European Journal of Integrative Medicine 7 (2015) 577–585

Contents lists available at ScienceDirect

European Journal of Integrative Medicine

journal homepage: www.elsevier.com/eujim

Review article

Traditional herbal medicine as an adjuvant treatment for non-small -cell lung cancer: A systematic review and meta-analysis

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ARTICLE INFO

Article history:
Received 9 February 2015
Received in revised form 16 August 2015
Accepted 16 August 2015

Keywords:
Traditional herbal medicine
Non-small-cell lung cancer
Chemotherapy
Systematic review
Meta-analysis

ABSTRACT

Introduction: Non-small-cell lung cancer (NSCLC) is one of the most common cancers and the leading cause of cancer-related deaths. In East Asia, traditional herbal medicine (THM) is commonly used in clinical settings for the treatment of cancer. Therefore, the aim of the present review was to systematically assess the efficacy of THM with varied components for the treatment of NSCLC.
Methods: This study identified randomized controlled trials (RCTs) that evaluated the effectiveness of combined THM and chemotherapy (CTx) in searches of English, Chinese, Japanese, and Korean language databases.
Results: This meta-analysis systematically reviewed 27 RCTs involving 2382 patients and found that THM improved the quality of life (QoL) significantly for patients with NSCLC. Improvement in QoL was seen in 19 studies using the Karnofsky Performance Status score, three studies using the Eastern Cooperative Oncology Group scale, three studies using the Functional Assessment of Cancer Therapy-Lung scale, and six studies using the European Organization for Research and Treatment of Cancer.
Conclusions: The pooled results of this systematic review and meta-analysis suggest that THM significantly improved the QoL for patients with NSCLC.

Contents

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http://dx.doi.org/10.1016/j.eujim.2015.08.005
1876-3820/

1. Introduction

Lung cancer is classified as either non-small-cell lung cancer (NSCLC) or small-cell lung cancer (SCLC) according to its tissue form; therefore, a lung cancer diagnosis depends on the evaluation of biopsy specimens to determine whether NSCLC or SCLC is present [1]. NSCLC may be further categorized as squamous cell carcinoma, adenocarcinoma, or large cell carcinoma [2]. In the United States in 2007, 86% of patients with lung cancer died within 5 years of their diagnosis [3]; as of 2008, lung cancer was the single most common cause of cancer-related deaths worldwide [4].

Despite improvements in conventional cancer treatments, the 5-year survival rate for NSCLC patients is approximately 15%, which is one of the lowest rates among cancers [4]. Surgical resection can be an effective therapy if the lung cancer is diagnosed at an early stage, but most patients are already in its advanced stages at the time of their initial diagnosis [3]. However, it is often difficult to diagnose lung cancer in its early stages because its symptoms, including coughing, hemoptysis, dyspnea, and pleurodynia, typically manifest after the cancer has progressed [3]. Since chemotherapy (CTx) is toxic, many patients have difficulty completing the recommended number of cycles due to the development of adverse effects such as neutropenia, anemia, nausea, and fatigue [5]. In comparison, complementary adjuvant therapies such as traditional herbal medicine (THM) or acupuncture may effectively alleviate the side effects of conventional cancer treatments. Thus, the present systematic review and meta-analysis evaluated THM as an adjuvant treatment during CTx in terms of the quality of life (QoL) of patients with NSCLC.

A literature search revealed that Chen et al. conducted a systematic review of the effects of adjuvant THM during CTx in patients with NSCLC in 2010 [6]; however, our systematic review incorporated several improvements. For example, because THM is commonly used in China, Japan, and South Korea, the present review identified randomized controlled trials (RCTs) using not only English and Chinese language databases but also Japanese and Korean language databases; Chen et al. [6] retrieved studies only from English and Chinese language databases. Additionally, the present review improves upon the work of Chen et al. [6] by including 16 additional RCTs, augmenting the outcome measures, and adding a meta-analysis graph, which was produced using Review Manager 5.1.

2. Methods

2.1. Search strategy

The following sources were used to search for RCTs that were published up to February 2014: English language databases, including the Allied and Complementary Medicine Database (AMED), MEDLINE, EMBASE, CINAHL, the Cochrane Central Register of Controlled Trials, and PsycINFO; Chinese language databases, including the Century Journal Project, China Proceedings Conference Full Text DB, China Academic Journal, and China Doctor/Master Dissertation Full Text DB; the Japanese language database Japan Science and Technology Information Aggregator Electronic; and Korean language medical databases, including KoreaMed, Korea Institute of Science Technology Information and Research Information Service System, Korean Studies Information Service System, National Assembly Library, and DBpia. In addition, clinical trial databases were searched, including the National Center for Complementary and Alternative Medicine (NCCAM) at the National Institutes of Health (http://nccam.nih.gov/), Current Controlled Trials (http://www.controlledtrial.com), and the Complementary and Alternative Medicine Specialist Library at the National Health Service National Library for Health (http://www.library.nhs.uk/cam/). The reference lists of the identified articles were examined for additional appropriate publications, and a number of experts in the field were asked for information concerning any other trials. Finally, a manual search was conducted for relevant conference proceedings, symposia, and journals, and all identified publications were cross-referenced.

The keywords used in the search for RCTs were as follows: (‘Bronchogenic Carcinoma’ OR ‘Non-Small-Cell Lung Carcinoma’ OR ‘Non-Small Cell Lung’ OR ‘Non-Small-Cell Lung’ OR ‘Non-Small-Cell Lung’ OR ‘Non-small-Cell Lung’ OR ‘NSCLC’) AND (‘Neoplasms’ OR ‘Neoplasms*’ OR ‘Cancer*’ OR ‘Tumor*’ OR ‘Tumour*’ OR ‘Carcinoma’ OR ‘Carcinoma*’ OR ‘Adenocarcinoma’ OR ‘Adenocarcinoma*’ OR ‘adenomatous’ OR ‘Lymphoma’ OR ‘lymphom*’ OR ‘lymphedema*’ OR ‘Sarcoma’ OR ‘Sarcoma*’ OR ‘Antineoplastic agents’ OR ‘antineoplas*’ OR ‘adenom*’ OR ‘adenopath*’) AND (‘randomized controlled trial’ OR ‘controlled clinical trial’ OR ‘random*’ OR ‘placebo’ OR ‘drug therapy’ OR ‘trial’ OR ‘groups’). Because the databases searched for the present review possessed their own subject headings; each database was searched independently.

2.2. Study selection

In this meta-analysis, only RCTs were selected. The experimental group included only studies using THM in combination with conventional cancer therapy, while the control group consisted of patients receiving only conventional therapy. The CTx regimens included bronchial arterial infusion chemotherapy (BAIC); cyclophosphamide, Adriamycin®, and cisplatin (CAP); cyclophosphamide, vincristine, and 5-fluorouracil (COF); docetaxel and cisplatin (DP); gemcitabine and paclitaxel (GP); methyl-CCNU, vincristine, and 5-fluorouracil (MOF); mitomycin, vinblastine, and cisplatin (MVP); cisplatin and vinorelbine (NP); paclitaxel and cisplatin (TP); and vinorelbine and cisplatin (VP) (Table 1).

The primary outcome in the present study was evidence of QoL improvement based on the scores of four different scales (Karnofsky Performance Status (KPS), Eastern Cooperative Oncology Group (ECOG), Functional Assessment of Cancer Therapy-Lung (FACT-L), and European Organization for Research and Treatment of Cancer (EORTC)). The secondary outcome included adverse effects of integrative THM treatment. Quasi-randomized and non-randomized trials were excluded from the present meta-analysis. Additionally, animal or *in vivo* studies and studies in which THM was applied using methods other than oral administration were excluded (Fig. 1).

2.3. Quality assessment

Each report identified using the abovementioned search strategy was evaluated by one of the present reviewers according to the inclusion criteria. When there was uncertainty about the eligibility of a study, a second reviewer evaluated the report and a judgment was reached through discussion and consensus following independent evaluations of that study. A quality assessment was performed following the descriptions of the categories in the “Assessing Risk of Bias” chapter from the *Cochrane Handbook for*