Outcomes of Chinese herb medicine for the treatment of multidrug-resistant tuberculosis: a systematic review and meta-analysis

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ABSTRACT

Several studies have suggested that Chinese herb medicine (CHM) in combination with chemotherapy has efficacy in the treatment of multidrug-resistant tuberculosis (MDR-TB). The purpose of this meta-analysis was to assess the efficacy of CHM as a concomitant therapy for MDR-TB. Six databases were searched up to October 2014. Controlled trials comparing CHM combined with chemotherapy (treatment group) with chemotherapy alone (control group) for the treatment of MDR-TB were analyzed. Twenty studies, comprising 1823 patients across China, were included in this review. The meta-analysis showed CHM combined with chemotherapy was associated with a superiority in treatment success (odds ratio [OR], 1.33; 95% confidence interval [CI]: 1.15–1.54; $P < 0.001$), and radiological improvement (OR, 1.32; 95% CI: 1.14–1.52; $P < 0.001$). Patients who received CHM combined with chemotherapy were associated with a similar likely to relapse (OR, 0.88; 95% CI: 0.62–1.25, $P = 0.478$). CHM combination with chemotherapy appeared to be associated with a low incidence of adverse effects for MDT-TB treatment. According to the pooled results and the poor quality of the included trials, it might be uncertainty that there was a superiority of CHM combined with chemotherapy for treating MDR-TB. More rigorous controlled trials are required to substantiate or refute these early findings.

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1. Introduction

Multidrug-resistant (MDR) tuberculosis (TB) is more difficult to treat than drug-susceptible TB. The main problems include the limited availability of effective drugs, the reduced efficacy of second-line drugs, the increased number of adverse reactions to the drugs, and the long duration of therapy. In 2011, there were an estimated 310,000 cases of MDR-TB among the world's 8.7 million prevalent cases of TB. China, India, Russian Federation and South Africa have almost 60% of the world's MDR-TB cases.[1] Treatment guidelines for MDR-TB has been already published; however, treatment outcomes for MDR-TB are poor. Thus, information on safety, tolerability and efficacy of other drugs and approaches potentially useful in treatment is urgent to improve individual outcomes and control the spread of MDR-TB.

In modern time, Chinese medicine practitioners use Chinese herb medicine (CHM) as an adjunctive method for conventional TB chemotherapy to manage MDR-TB, claiming that CHM can help stimulate the immune system, alleviate the adverse effects of conventional TB chemotherapy, improve quality of life, and even promote sputum culture conversion to negative. Basic studies have also proved evidence supporting the beneficial effects of CHM in TB. The previous research showed that some Chinese herbs could inhibit the growth of M. tuberculosis in vitro and in vivo.[2] Lots of clinical trials have also tested and used CHM as a concomitant therapy for MDR-TB. However, the ability of MDR-TB patients to respond to CHM has still been questioned. Therefore, we performed a systematic review and meta-analysis to evaluate the efficacy of CHM for MDR-TB.

2. Methods

In the present study, we examined whether CHM combined with chemotherapy could improve treatment efficacy, and reduce the incidence of chemotherapy-related adverse effects compared with

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chemotherapy alone for MDR-TB. This meta-analysis was completed in accordance with the quality of reporting of meta-analyses statement, and the current practices for conducting systematic review and meta-analysis of the literatures.[3,4]

2.1. Search strategy and selection criteria

The following electronic databases were retrieved and no language restriction was applied:

1. WANGFAN (wangfan database, 1990–October 2014).
2. CBM (China BioMedical Literature Database, 1979–October 2014).
3. CNKI (China Knowledge Resource Integrated Database, China academic journals, conference proceedings, and theses; 1979–October 2014).
4. EMBASE (1980–October 2014).
5. MEDLINE (1966–October 2014).
6. The Cochrane Central Register of Controlled Trials (1991–October 2014).

The common search strategy in the study is listed as below, and Chinese language database was retrieved with similar search strategy.

1. Clinical trial.mp.
2. Clinical study.mp.
3. Efficacy.mp.
4. Effectiveness.mp.
5. 1 OR 2 OR 3 OR 4.
6. Random$.mp.
7. Tuberculosis.mp.
8. Drug-resistant.mp.
9. Multidrug resistant.mp.
10. multi-drug resistant.mp.
11. MDR.mp.
12. Multiple drug-resistant.mp.
13. 7 AND 8 OR 9 OR 10 OR 11 OR 12.
14. Herb$.mp.
15. Herbal medicine.mp.
16. Chinese medicine.mp.
17. 14 OR 15 OR 16.
18. 5 AND 6 AND 13 AND 17.

Two reviewers (H.-B.X. and R.-H.J.) selected articles in the following two stages: titles and abstracts, and then full-text articles. Discrepancies between the two reviewers were resolved by consensus or through discussion with a third reviewer (J. F.). The ratings given by the two reviewers were in complete agreement.

2.2. Selection of studies

Studies were required to meet the following inclusion criteria: (1) treatment outcome definitions specified by mycobacterial culture endpoints; (2) studies used CHM combination with chemotherapy as the treatment group, chemotherapy alone as the control group; (3) articles were written in either English or Chinese language; and (4) at least 10 patients in each group. When two or more articles reported the same data, the most recently updated data were included. References of the identified articles were also checked and principal investigators were asked if they were aware of other trials. Because this study was a systematic review, ethics committee approval or written informed consent from the participants was not required.

2.3. Data extraction and management

The primary outcome was treatment success; secondary outcomes were failure, default, transfer, death, radiological improvement and adverse events. Treatment outcomes were recorded in line with adapted definitions of those given in WHO guidelines, as follows: treatment success, defined as the number of patients cured or who completed treatment combined; failure, defined as unsuccessful treatment as determined by positive cultures at the end of the treatment regimen; default, defined as dropout from the program with unknown outcome; transfer, defined as transfer to another facility but known to be still under care; and death, defined as death from any cause while on treatment.[5] Study quality was assessed using a modified Newcastle–Ottawa scale.[6]

A data extraction form was developed in consultation with experts, and was designed by two reviewers (H.-B.X. and R.-H.J.). Two reviewers (H.-B.X. and R.-H.J.) performed data extraction for all articles and a third reviewer (J. F.) independently performed data extraction for one-third of the articles to assess accuracy in the data extraction. For each study, we gathered data on study characteristics (authors, study design and hospitalization), patient characteristics [age, populations, drug susceptibility testing (DST) availability, drug resistance pattern, previous TB regimens, and HIV status], treatment characteristics (number of patients receiving CHM, duration of whole treatment, duration of treatment involving CHM, drugs included in chemotherapy, and definition of cure if available) and treatment outcomes.

2.4. Data analysis

CHM combined with chemotherapy group was considered an investigational treatment, and chemotherapy group was used as control treatment. All calculations were performed using Stata software (Stata, version 10; Stata Corporation, College Station, TX, USA). Standard mean difference was given for continuous outcome variable with 95% confidence interval (CI), while odds ratio (OR) was given for dichotomous outcome variable with 95% CI. An OR <1 indicates a lower risk for treatment group than control group, and an OR >1 demonstrates a greater risk for treatment group than control group. Study of heterogeneity was assessed using the X^2 statistic, significant difference for heterogeneity test was considered when $P < 0.01$.[7] Random-effects models were used to analyze pooled effects when heterogeneity was significant otherwise fixed-effects models were used. The Z test was used to compare the overall effects of treatment group with control group, and differences were considered to be statistically significant when $P < 0.05$.

Publication bias is a common concern in meta-analysis that is related to the tendency of journals to favor the publication of large and positive studies. We chose a commonly used method for detecting publication bias, which is a graphical plot of estimates of the log OR from the individual studies versus the SE of log OR.

3. Results

3.1. Description of included trials

The search strategy retrieved 919 potential articles, of which 50 were screened as full-text articles and nineteen were taken through for analysis.[8–19,21–27] One additional article was included through bibliography screening,[20] giving a total of 20 trials comprising 1823 patients for analysis (Fig. 1). Study and treatment characteristics are summarized in Tables 1 and 2. All trials were prospective cohort study, and included only patients with MDR-TB. Fifteen trials reported that DST was carried out for all patients