Original Article Safety and efficacy of Kanglaite injection in the treatment of malignant pleural effusion: a meta-analysis

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Abstract: Background: Kanglaite injection (KLT) has been increasingly used to control malignant pleural effusion (MPE); however, it remains unclear whether KLT combined with chemotherapy is more effective than chemotherapy alone. In this review, we performed a meta-analysis to evaluate the efficacy and safety of KLT combined with cisplatin in the treatment of MPE. Methods: A literature search was performed using the following databases: MEDLINE (PubMed), Embase, PsycINFO, Chinese Biomedical (1980-2014), Chinese Journal Full-text (1980-2014), Weipu Scientific Journal (1989-2014), and Cochrane Central Register of Controlled Trials (CENTRAL database, updated to December 15, 2014). All reports that compared KLT and cisplatin with cisplatin monotherapy in the treatment of MPE were included. Primary outcomes were complete response (CR) and partial response (PR). Secondary outcomes were complications and Karnofsky performance status (KPS) results. Meta-analysis of pooled CR, PR, and KPS was performed using a random-effects model with inverse-variance weighting. Results: In total, seven randomized controlled studies and three controlled studies comprising 488 participants (age range, 18-35 years) were included in the meta-analysis. The results identified a significant difference between the combined therapy and monotherapy groups in response rates, with response rates higher in patients receiving Kanglaite and cisplatin (Risk ratio (RR), 2.46; 95% confidence interval (CI), 1.68-3.59; P<0.001). Combined therapy significantly improved KPS (RR, 3.07; 95% CI, 1.30-7.23). A significant reduction in nausea and vomiting was found in the combined therapy group compared with the monotherapy group (RR, 0.22; 95% CI, 0.10-0.48; P=0.9, from four studies comprising 62 patients). There was no significant difference between the test and control groups regarding leucopenia, chest pain, and fever.

Keywords: Chinese traditional herb, kanglaite injection, cisplatin, malignant pleural effusion, systematic review

Introduction

Malignant pleural effusion (MPE) occurs frequently in patients with advanced malignancies due to metastases originating from tumors in the lung, breast, and ovary, and from lymphomas. MPE results in chest tightness, chest pain, and respiratory symptoms that seriously impact quality of life and is associated with a shorter life expectancy. Despite recent progress in multidisciplinary treatment with chemotherapy, radiotherapy, immunotherapy, hyperthermia, and other therapies, the prognosis for patients with MPE is poor. Identification of novel therapeutic methods for the treatment of patients with MPE is becoming increasingly urgent. Traditional Chinese Medicine (TCM) is one of the most important forms of medicine in China. Nowadays, TCM is increasingly used as an adjuvant treatment for MPE. Kanglaite injection (KLT) is primarily composed of Coix seed oil, a TCM, and is mainly used for the treatment of non-small-cell lung cancer [1, 2], liver cancer [3], gastric cancer [4, 5], and breast cancer [6]. KLT is effective in the treatment of MPE [7].

Although KLT has been widely studied in the treatment of MPE, its precise practical value remains unclear. The aim of this study was to assess the available evidence on the clinical efficacy and safety of KLT in the treatment of MPE in patients with various cancers via a systematic review and meta-analysis.

Methods

Search strategy

A literature search was conducted using the following databases: MEDLINE (PubMed), Embase, PsycINFO, Chinese Biomedical (1980-2014), Chinese Journal Full-text (1980-2014), Weipu Scientific Journal (1989-2014), and Cochrane Central Register of Controlled Trials (CENTRAL database; updated to December 15, 2014). Keyword searches included various combinations of the following terms: "Kanglaite", "traditional Chinese herb", "cisplatin", and "pleural effusion". This search strategy was amended for each database. Two authors independently screened all citations and abstracts identified by the search strategy to identify eligible studies.

Inclusion and exclusion criteria

The inclusion criteria were as follows: randomized controlled trials (RCTs) or non-randomized controlled trials (non-RCTs); patients with cytologically or histologically confirmed MPE; patients with intrathoracic injection or infusion of KLT combined with cisplatin or cisplatin alone; patients with a Karnofsky performance status (KPS) of 50% or greater; patients with a life expectancy of greater than 2 months; and adequate hematologic, renal, hepatic, and cardiac function.

Patients were excluded from the study if they had undergone chemotherapy or radiotherapy treatment within the previous 2 months; received local antitumor drugs; had severe heart, hepatic, or renal disease; had markedly abnormal blood biochemistry findings; or had hepatic or renal dysfunction. Editorials, letters to the editor, review articles, case reports, and animal experimental studies were excluded.

Data extraction

Independent extraction of the full-text articles that met our eligibility criteria was performed by two authors (L.C. and J.X.). The primary outcome measures were as follows: a complete response (CR) when no pleural effusion was observed; a partial response (PR) when pleural effusion was observed, but the level of effusion was less than 25% of the long axis of the hemithorax; and no response (NR) when effusion was larger than that defined by PR. The secondary outcomes were KPS results and adverse events such as nausea, vomit and fever and chest pain.

Quality assessment

The Cochrane Collaboration's tool was used to assess the risk of bias of the included trials. The risk of bias tool comprises six domains: random sequence generation (selection bias), allocation concealment (selection bias), blinding of participants, personnel, and outcome assessment (performance and detection bias), assessment of incomplete data outcome (attrition bias), selective reporting (reporting bias), and other sources of bias. Each item was graded as a low or high risk of bias if there was sufficient information to assess; otherwise, the item was graded as unclear. Two authors (L.C. and J.X.) independently assessed the quality, and any disagreement between the review authors was resolved by discussion.

Statistical analyses

Statistical analyses were performed using the RevMan 5.1 software (Nordic Cochrane Center, Copenhagen, Denmark). Dichotomous data were expressed as relative risks. Continuous data were expressed as the weighted mean differences (WMD). l^2 statistic was used to evaluate heterogeneity among the studies. Heterogeneity was considered statistically significant when l^2 >50%. The data from the studies were pooled on the basis of a random-effects model or a fixed-effects model depending on the presence of heterogeneity.

Results

Search results and study selection

The electronic and manual search resulted in the initial identification of 1139 relevant articles. Following review of titles and abstracts, 531 duplicates were excluded, 224 reviews were excluded, 259 NCTs were excluded, and 27 interventions that did not meet the inclusion criteria were excluded. Full-text evaluation of the remaining 56 articles was performed. An additional 46 articles were excluded as they did not meet the requirements. Of these, three articles lacked original data, 30 articles did not have outcomes that met the criteria, the interventions of seven articles did not meet the inclusion criteria, and six studies were found to

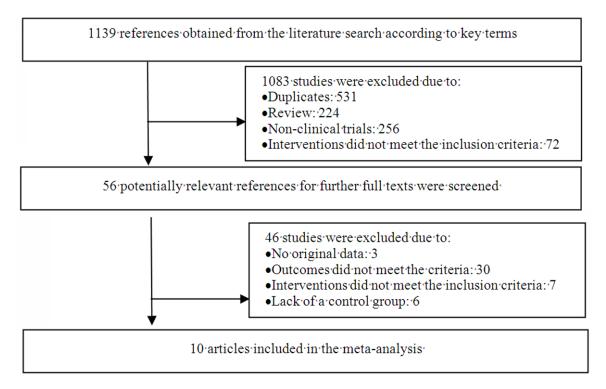


Figure 1. Diagram of the study selection procedures.

Author (year)	Design	Study period	Age range (years)	No. of partic- ipants T/C	Duration (weeks)
Chen X 2010 [8]	RCT	June 2005-June 2006	42-81	25/23	4
Chen YY 2009 [9]	RCT	January 2005-January 2009	32-70	22/24	4
Jia F 2005 [10]	Non-RCT	October 1998-October 2000	39-87	25/23	4
Lan GC 2012 [11]	Non-RCT	August 2008-October 2010	38-76	21/21	4
Li HH 2012 [12]	RCT	September 2010-January 2012	35-78	30/30	4
Tian HW 2005 [13]	RCT	August 1999-August 2002	Not mentioned	42/38	4
Wang LR 2002 [14]	RCT	1999-2002	22-73	30/30	4
Yang SF 2005 [15]	RCT	June 2000-June 2005	Not mentioned	27/27	4
Zhang H 2006 [16]	Non-RCT	May 2003-August 2005	50-75	12/8	4
Zhang H 2009 [17]	RCT	February 2007-February 2008	Not mentioned	20/14	4

Table 1. Characteristics of	f the studies	included in	the meta-analy	sis
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RCT, randomized control trial; Non-RCT, non-randomized controlled trial; T, test group; C, control group.

lack a control group. In total, seven RCTs and three non-RCTs were selected for data extraction and analysis. The included trials involved 488 patients. The detailed steps of our literature search are shown in **Figure 1**.

Study characteristics

All of the RCTs and non-RCTs were conducted in patients with MPE in China. In these studies, CR, PR, KPS, and reported adverse events were assessed in patients with a combination therapy of KLT and cisplatin (test group, T) and patients with cisplatin alone (control group, C). All eligible studies were published between 2005 and 2012. All of the participants were at least 18 years old. The length of the intervention was 4 weeks. Detailed characteristics of the ten studies are summarized in **Table 1**.

Quality of the included studies

The risk of bias (Figure 2) in the included studies was evaluated using the Cochrane Risk of

Kanglaite in malignant pleural effusion

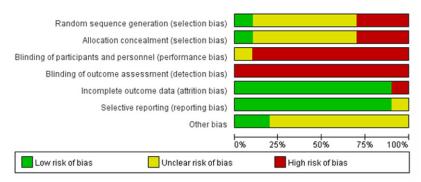
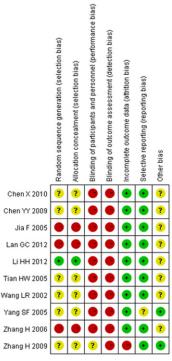
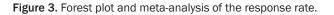


Figure 2. Risk of bias in the included studies.



	kanglaite combined with cisplatin		cisplatin		Odds Ratio		Odds Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% Cl	M-H, Fixed, 95% Cl
Chen X 2010	17	25	8	23	13.5%	3.98 [1.20, 13.24]	
Chen YY 2009	19	22	15	24	9.9%	3.80 [0.87, 16.55]	
Jia F 2005	20	25	12	23	12.7%	3.67 [1.02, 13.14]	
Lan GC 2012	19	21	12	21	5.8%	7.13 [1.31, 38.77]	│ ────→
Li HH 2012	26	30	16	30	10.8%	5.69 [1.59, 20.33]	
Tian HW 2005	36	42	22	38	16.8%	4.36 [1.49, 12.82]	
Wang LR 2002	26	30	20	30	13.5%	3.25 [0.89, 11.90]	
Yang SF 2005	23	27	13	23	10.6%	4.42 [1.15, 16.96]	
Zhang H 2006	11	12	6	8	3.0%	3.67 [0.27, 49.29]	
Zhang H 2009	19	20	11	14	3.3%	5.18 [0.48, 56.09]	
Total (95% CI)		254		234	100.0%	4.33 [2.78, 6.75]	•
Total events	216		135				
Heterogeneity: Chi ² =	0.85, df = 9 (P = 1.00); l ² = 0%						0.05 0.2 1 5 20
Test for overall effect:	Z = 6.49 (P < 0.00001)						Favours [cisplatin] Favours [kanglaite combined with
							Favous (cispiani) - Pavous (Kangiane complied with



Bias Tool. Ten studies comprising seven RCTs [8, 9, 12-15, 17] and three controlled trials [10, 11, 16, 17] were included in the analysis. Methods of generating randomization sequences using a random digital table were described in only one study [12]. The blinding method was not reported in any of the studies.

Pooled analysis

Response rate: All of the included RCTs reported response rates. Results of the response rate are depicted in **Figure 3**. The response rate was analyzed in 488 patients treated with both KLT and cisplatin, and cisplatin alone. There was no significant heterogeneity and the fixedeffects model was used (P=1.00; l^2 =0%). Results of the pooled analysis of response rates showed a significant difference between the combined therapy and cisplatin control groups, with a higher rate observed in patients receiving both KLT and cisplatin (risk ratio (RR), 4.33; 95% confidence interval (CI), 2.78-6.75; P<0.00001).

Improvement in quality of life: A change in the KPS score was reported in three of ten studies comprising 114 patients [12, 16, 17] (**Figure 4**). No heterogeneity was found, and the fixed-effects model was used (P=0.75; l^2 =0%). An improvement in the KPS score (increase of KPS≥10) was reported in 66.13% of patients in

Kanglaite combinded with cisplatin			cispla	tin		Odds Ratio	Odds Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI	M-H, Fixed, 95% Cl
Li HH 2012	25	30	18	30	48.4%	3.33 [1.00, 11.14]	
Zhang H 2006	9	12	3	8	14.5%	5.00 [0.72, 34.73]	
Zhang H 2009	7	20	3	14	37.0%	1.97 [0.41, 9.52]	
Total (95% CI)		62		52	100.0%	3.07 [1.30, 7.23]	
Total events	41		24				
Heterogeneity: Chi² = Test for overall effect:	0.56, df = 2 (P = 0.75); I ² = 0% Z = 2.57 (P = 0.01)						0.05 0.2 1 5 20 Favours [cisplatin] Favours [Kanglaite combinded with

Figure 4. Forest plot and meta-analysis of improvement in quality of life.

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$ \begin{array}{c ccccccccccccccccccccccccccccccccccc$	Jia F 2005	9	25	15	23	18.3%	0.30 [0.09, 0.98]	
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Test for subgroup differences: Chi ² = 8.23, df = 3 (P = 0.04), I ² = 63.6%							,	
	Test for subgroup diff	erences: Chi² = 8.23. df = 3 (P =	0.04).	² = 63.6%			1	avours (experimental) Favours (control)

Figure 5. Forest plot and meta-analysis of adverse events.

the combined KLT and cisplatin group (n=62) and 46.15% of patients in the cisplatin monotherapy group (n=52). Combined treatment significantly improved KPS compared with monotherapy (RR, 3.07; 95% CI, 1.30-7.23).

Adverse events: Mild and low-grade adverse events were reported in four studies comprising 150 patients [8, 10, 18]. The most common adverse events arising from treatment were nausea and vomiting. A significant reduction in nausea and vomiting was observed in the combined therapy group compared with the monotherapy group (RR, 0.22; 95% Cl, 0.10-0.48; P=0.9 from four studies) [8, 10, 17] (Figure 5). Leucopenia was reported in one study (48 patients) [10], although there was no significant difference between the two groups. Chest pain was reported in three studies comprising 102 patients [8, 16, 17], and an additional three studies (130 patients) [8, 10, 16, 17] reported fever as an adverse effect. Statistical analyses did not reveal a significant difference between both groups for both of the reported adverse effects.

Discussion

The combination of TCM and Western medicine for the treatment of MPE is widely recognized. TCM has the advantage of increasing the curative effect and controlling adverse reactions. Preclinical studies demonstrated that KLT may block the tumor cell cycle at the G2/M phase, inhibit proliferation of tumor cells, and induce tumor cell apoptosis by activating the expression of apoptotic factors [19]. KLT may activate a series of cytokines and, hence, inhibit the generation of fibrinolytic activity and promote fibrin deposition in the lung [20]. Various clinical studies show that Kanglaite significantly decreases cancer cachexy, improves the quality of life of cancer patients, and may ameliorate multiple drug resistance of cancers when combined with radiotherapy and chemotherapy in clinical use [21-23].

In the present study, a systematic review and meta-analysis of all controlled clinical trials published to date that involved the treatment of MPE via combined therapy with KLT and cisplatin and cisplatin alone were performed. We included ten studies comprising 488 participants in our analysis. Following comparison of combined therapy with monotherapy, a significant difference in response rates was observed between the combined therapy and monotherapy groups, with a higher rate observed in patients receiving both KLT and cisplatin (RR, 4.33; 95% CI, 2.78-6.75; P<0.00001). Combined treatment significantly improved KPS (RR, 3.07; 95% CI, 1.30-7.23]. Regarding adverse events, a significant reduction in nausea and vomiting was observed in the combined therapy group compared with the monotherapy group (RR, 0.22; 95% CI, 0.10-0.48; P=0.0001, from four studies comprising 62 patients). Furthermore, there was no significant difference between the combined therapy and mon-otherapy groups regarding leucopenia, chest pain, and fever.

To date, our study was the first to evaluate the clinical efficacy and safety of the administration of KLT in the treatment of MPE in patients with different types of cancers. The risk of bias in the included studies was evaluated using the Cochrane Risk of Bias Tool. We included ten studies that comprised seven RCTs and three controlled trials. All of the included studies reported data with a small sample size, and the quality of the included studies was uniformly poor. Methods of generating randomization sequences using a random digital table were described in only one study. None of the studies provided information on allocation concealment and blinding methods that lead to the reduced reliability of evaluation results.

Other limitations of the present study are as follows: publication bias in the meta-analysis of the published studies; the number of available studies in the literature was too small and the studies were of low sample size: the search was expanded to non-RCTs, and the risk of bias in such studies is high; the meta-analysis in this study was based on Chinese research, and studies from other parts of the world were not found, which may generate a partial result; lack of data on different tumor subgroups: and lack of data on Kanglaite combined with other chemotherapeutic agents, hence it was difficult to comprehensively compare the efficacy and safety of combination therapy with chemotherapy alone. Future prospective cohort studies are required to address many of the limitations of our meta-analysis.

In conclusion, the results of the meta-analysis presented here suggest that combination therapy comprising KLT and cisplatin achieves an increased curative effect and decreased adverse reactions compared with cisplatin monotherapy. Given the generally low methodological quality of the included studies, to test the efficacy and safety of Kanglaite in MPE and determine further clinical application, additional studies with methodologically rigorous trials are required.

Disclosure of conflict of interest

None.

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