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Research paper

Oral administration of herbal medicines for radiation pneumonitis in lung cancer patients: Protocol for a systematic review

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ABSTRACT

Introduction: Radiation pneumonitis is a common and serious complication of radiotherapy. Many published, randomised controlled studies reveal a growing trend utilizing herbal medicines as an adjuvant therapy to prevent radiation pneumonitis; however, its efficacy and safety remains unexplored. The goal of this systematic review is to evaluate the current evidence regarding the efficacy and safety of herbal medicines as an adjunctive therapy to prevent radiation pneumonitis in patients receiving radiotherapy for lung cancer.

Methods and analysis: The following databases will be utilized in this study; three English medical databases (MEDLINE (PubMed), EMBASE and The Cochrane Central Register of Controlled Trials (CENTRAL)), five Korean Medical Databases (Korean Studies Information, Research information Service System, KoreaMed, DBPIA, National Digital Science Library) and three Chinese Medical Databases (the China National Knowledge Database (CNKI), Journal Integration Platform (VIP), and WanFang Database). Two independent reviewers will screen the searched studies, determine suitability for inclusion and perform data extraction. When appropriate, the data will be pooled across studies for meta-analysis using a fixed or random effects model. When quantitative synthesis is not appropriate, the evidence will be summarized qualitatively. The risk of bias will be assessed using the Cochrane Risk of Bias tool.

Results: Results will be published in a peer-reviewed journal and disseminated electronically and in print. This study will also be presented at a relevant conference. Clinicians and patients may find this review useful in making decisions regarding the use of herbal medicines for patients undergoing lung cancer radiotherapy.

Trial registration number: PROSPERO CRD 42016048066.

1. Introduction

Radiotherapy has been widely used to treat unresectable and locally advanced non-small cell lung cancer (NSCLC) as well as localized small-cell lung cancer (SCLC) [1,2]. In comparison to other organs, the lung is especially vulnerable to radiation and radiotherapy may lead to pulmonary toxicity [3,4]. Radiation pneumonitis (RP) is the primary risk, when treating lung cancer with pulmonary radiation [5,6]. The clinical symptoms of RP, which include shortness of breath, cough, and occasionally mild fever, typically present 1–6 months after radiation therapy [4,5,7,8]. The incidence of moderate to severe RP is 10–20% with radiotherapy, but its incidence varies amongst clinical studies [5,9].

Shortness of breath, the primary symptom of RP, diminishes the quality of life and decreases daily activity. Since the purpose of lung cancer treatment is typically to alleviate symptoms rather than to increase life span, dyspnoea is a particularly difficult complication for lung cancer patients [5]. Moreover, RP can affect the patient's clinical course, if it becomes necessary to discontinue treatment or limit the radiation dose. It can lead to a decrease in treatment efficacy and a decline in the survival rate. Severe RP can increase

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the mortality rate up to 50% in comparison to patients without RP or patients with mild RP [10,11]. Therefore, the prevention of RP is important for improving both tumour control and the patient's quality of life.

Although much effort has been directed towards developing an effective agent to ameliorate RP, there was no widely accepted agent until the recent development of amifostine [12,13]. Amifostine has broad applicability as a protective agent, but the results of clinical trials are controversial [14–17]. Some clinical trials of amifostine show a protective effect [14–16]. However, a large randomised Phase III study did not demonstrate a reduction in the incidence of RP with the application of amifostine [17]. The results have not been replicated and current guidelines and systematic reviews do not advocate the use of amifostine for the prevention of radiation-induced pneumonitis [12,18].

Herbal medicines (HMs) are the most widely used complementary and alternative therapies in cancer treatment [19]. HM have also become increasingly popular for use with lung cancer patients receiving chemotherapy or radiotherapy. Some studies have carried out a systematic review regarding the efficacy of Chinese HMs as an adjunctive therapy for advanced lung cancer patients undergoing chemotherapy [20,21]. Oral Chinese HM used in combination with chemotherapy showed a potential to improve the quality of life for patients with NSCLC [20]. Meta-analysis of HM for lung cancer showed that HM may reduce chemotherapy toxicity, increase survival rates and enhance immediate tumour response [21]. Studies indicate that HMs may be used as radioprotectors to ameliorate the radiation-induced toxicity in normal tissue in cancer patients undergoing radiotherapy [22]. A recent systematic review reported that Astragalus-containing HMs may increase therapeutic effectiveness and reduce the toxicity of radiotherapy when provided as an adjunctive therapy during radiotherapy [23]. There are many other published trials of HMs other than Astragalus, which study their protective effect against RP [24–28]. However, no systematic reviews assessing the protective or minimizing effects of HM against RP have been conducted to date. Therefore, the aim of this study is to carry out a comprehensive systematic review to clarify the current evidence for the efficacy and safety of HM as an adjunctive therapy to prevent RP in patients receiving radiotherapy.

2. Methods

2.1. Study registration

This study has been registered with the international Prospective Register of Systematic Reviews (PROSPERO): CRD 42016048066.

2.2. Eligibility criteria

2.2.1. Types of studies

Only randomised controlled trials (RCTs) will be included in this study. Quasi-RCTs, observational, case reports and case series will be excluded. Crossover studies will also be excluded.

2.2.2. Types of participants

This study will include patients who were diagnosed with lung cancer, aged 18 or older, who planned to undergo radiotherapy, regardless of tumour stage.

2.2.3. Type of interventions and controls

Studies reporting orally administered HM treatments as an adjunctive therapy during radiotherapy will be included. HMs refers to a treatment involving single herb or a combination of herbs. There will be no limitation on the number of herbs used. Only orally administered herbal medication will be included. Studies that include other alternative and complementary therapies, such as acupuncture, moxibustion or massage will be excluded.

The control groups will consist of routine radiotherapy or routine radiotherapy combined with a placebo control. Trials involving other chemotherapy or conventional treatment will be excluded.

2.2.4. Type of outcome measures

2.2.4.1. Primary outcome

2.2.4.1.1. The incidence rate of RP. The incidence rate of RP after radiotherapy will be analysed as a primary outcome. Trials which reported the diagnostic criteria of RP, utilizing grading systems such as the National Cancer Institute Common Terminology Criteria (NCICTC) for Adverse Events, the Radiation Therapy Oncology Group (RTOG) or the Common Terminology Criteria for Adverse Events (CTCAE) will be included in this study [8]. Studies using clinical criteria for RP, where the diagnosis was made based on the patients' symptoms (including shortness of breath, intermittent low fever, cough, congestion, etc.) combined with radiological manifestations [29] will also be included.

2.2.4.2. Secondary outcomes.

1) Quality of life: measured using a validated questionnaire, such as European Organisation for Research and Treatment of Cancer (EORTC) Quality-of-Life Questionnaire QLQ-LC13 or another validated scale.
2) Performance status: measured using a Karnofsky or Eastern Cooperative Oncology Group (ECOG) performance status.
3) Pulmonary function test: forced vital capacity (FVC), forced expiratory volume in 1 s (FEV1), carbon monoxide diffusion in the lung (DLCO).
4) Adverse events: The incidence and the severity of adverse events from HM, the proportion of patients requiring discontinuation of the HM.

2.3. Search methods for the identification of studies

2.3.1. Electronic searches

We will search the following databases: English medical databases (PubMed, EMBASE, The Cochrane Library), five Korean Medical Databases (Korean Studies Information, Research information Service System, KoreaMed, DBPIA, National Digital Science Library), three Chinese Medical Databases (the China National Knowledge Database (CNKI), Journal Integration Platform (VIP), and WanFang Database). Dissertations and abstracts will also be included if these documents contain sufficient detail for critical evaluation. Studies will not be limited by language.

2.3.2. Other sources

- The reference lists of the retrieved articles;
- Relevant systematic reviews;
- Google scholar (http://scholar.google.co.uk/);
- Unpublished conference proceedings will be reviewed, if available.

2.3.3. Search strategy

Our key search terms will be 'radiation pneumonitis' and 'herbal medicine'. We will use related Medical Subject Heading terms and synonyms in various combinations. The search strategies are presented in the supplementary Appendix A.