INPLASY PROTOCOL

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None declared.

Efficacy of Aidi injection combined with chemotherapy, radiotherapyor chemoradiotherapy for unresectable esophageal cancer treatment: A meta-analysis and systematic review of 29 randomized controlled trials

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Review question / Objective: **In recent years, many articles have shown the significant clinical effects of traditional Chinese medicine for esophageal cancer (EC) treatment. These studies involved Chinese medicine injection, decoction, acupuncture, and moxibustion. Chinese medicine injections, including Aidi injection (Aidi) (Z52020236, China food and Drug Administration; composed of 0.15 g/ml cantharis, 5 g/ml ginseng, 10 g/ml Astragalus and 15 g/ml Eleutherococcus senticosus at a ratio of 0.03:1:2:3. The three plant names have been checked with http://www.theplantlist.org 2022/6/4), Shenqifuzheng injection, Kanglaite injection, compound Kushen injection, and Kangai injection, are widely used to treat cancer in clinical practice because of their efficacy and convenience. Aidi combined with standard treatment, including chemotherapy, radiotherapy, or chemoradiotherapy (CR) (Aidi-based combination therapy), showed significant efficacy in the treatment of unresectable EC. However, existing studies are limited to small sample sizes, and the efficacy of Aidi in the treatment of unresectable EC has not been confirmed in large-scale phase III clinical trials. Therefore, it is important to derive more convincing results by analyzing all the reported data. Herein, we conducted a literature search for all randomized controlled trials (RCTs) that applied Aidi-based combination therapy in unresectable EC treatment, and a meta-analysis was performed to evaluate the efficacy of Aidi-based combination therapy in unresectable EC treatment.**

INPLASY registration number: This protocol was registered with the International Platform of Registered Systematic Review and Meta-Analysis Protocols (INPLASY) on 05 September 2022 and was last updated on 05 September 2022 (registration number INPLASY202290020).

INTRODUCTION

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(Aidi) (Z52020236, China food and Drug Administration; composed of 0.15 g/ml cantharis, 5 g/ml ginseng, 10 g/ml Astragalus and 15 g/ml Eleutherococcus senticosus at a ratio of 0.03:1:2:3. The three plant names have been checked with http://www.theplantlist.org 2022/6/4), Shenqifuzheng injection, Kanglaite injection, compound Kushen injection, and Kangai injection, are widely used to treat cancer in clinical practice because of their efficacy and convenience. Aidi combined with standard treatment, including chemotherapy, radiotherapy, or chemoradiotherapy (CR) (Aidi-based combination therapy), showed significant efficacy in the treatment of unresectable EC. However, existing studies are limited to small sample sizes, and the efficacy of Aidi in the treatment of unresectable EC has not been confirmed in large-scale phase III clinical trials. Therefore, it is important to derive more convincing results by analyzing all the reported data. Herein, we conducted a literature search for all randomized controlled trials (RCTs) that applied Aidi-based combination therapy in unresectable EC treatment, and a meta-analysis was performed to evaluate the efficacy of Aidi-based combination therapy in unresectable EC treatment.

Condition being studied: Globally, esophageal cancer (EC) is a frequently occurring malignancy, ranking sixth in mortality and eighth in morbidity rates among all tumors , with approximately 600,000 new cases and 500,000 related deaths reported in 2018 alone. China is one of the countries with high EC morbidity, and approximately half of all new EC cases worldwide occur in China every year. In China, esophageal squamous cell carcinoma (ESCC) comprises approximately 90% of the total reported EC cases. EC at the earlier stage is curable by surgery. However, its insidious nature delays its early diagnosis, resulting in more than 80% of patients being diagnosed in intermediate to advanced stages, thereby losing the opportunity for surgery or showing a high recurrence rate after surgery. The goal of treatment for unresectable EC is to maximize survival and improve patients' quality of life. Radiotherapy (R) and chemotherapy (C) are crucial treatment options for these patients, but their efficacy is far from ideal, and experts have been struggling to find improved treatment methods. On the other hand, these treatments also induce adverse effects, such as radiation esophagitis (RE), bone marrow suppression (BMS), nausea, and vomiting, thus resulting in low immunity and a reduced quality of life. Some patients must even discontinue their treatment due to the inability to tolerate these adverse effects. Thus, the development of a novel treatment method is necessary to maximize efficacy, attenuate radiotherapy- and chemotherapy-induced adverse effects, and improve the patients' quality of life.

METHODS

Search strategy: The inclusion and exclusion criteria and search strategy were developed following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement (http://www.prisma-statement) . A literature search was performed using a combination of electronic databases and manual searches. Eight electronic databases, including PubMed, Embase, MEDLINE, Cochrane Library, Vip China Science and Technology Journal Database (VIP), Chinese National Knowledge Infrastructure (CNKI), China Biology Medicine Disc (CBM), and Wanfang Academic Journal Database, were queried for population, intervention, comparators, outcomes, and study design principles (PICOS principles). The search terms included esophageal neoplasm, radiotherapy, chemotherapy, Aidi injection, and RCTs. To prevent missing any reports, a manual search of the references of the original literature was conducted to retrieve relevant studies that fit our objective. All searches were restricted to human RCTs, excluding animal trials and basic research. The searches were independently conducted by two researchers.

Search strategy : Search terms included the following: ((((((((((((((((((Esophageal

Neoplasm[Title/Abstract]) OR (Neoplasm, Esophageal[Title/Abstract])) OR (Esophagus Neoplasm[Title/Abstract])) OR (Esophagus Neoplasms[Title/Abstract])) OR (Neoplasm, Esophagus[Title/Abstract])) OR (Neoplasms, Esophagus[Title/Abstract])) OR (Neoplasms, Esophageal[Title/Abstract])) OR (Cancer of Esophagus[Title/Abstract])) OR (Cancer of the Esophagus[Title/Abstract])) OR (Esophagus Cancer[Title/Abstract])) OR (Cancer, Esophagus[Title/Abstract])) OR (Cancers, Esophagus[Title/Abstract])) OR (Esophagus Cancers[Title/Abstract])) OR (Esophageal Cancer[Title/Abstract])) OR (Cancer, Esophageal[Title/Abstract])) OR (Cancers, Esophageal[Title/Abstract])) OR (Esophageal Cancers[Title/Abstract])) AND (((((AiDi injection[Title/Abstract]) OR (Chinese medicine injection[Title/Abstract])) OR (Traditional Chinese medicine[Title/Abstract])) OR (Proprietary Chinese medicine[Title/Abstract])) OR (Chinese patent medicine injection[Title/Abstract]))) AND ((((((((((((((((((((((((((Therapy, Drug[Title/Abstract]) OR (Drug Therapies[Title/Abstract])) OR (Therapies, Drug[Title/Abstract])) OR (Chemotherapy[Title/Abstract])) OR (Chemotherapies[Title/Abstract])) OR (Pharmacotherapy[Title/Abstract])) OR (Pharmacotherapies[Title/Abstract])) OR (Radiation[Title/Abstract] AND chemotherapy[Title/Abstract])) OR (chemoradiotherapy[Title/Abstract])) OR (Radiotherapies[Title/Abstract])) OR (radiotherapy[Title/Abstract])) OR (Radiation Therapy[Title/Abstract])) OR (Radiation Therapies[Title/Abstract])) OR (Therapies, Radiation[Title/Abstract])) OR (Therapy, Radiation[Title/Abstract])) OR (Radiation Treatment[Title/Abstract])) OR (Radiation Treatments[Title/Abstract])) OR (Treatment, Radiation[Title/Abstract])) OR (Radiotherapy, Targeted[Title/Abstract])) OR (Radiotherapies, Targeted[Title/Abstract])) OR (Targeted Radiotherapies[Title/Abstract])) OR (Targeted Radiotherapy[Title/Abstract])) OR (Targeted Radiation Therapy[Title/Abstract])) OR (Radiation Therapies, Targeted[Title/Abstract])) OR (Targeted Radiation Therapies[Title/Abstract])) OR (Therapies, Targeted Radiation[Title/Abstract])) OR (Therapy, Targeted Radiation[Title/Abstract])) OR (Radiation Therapy, Targeted[Title/Abstract]))) AND ((((((Randomized controlled[Title/Abstract]) OR (Randomized Controlled Trial[Title/Abstract])) OR (RCT[Title/Abstract])) OR (random[Title/Abstract])) OR (Allocation, Random[Title/Abstract])) OR(Randomization[Title/Abstract])).

Participant or population: Unresectable esophageal cancer with chemotherapy, radiotherapy, or chemoradiotherapy.

Intervention: Patients in the experimental group underwent treatment with Aidi-based combination therapy.

Comparator: Patients in the control group underwent standard treatment, including chemotherapy, radiotherapy, or chemoradiotherapy. Radiotherapy doses ranged from 50–70 Gy. Chemotherapy was based on cisplatin, with drugs including cisplatin, 5-FU and docetaxel.

Study designs to be included: (1) Study design type consistent with an RCT, regardless of the blinding method; (2) Availability of complete data on outcome indicators, allowing for direct or indirect data extraction for statistical analyses.

Eligibility criteria: The inclusion criteria for the literature in this meta-analysis were as follows: (1) unresectable EC; (2) age 18 years or above, irrespective of sex; (3) pathologically confirmed diagnosis of EC with at least one evaluable lesion; (4) no history of chemotherapy or radiotherapy for the esophagus; (5) absence of any other severe medical disease, infection, or esophagitis caused by other diseases; (6) Karnofsky Performance Status (KPS) score of 70 or more; (7) study design type consistent with an RCT, regardless of the blinding method; and (8) availability of complete data on outcome indicators, allowing for direct or indirect data extraction for statistical analyses.The exclusion criteria were as follows: (1) studies that did not meet the inclusion criteria; (2) animal studies, reviews, and duplicated reports; (3) patients with EC

showing metastatic lesions; and (4) studies with inconsistent outcome indicators or a poor trial design.

Information sources: A literature search was performed using a combination of electronic databases and manual searches. Eight electronic databases, including PubMed, Embase, MEDLINE, Cochrane Library, Vip China Science and Technology Journal Database (VIP), Chinese National Knowledge Infrastructure (CNKI), China Biology Medicine Disc (CBM), and Wanfang Academic Journal Database, were queried for population, intervention, comparators, outcomes, and study design principles (PICOS principles).

Main outcome(s): The following were the outcome indicators for this meta-analysis: (1) objective response rate (ORR); (2) disease control rate (DCR); (3) one-year overall survival (OS) rate; (4) BMS; (5) chemotherapy-induced nausea and vomiting (CINV); (6) RE, and (7) KPS score.

Data management: Two trained researchers independently performed the literature search and data extraction and evaluated the methodological quality of the included studies based on the exclusion and inclusion criteria described above . Any disagreements were resolved through discussion or referred to a third party for resolution to arrive at a consensus. A self-administered form for data extraction was used to obtain the following information: (1) basic information, including the title of the report, year of publication, and first author; (2) study characteristics, including general information about the study population, sample size, Aidi dose, chemotherapy drug dose, and radiotherapy dose; and (3) the above mentioned outcome indicators.

Quality assessment / Risk of bias analysis: Three trained researchers evaluated the risk of bias of the included studies using the risk of bias assessment tool for RCTs recommended by the Cochrane Handbook for Systematic Reviews of Interventions with RevMan (version: 5.4) software. A fourth trained researcher discussed and resolved any disagreements.

Strategy of data synthesis: The data were collated according to the requirements of the meta-analysis and analyzed using RevMan software (version: 5.4) provided by the Cochrane Collaboration. As all outcome indicators in this study were dichotomous variables, the risk ratio (RR) was used as the effect indicator, and all effect sizes were expressed using a 95% confidence interval (95% CI). The $\chi 2$ test was used to evaluate any heterogeneity between the studies, with $P \geq 0.10$ and $I2 \leq 50\%$ indicating no statistically significant heterogeneity. Herein, a fixed-effects model was used to evaluate the data, unless statistical heterogeneity was present between the studies, whereby a random-effects model was employed; sensitivity or subgroup analysis was conducted, if necessary. Additionally, to assess any potential publication biases, funnel plots were generated. $P<0.05$ indicated a statistically significant difference.

Subgroup analysis: When $P < 0.10$ and $I 2 > 50\%$ indicated statistical heterogeneity among studies, subgroup analysis was conducted.

Sensitivity analysis: When $P < 0.10$ and $I 2 > 50\%$ indicated statistical heterogeneity among studies, sensitivity analysis was conducted.

Country(ies) involved: China.

Keywords: Aidi injection, radiotherapy, chemotherapy, chemoradiotherapy, esophageal cancer, meta-analysis.

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