Chinese Herb Injections Combined with FOLFOX for Gastric Cancer? Meta-analysis of Randomized Controlled Trials

Jian-Cheng Wang¹&, Jin-Hui Tian¹&, Long Ge³&, Yu-Hong Gan¹, Ke-Hu Yang¹,2*  

Abstract

Background: Few studies have directly compared clinical efficacy and safety among Chinese herb injections (CHIs) for gastric cancer (GC). The present study aimed to compare CHIs combined with FOLFOX regimens for GC to show which provides the best CHIs results. Materials and Methods: 9 electronic databases and 6 gray literature databases were comprehensive searched in April 20, 2013. According to inclusion and exclusion criteria, two reviewers independently selected and assessed the included trials. The risk of bias tool described in the Cochrane Handbook version 5.1.0 and CONSORT statement were used to assess the quality of the trials. All calculations and graphs were performed and produced using ADDIS 1.16.5 software. Results: A total of 541 records were searched and 38 RCTs met the inclusion criteria (2,761 participants), involving 10 CHIs. The results of network meta-analysis showed that compared with FOLFOX alone, combinations with Kanglaite, Astragalus polysaccharides, Cinobufacini, or Yadanziyouru injections could further strengthen ORR, improve the quality of life, reduce nausea and vomiting, and reduce the incidence of leukopenia (III-IV). Conclusions: Kanglaite injection, Astragalus polysaccharides injection, Yadanziyouru injection were superior to other CHIs in clinical efficacy and safety for GC. The conclusions now need to be confirmed by large sample size direct head-to-head studies.

Keywords: Chinese herbs injection - gastric cancer - FOLFOX - network meta-analysis

Introduction

Gastric cancer (GC) is one of the major malignant carcinoma. With an incidence of 989,600, GC was the fourth most frequent malignant cancer and the second most common cause of death with 738,000 world wide in 2008 (Jemal et al., 2011). Over 70% of new cases and deaths appeared in developing countries (Singh et al., 2013). In China, there are 258,000 new cases and 210,000 deaths, which account for over fifty percent of total morbidity and mortality in the whole world (Lu et al., 2014). It is self-evidenced that GC becomes a severe public health burden over the world. Current surgical therapies, radiotherapies and chemotherapies were considered as three mainstays for GC therapy. Unfortunately, almost half of the patients present with middle-advanced stage gastric cancer and inoperable with a median survival time (MST) of 6-10 months. Thus chemical comprehensive treatment programs primarily were the main therapy method to GC (Jin et al., 2007).

FOLFOX regimen refers to 5-Fluorouracil (5-FU) plus Leucovorin (LV) combined with Oxaliplatin, it is a standard first line combination chemotherapy for GC (Xiao et al., 2008). FOLFOX has good evidence of efficacy for GC and is widely used but there are still some short and long term side effects. Chinese Herb Injection (CHI) has been reported to alleviate adverse events induced by conventional cancer therapy, improve patient’s quality of life (Molassiotis et al., 2009), enhance cellular immunity of cancer patients receiving chemotherapy/radiotherapy (Zhuang et al., 2009), reduce cancer pain (Xu et al., 2007), relieve cancer-related fatigue (Jeong et al., 2010) and improve anorexia and cachexia (Lee et al., 2010). Current 16 CHIs are available for the treatment of cancer. Previous meta-analysis focus on CHI combined with chemotherapy in postoperative patients with GC showed that CHI combined with chemotherapy in postoperative patients with GC could reduce the adverse effects of chemotherapy and prolong survival time when compared with chemotherapy alone (Xu et al., 2013). Currently, some randomized controlled trials of several CHIs combined with FOLFOX regimens versus FOLFOX regimen alone are available. One randomized controlled trial (RCT) of CHI plus FOLFOX4 regimen versus
FOLFOX regimen alone in the treatment of advanced GC has been conducted (Xu et al., 2011). Nevertheless, the sample size of this trial is small, and the components of CHI are not reported. There are no direct head-to-head evidences to declare which is the best CHI for GC. As such, it is difficult to determine the superiority of a treatment using pairwise comparison meta-analysis (Gupta et al., 2013).

Network meta-analysis is an extension of traditional meta-analysis and is a method that synthesizes available evidence to allow for simultaneous comparisons of different treatment options that lack direct head-to-head evaluations (Lu et al., 2004; Jansen et al., 2008; Sutton et al., 2008; Ouwens et al., 2011). When the network consists of a mixture of direct and indirect evidence with comparable study and patient characteristics, the relative treatment effect of drug B vs drug C may be indirectly estimated by comparing studies of drug A vs drug B and drug A vs drug C (dbc=dac-dab) (Ouwens et al., 2011; Jansen et al., 2011). The value of a network meta-analysis is that it can include both direct and indirect evidence and it preserves the strength of randomization within individual RCTs (Cheng et al., 2012).

The study aims to conduct a network meta-analysis to compare the clinical efficacy and safety of 16 CHI combined with FOLFOX regimens to show the best CHI for GC.

Materials and Methods

Inclusion and exclusion criteria

Studies considered in this review met the following inclusion criteria: 1) Tapes of studies, only RCTs of 16 CHI combined with FOLFOX regimens for GC patients; 2) Tapes of participants, were pathologically or computed tomography diagnosed with advanced GC, whose age is limited to eighteen years, regardless of sex, nationality; 3) Tapes of intervention, 16 CHI combined with FOLFOX chemotherapy vs FOLFOX chemotherapy alone. 4) Outcome measures, included overall response rate (ORR), Karnofsky (KPS) scores, leukopenia, nausea/vomiting and so on.

Studies were excluded as following: 1) The patients can not be confirmed of advanced GC; 2) Neither RCT nor “random” is not mentioned in group; 3) The control measures was not FOLFOX chemotherapy regimen; 4) The data can not be extracted; 5) reviews or meta-analysis, animal researches, case reports, and conference abstracts or letters to the journal editors.

According to preestablished inclusion criteria, two independent reviewers read all title and abstract, to identify potentially eligible articles and citations for which a decision could not be made from the abstract. We then managed to retrieve the full - text of these articles to determine whether they were eligible. Disagreements were resolved in consultation with Pro. Yang.

Search strategy


Data extraction and quality assessment

An abstractly standard data extraction form was designed, included the authors, publication year, intervention, number of sample, outcome etc. Quality assessment was according to the Cochrane Handbook version 5.1.0 (Higgins et al., 2011) and methodological section of CONSORT statement (Moher et al., 2010) (randomization, blinding, loss to follow-up or drop-out, eligibility criteria for participants, adverse events, statistical methods). The judgments for each entry involve assessing the risk of bias as ‘low risk’, as ‘high risk’, or as ‘unclear risk’. Data extraction and quality assessment were performed by two independent reviews, and disagreements were resolved by consensus.

Statistical analysis

The dichotomous data and continuous outcomes were presented as odds ratio (OR), and weighted mean difference (WMD) relatively, with 95% confidence intervals (CI). All calculations and graphs were performed by using ADDIS 1.16.5 soft (van Valkenhoef et al., 2013).

Results

Literature search

We identified 541 potentially relevant studies in the primary literature search (Figure 1), 38 RCTs published in Chinese that met the inclusion criteria and involved a total of 2,761 gastric cancer patients. Ten CHIs were involved including Aidi injection, Astragalus polysaccharides injection, Cinobufacini injection, Compound matrine injection, Delisheng injection, Ginseng polysugar injection, Kangai injection, Kanglaite injection, Shenqifuzheng injection, Yadanziyouru injection. The basic characteristic of the studies included number of sample, age, sex, interventions, pathological type, dosages of injection, KPS scores, durations (Table 1).

Quality assessment

The methodological qualities of included studies were assessed by the Cochrane Handbook version 5.1.0 and CONSORT statement. Only four of thirty-eight studies described a satisfactory method of randomization
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Results of network meta-analysis

Overall response rate: Overall response rate were reported in thirty-three studies. Table 2 showed that Kanglaite injection was statistically significantly superior to Astragalus polysaccharides injection (OR=1.33, 95%CI: 0.25-7.79), Yadanziyouru injection (OR=1.55, 95%CI: 0.35-7.56), Shenqifuzheng injection (OR=2.21, 95%CI: 0.60-8.61), Cinobufacini injection (OR=2.46, 95%CI: 0.62-11.48), Compound matrine injection (OR=2.47, 95%CI: 0.65-9.42), Kangai injection (OR=3.21, 95%CI: 0.85-12.94), Ginseng polysugar injection (OR=3.30, 95%CI: 0.53-17.98), Delisheng injection (OR=3.35, 95%CI: 0.73-17.51), Aidi injection (OR=3.45, 95%CI: 0.93-13.17), and FOLFOX regimen (OR=4.28, 95%CI: 1.26-15.64). Consistent with these observations and based on the calculated probabilities, the CHIs were ranked as followed: Kanglaite>Astragalus polysaccharides>Yadanzi youru>Shenqifuzheng>Cinobufacini>Compound matrine >Kangai>Aidi>FOLFOX>Ginseng polysugar>Delisheng.

Table 1. The Basic Characteristic of Included Studies

Table 2. Flow Chart of Studies Screening and Selection Process

Figure 1.
Nausea and vomiting: Sixteen studies reported the incidence of nausea and vomiting, involved eight CHIs. Compared with FOLFOX alone regimen, all CHIs combined with FOLFOX regimens can reduce the incidence of nausea and vomiting, and the ranks of incidence of nausea and vomiting for CHIs were Cinobufacini>Ka nglaite>Yadanziyouru>Shenqifuzheng>Comp ound matrine>Kangai>Delisheng>Aidi (see Table 3).

Leukopenia (III-IV): Twelve studies reported the incidence of leukopenia (III-IV), covered six CHIs. Table 3 showed the results of network meta-analysis. Compared with FOLFOX alone, Yadanziyouru injection combined with FOLFOX regimen and Astragalus polysaccharides combined with FOLFOX regimen can significantly reduce the incidence of leukopenia (III-IV).

Discussion

Summary of key findings: The CHIs have been widely used to reduce the incidence of adverse events, improve the quality of life, and strengthen the clinical efficacy for the treatment of cancer. There was no direct head-to-head evidence to evaluate the clinical efficacy among CHIs. Our network meta-analysis compared the clinical efficacy and safety of available sixteen CHIs combined with FOLFOX regimens with FOLFOX alone to show which is the best CHIs for GC. Our results showed that all CHIs can reduce the incidence of adverse events, improve the quality of life, and strengthen the clinical efficacy. Kanglaite, Astragalus polysaccharides, and Yadanziyouru injection were superior to other CHIs regarding ORR. Astragalus polysaccharides, Kangai, and Shenqifuzheng injection were better than other CHIs to improve the quality of life. Cinobufacini, Kanglaite, Yadanziyouru, and Astragalus polysaccharides injection can significantly reduce the incidence of nausea and vomiting and leukopenia (III-IV) than other CHIs.

Strengths and limitations: This is the first indirect evidence which compared the clinical efficacy and safety among ten CHIs combined with chemotherapy for GC. Through we performed a systematic literature search including common databases searching and other sources, possible that not all the relevant studies were identified. Our network meta-analysis also had several potential biases. Most of studies
Table 2. Odds Rations and 95% Credible Intervals for Overall Response Rate and KPS

<table>
<thead>
<tr>
<th>Overall response rate</th>
<th>PFS</th>
<th>Aidi</th>
<th>Astragalus polysaccharides</th>
<th>Cinobufacini</th>
<th>Compound matrine</th>
<th>Delisheng</th>
<th>FOLFOX</th>
<th>Ginseng polysugar</th>
<th>Kangai</th>
<th>Kanglaite</th>
<th>Shenqifuzheng</th>
<th>Yadanziyouru</th>
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<tr>
<td>Aidi+FOLFOX</td>
<td></td>
<td>0.06</td>
<td>(0.01, 0.34)</td>
<td>(0.03, 0.25)</td>
<td>2.51</td>
<td>1.38</td>
<td>1.00</td>
<td>1.38</td>
<td>0.96</td>
<td>1.00</td>
<td>1.38</td>
<td>0.96</td>
</tr>
<tr>
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<td>(1.36, 0.38)</td>
<td>2.51</td>
<td>1.38</td>
<td>1.00</td>
<td>1.38</td>
<td>0.96</td>
<td>1.00</td>
<td>1.38</td>
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<td>Kangai+FOLFOX</td>
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<td>0.96</td>
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