer. Clinical efficacy evaluation: According to the WHO's unified standards for the evaluation of the efficacy of solid tumors, all patients should be re-examined with upper abdominal CT after 4 months of treatment, and are divided into complete remission (CR), partial remission (PR), stable (NC) and progression (PD), and the sum of CR and PR is the total effective rate. Toxic side effects: During treatment, gastrointestinal reactions, decreased blood pictures, and peripheral nerve damage

should be recorded. Adverse events should be reported as a result of safety.

Quality assessment / Risk of bias analysis: Two researchers used the Cochrane risk of bias assessment tool to separately assess the quality of the randomized studies. The evaluated content included whether the random method was correct; whether allocation concealment was achieved; whether a blinding method was implemented; whether the result data were complete; whether there was selective reporting bias; and whether there were other biases. We used Begg's and Egger's tests, a P<0.1 was considered statistically significant, and a funnel chart was used to evaluate publication bias. When the evaluation quality of the research was inconsistent, it was resolved by consensus of all authors.

Strategy of data synthesis: We used Review Manager software (REVMAN v5.3 Cochrane Collaboration) to meta-analyze the included literature, and a P0.05 and I2 <50%, there was homogeneity among the studies, and the fixed effects model was used for meta-analysis. If P ≤0.05 and I2 ≥50%, there was heterogeneity among the studies. Sensitivity analysis was used to analyze the sources of heterogeneity. After excluding the influence of clinical heterogeneity, the random effects model was used for meta-analysis.

Subgroup analysis: We used Review Manager software (REVMAN v5.3 Cochrane Collaboration) to meta-analyze the included literature, and a P0.05 and I2 <50%, there was homogeneity among the studies, and the fixed effects model was used for meta-analysis. If P ≤0.05 and I2 ≥50%, there was heterogeneity among the studies. Sensitivity analysis was used to analyze the sources of heterogeneity. After excluding the influence of clinical heterogeneity, the random effects model was used for meta-analysis.

Sensitivity analysis: We used Review Manager software (REVMAN v5.3 Cochrane Collaboration) to meta-analyze the included literature, and a P0.05 and I2 <50%, there was homogeneity among the studies, and the fixed effects model was used for meta-analysis. If P ≤0.05 and I2 ≥50%, there was heterogeneity among the studies. Sensitivity analysis was used to analyze the sources of heterogeneity. After excluding the influence of clinical heterogeneity, the random effects model was used for meta-analysis.

Country(ies) involved: China.

Keywords: chemotherapeutics, Chinese herbal medicine, hepatocellular carcinoma, meta-analysis, protocol, safety, systematic review.

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