RESEARCH ARTICLE

Which is the Best Chinese Herb Injection Based on the FOLFOX Regimen for Gastric Cancer? A Network Meta-analysis of Randomized Controlled Trials

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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 furthest 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

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Introduction

Gastric cancer (GC) is one of the major malignant carcinoma. With an incidence of 989,600, GC was the fourth most frequent malignant caner 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 development 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

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FOLFOX regimen alone in the treatment of advanced GC has been conducted (Xu et al., 2011). Nevertheless, the sample size of this trail 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

We comprehensive searched the following databases: China Academic Journal Network Publishing Database (CAJD, 1994-2013.4), Chinese Biomedical Literature Database (CBM, 1978-2013.4), Chinese Technological Periodical Full-text Database (VIP, 1989-2013.4), China Online Journals (COJ, 1997-2013.4), Chinese Science Citation Database (CSCD, 1989-2013.4), PubMed (1966-2013.4), EMBASE.com (1974-2013.4), Cochrane Library (-2013.4), Science Citation Index Expanded (SCI-EXPANDED, 2000-2013.4). Grey literatures were obtained from the China Proceedings of Conference Full-text Database (CPCD, 1994-2013.4), Academic Conferences in China (ACIC, 1990-2013.4), Chinese-foreign Conference Database (via to National Science and Technology Library, 1985-2013.4), China Doctoral Dissertations Full-text Database (CDFD, 1994-2013.4), China Master's Theses Full-text Database (CMFD, 1994-2013.4), Dissertations of China (DOC, 1990-2013.4). The searches were performed in April 20, 2013.

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

KPS scores: Twenty-six studies assessed the quality of life by KPS scores. The results of indirect comparison showed that all CHIs combined with FOLFOX can significantly improve the quality of life when compared with FOLFOX alone. And the CHIs were ranked as followed: Astragalus polysaccharides injection>Kangai >Shenqifuzheng>Delisheng>Cinobufacini>Ginseng po

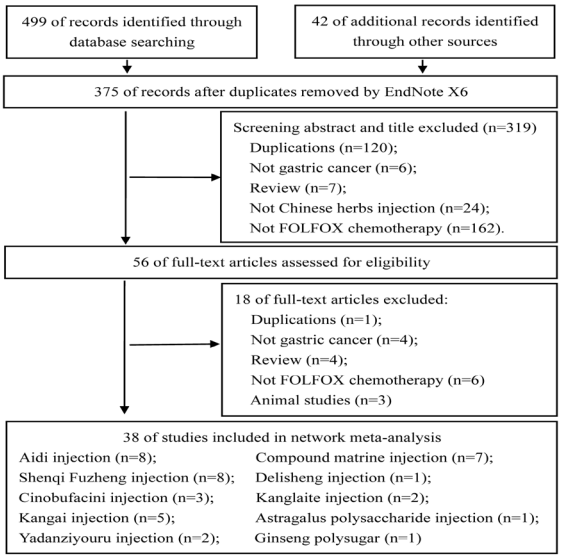

Figure 1. Flow Chart of Studies Screening and Selection Process

including random number table, coin tossing, and drawing of lots. One study described a non-random component based on date of admission in the sequence generation process. One study reported information about blinding. Most of studies (71.1%) provided the information of loss to follow-up or drop-out. 76.3% of studies reported the eligibility criteria for participants. 92.1% provided the information about adverse events. 97.4% reported statistical methods.

Results of network meta-analysis

Overall response rate: Overall response rate were reported in thirty-three studies. Table 2 showed that Kanglaite injection was statistical 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 CHI 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

Studies	No. sample		Sex(M/W)		Age		Type of CHI	pathological type		Dosages/ml	KPS scores	Durations
	CHI+ FOLFOX	FOLFOX	CHI+ FOLFOX	FOLFOX	CHI+ FOLFOX	FOLFOX		Early	Advanced			
Miao YQ 2011	41	43	65/19		M62		Aidi		√	50-80	>60	≥2
Chen NJ 2008	36	34	38/32		40-68/A56.7		Aidi		√	50	>70	3
Zeng QB 2006	23	22	30/15		M52.4		Aidi		√	50	NR	≥2
Huo CS 2012	32	33	43/22		36-71/A48,5		Aidi		√	50	NR	2
Chen YD 2012	29	28	20/9	19/9	43-69/M56	42-68/M55	Aidi		√	80	50-80	2
Yan HX 2012	32	34	57/9		42-75/A61.7		Aidi	NR		100	>70	1
Zhang AX 2009	35	32	20/15	19/13	30-71/A55	32-68/A53	Aidi		√	50	NR	3
Wen X 2010	27	29	46/10		47-78/A60.3		Aidi		√	80	≥60	≥2
Zhang LQ 2010	34	34	39/29		37-75		Compound matrine	NR		20	≥70	6
Qin HB 2012	27	21	35/13		29-72/M54.5		Compound matrine		√	20	NR	2
Han QL 2011	39	39	21/18		39-72		Compound matrine		√	15	>60	2
Yang JW 2012	30	28	18/12		48-72/M63.6		Compound matrine	NR		15	NR	6
Liu YH 2010	83	83	57/26		60-83		Compound matrine	NR		20	≥70	4
Zhang MJ 2010	48	48	28/20		NR		Compound matrine		√	20	≥60	2
Chen ZT 2004	20	20	16/4		NR		Compound matrine		√	20	≥50	3
Liu H 2011	45	40	25/20	21/19	64.82±7.08	65.15±6.96	Shenqifuzheng		√	250	≥60	2
Wang M 2011	40	40	22/18	21/19	49-78/52		Shenqifuzheng		√	250	NR	4
Fang XY 2010	36	34	37/33		41-68/56.7		Shenqifuzheng		√	250	>70	4
Jia JW 2009	24	24	14/10	13/11	32-74/M52	33-73/M53	Shenqifuzheng		√	250	≥60	4
Zhao QF 2012	61	61	38/23	40/21	40-62/52±6	41-64/49±8	Shenqifuzheng	NR		250	NR	NR
Ren YZ 2012	33	32	30	35	52-73/M62		Shenqifuzheng		√	250	>70	3
Chen LL 2012	35	35	21/14	22/13	44-75/M48	47-76/M51	Shenqifuzheng		√	250	≥60	4
Li ZY 2006	42	40	42	40	35-70/58	30-73/60	Shenqifuzheng	NR		250	>60	2
He ZQ 2008	65	58	35/30	33/25	38-72/A57.6	40-72/A59.5	Delisheng		√	40	>60	3.2/3.6
Wang ZF 2012	24	24	19/5	20/4	M58.7	M59.1	Cinobufacini		√	10-20	>60	8
Wang YH 2009	36	32	48/20		40-72/M54		Cinobufacini		√	20	>60	4
Wang WM 2010	20	23	27/16		40-75/M52		Cinobufacini		√	10-20	>60	8
Liu YH 2011	33	32	38/27		35-72/A56		Astragalus polysaccharides		√	250	≥60	4
Chen WJ 2006	35	38	24/11	25/13	31-65/M54	20-63/M56.4	Kangai		√	40-60	≥50	2
An GW 2012	38	32	18/20	18/14	45-70/M58	44-71/M55	Kangai		√	60		2
Li YY 2008	48	42	29/19	26/16	18-74	24-68	Kangai		√	40	≥70	2
Wang LJ 2008	42	38	68/12		28-68, A53		Kangai		√	30	>60	2
Wu L 2009	40	40	28/12	26/14	31-76	33-78	Kangai		√	50	≥60	2
Xu XX 2011	35	35	20/15		A59		Kanglaite		√	200	≥70	4~6
Xu XX 2011	30	30	35/25		A48.2		Kanglaite		√	100	≥70	4~6
Zhang JX 2010	38	25	36/27		29-72/M55		Ginseng polysugar		√	24	≥60	3
Wu YC 2012	50	50	38/12	33/17	34-78/58M	31-82/57M	Yadanziyouru		√	30	NR	2
Fan XQ 2008	24	18	14/10	13/5	70-85	70-85	Yadanziyouru		√	30	≥60	3-4

*CHI: Chinese Herbs Injection; NR: not reported; M: man; W: woman

Table 3. Odds Rations and 95% Credible Intervals for Nausea and Vomiting, Leukopenia (III-IV)

Nausea and vomiting	Aidi+FOLFOX	Astragalus polysaccharides +FOLFOX	Cinobufacini +FOLFOX	Compound matrine +FOLFOX	Delisheng +FOLFOX	FOLFOX	Kangai +FOLFOX	Kanglaite +FOLFOX	Shenqifuzheng +FOLFOX	Yadanziyouru +FOLFOX
Aidi+FOLFOX	—	741787841.48 (1.88, 54934388 39724508000000000000.00)	—	0.45 (0.03, 5.38)	—	0.26 (0.04, 1.43)	0.91 (0.05, 18.21)	—	1.26 (0.02, 104.23)	158134272917.63 (2.40, 3626321 923541627000000000000000.00)
Astragalus polysaccharides+FOLFOX	—	—	—	0.00 (0.00, 0.27)	—	0.00 (0.00, 0.13)	0.00 (0.00, 0.65)	—	0.00 (0.00, 1.41)	45.20 (0.00, 105628053 86077452000000000.00)
Cinobufacini+FOLFOX	3.27 (0.39, 29.10)	—	—	—	—	—	—	—	—	—
Compound matrine+FOLFOX	1.59 (0.33, 8.23)	—	0.46 (0.07, 3.70)	—	—	0.57 (0.10, 3.29)	2.03 (0.12, 42.64)	—	2.75 (0.06, 262.60)	352590122766.81 (5.25, 5910276 481196190500000000000000.00)
Delisheng+FOLFOX	1.35 (0.22, 8.47)	—	0.39 (0.05, 3.99)	0.83 (0.18, 3.88)	—	—	—	—	—	—
FOLFOX	3.37 (1.01, 13.81)	—	1.01 (0.19, 5.90)	2.11 (0.92, 5.32)	2.58 (0.76, 9.85)	—	3.59 (0.40, 38.86)	—	4.80 (0.16, 323.73)	559114118822.57 (8.97, 14036346 574872680000000000000000.00)
Kangai+FOLFOX	1.34 (0.31, 6.88)	—	0.42 (0.06, 2.91)	0.88 (0.27, 2.83)	1.04 (0.24, 5.01)	0.42 (0.18, 0.90)	—	—	—	—
Kanglaite+FOLFOX	2.29 (0.48, 13.89)	—	0.69 (0.10, 5.20)	1.41 (0.41, 5.45)	1.77 (0.37, 9.18)	0.67 (0.25, 1.80)	1.65 (0.46, 5.82)	—	1.39 (0.02, 158.35)	163229285514.57 (2.52, 2926777 906267181600000000000000.00)
Shenqifuzheng+FOLFOX	1.72 (0.24, 14.09)	—	0.52 (0.05, 4.51)	1.09 (0.17, 6.81)	1.31 (0.17, 9.95)	0.51 (0.10, 2.37)	1.25 (0.19, 6.65)	0.76 (0.11, 4.30)	—	123702588210.78 (1.12, 4769158 362923775000000000000000.00)
Yadanziyouru+FOLFOX	1.97 (0.41, 11.83)	—	0.61 (0.09, 4.66)	1.32 (0.33, 4.99)	1.55 (0.33, 8.47)	0.60 (0.21, 1.69)	1.49 (0.42, 5.48)	0.92 (0.21, 3.69)	1.18 (0.20, 8.44)	leukopenia (III-IV)

lysugar>Aidi>Yadanziyouru>Compound matrine (see Table 2).

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>Kanglaite>Yadanziyouru>Shenqifuzheng>Compound 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

Overall response rate	Aidi +FOLFOX	Astragalus polysaccharides +FOLFOX	Cinobufacini +FOLFOX	Compound matrine +FOLFOX	Delisheng +FOLFOX	FOLFOX	Ginseng polysugar +FOLFOX	Kangai +FOLFOX	Kanglaite +FOLFOX	Shenqifuzheng +FOLFOX	Yadanziyouru +FOLFOX
Aidi+FOLFOX	—	0.06 (0.01, 0.34)	0.90 (0.33, 2.35)	1.19 (0.40, 3.22)	0.76 (0.17, 2.81)	2.42 (1.40, 4.02)	0.87 (0.20, 3.23)	0.61 (0.27, 1.39)	—	0.74 (0.34, 1.44)	1.19 (0.23, 5.33)
Astragalus polysaccharides +FOLFOX	2.51 (0.71, 9.04)	—	14.99 (2.25, 141.06)	20.40 (2.75, 178.04)	13.16 (1.32, 188.07)	39.08 (7.44, 351.38)	15.61 (1.62, 160.06)	9.81 (1.74, 92.46)	—	11.80 (1.99, 116.20)	19.51 (1.82, 252.81)
Cinobufacini +FOLFOX	1.33 (0.56, 3.29)	0.52 (0.13, 2.15)	—	1.35 (0.39, 4.12)	0.82 (0.17, 3.67)	2.61 (1.17, 6.01)	0.98 (0.19, 4.14)	0.67 (0.25, 1.91)	—	0.82 (0.31, 1.97)	1.25 (0.22, 6.90)
Compound matrine +FOLFOX	1.38 (0.72, 2.64)	0.55 (0.15, 1.99)	1.03 (0.44, 2.53)	—	0.64 (0.12, 3.03)	2.01 (0.87, 5.18)	0.74 (0.15, 3.59)	0.50 (0.18, 1.61)	—	0.60 (0.23, 1.72)	1.01 (0.17, 5.63)
Delisheng +FOLFOX	1.00 (0.35, 2.87)	0.38 (0.09, 1.80)	0.75 (0.22, 2.54)	0.73 (0.24, 2.05)	—	3.22 (0.87, 13.05)	1.12 (0.18, 7.58)	0.82 (0.20, 3.79)	—	0.98 (0.24, 4.17)	1.50 (0.22, 11.72)
FOLFOX	0.81 (0.50, 1.27)	0.32 (0.10, 1.04)	0.60 (0.28, 1.27)	0.58 (0.36, 0.89)	0.80 (0.31, 2.12)	—	0.37 (0.09, 1.26)	0.25 (0.14, 0.48)	—	0.31 (0.18, 0.46)	0.48 (0.11, 2.04)
Ginseng polysugar +FOLFOX	1.06 (0.31, 4.10)	0.43 (0.08, 2.34)	0.81 (0.20, 3.70)	0.77 (0.22, 2.98)	1.06 (0.25, 5.18)	1.32 (0.41, 4.88)	—	0.70 (0.18, 3.23)	—	0.82 (0.22, 3.63)	1.35 (0.19, 9.06)
Kangai +FOLFOX	1.06 (0.51, 2.11)	0.41 (0.11, 1.53)	0.78 (0.31, 2.02)	0.77 (0.36, 1.55)	1.06 (0.35, 3.21)	1.32 (0.74, 2.32)	0.99 (0.25, 3.73)	—	—	1.20 (0.51, 2.70)	1.93 (0.36, 8.96)
Kanglaite +FOLFOX	3.45 (0.93, 13.17)	1.33 (0.25, 7.79)	2.46 (0.62, 11.48)	2.47 (0.65, 9.42)	3.35 (0.73, 17.51)	4.28 (1.26, 15.64)	3.30 (0.53, 17.98)	3.21 (0.85, 12.94)	—	—	—
Shenqifuzheng +FOLFOX	1.57 (0.81, 2.93)	0.62 (0.18, 2.12)	1.16 (0.49, 2.76)	1.13 (0.59, 2.06)	1.56 (0.53, 4.45)	1.93 (1.26, 2.9z8)	1.47 (0.36, 4.99)	1.46 (0.73, 3.07)	0.45 (0.12, 1.65)	—	1.55 (0.35, 7.61)
Yadanziyouru +FOLFOX	2.16 (0.80, 5.91)	0.86 (0.20, 3.67)	1.67 (0.51, 5.01)	1.58 (0.58, 4.11)	2.21 (0.59, 7.85)	2.72 (1.16, 6.39)	2.04 (0.42, 8.46)	2.06 (0.75, 5.87)	0.65 (0.13, 2.89)	1.39 (0.55, 3.63)	KPS

did not report the satisfactory methods of randomization and blinding, which would lead to selection bias, performance bias, and measurement bias. In addition, the quantity of included RCTs was less (Tian et al., 2012), the sample size of 89.47% included studies was less than 100, and the methods of sample estimation were not provided. Moreover, there were no direct head-to-head evidences for different CHIs. So we eagerly demanded the other direct head-to-head studies to confirm.

Clinical implications: Our network meta-analysis showed that the Kanglaite injection, Astragalus polysaccharides injection, Cinobufacini injection, and Yadanziyouru injection were the best CHIs regarding to strengthen ORR, improve the quality of life, reduce nausea and vomiting, and reduce incidence of leukopenia (III-IV), respectively. Overall, compared with FOLFOX alone, Kanglaite injection combined with FOLFOX regimen, Astragalus polysaccharides injection combined with FOLFOX regimen, Yadanziyouru injection combined with FOLFOX regimen were superior to all other CHIs combined with FOLFOX regimens in the clinical efficacy and safety. The CHIs can be chosen according to different treatment purposes.

Future directions: Both the number of studies of adverse events and the sample size were small. The large sample size studies about adverse events were needed. The methodological quality of included studies was poor, most of studies did not report the method of randomization and use of blinding. More rigorously designed randomized controlled trials with scientific methods were urgently needed. In addition, researchers should conduct large sample size RCTs to directly compare the clinical efficacy and adverse events among CHIs for GC. For editor, the instructions to authors should include related reporting items, and the submission of CONSORT checklist.

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