RESEARCH ARTICLE

Effect of Matrine Injection Combined with First-line Chemotherapy in the Treatment of Lung Cancer: a Meta-analysis

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Yizhen Zhang[1†], Haihua Guo[2†], Guohua Cheng[3*]

[1]Traditional Chinese medicine, College of Pharmacy, Jinan University, No. 601 Huangpu Avenue West, Guangzhou, China, P.C. 510632

[2]Clinical Pharmacy, College of Pharmacy, Jinan University, No. 601 Huangpu Avenue West, Guangzhou, China, P.C. 510632

[3]School of Pharmacy, Jinan University, No. 601 Huangpu Avenue West, Guangzhou, China, P.C. 510632

[†]Contributed equally to this work and should be considered as co-first authors.

Address reprint requests to:
*Guohua Cheng, School of Pharmacy, Jinan University, No.601 Huangpu Avenue West, Guangzhou, China, P.C. 510632
Email: ghcheng661203@126.com

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ABSTRACT

The aim of this study is to systematically evaluate the efficacy and safety of matrine injection (MI) combined with first-line chemotherapy in the treatment of lung cancer. The search was applied to Cochrane Library, EMBASE, PubMed, Web of Science, CNKI, WANFANG DATA, VIP and CBM database from 2006 to 2016. Randomized controlled trials (RCTs) of MI combining first-line chemotherapy (versus chemotherapy alone) in any language were included. Two authors extracted data and assessed literature quality independently. Meta-analysis was conducted by using RevMan 5.3 software. Ten studies total 906 cases were included. The meta-analysis showed that compared with the first-line chemotherapy alone, the combination of MI and first-line chemotherapy in the treatment of lung cancer could not only improve the short-term clinical efficacy [RR = 1.17, 95% CI (1.02, 1.34), $P = 0.02$], complete response (CR) [RR = 1.46, 95% CI (0.99, 2.15), $P = 0.06$] and the quality of life [RR = 1.62, 95% CI (1.19, 2.20), $P = 0.002$], but also reduce WBC toxicity [RR = 0.39, 95% CI (0.27, 0.55), $P < 0.00001$] and the nausea and vomiting [RR = 0.52, 95% CI (0.37, 0.73), $P = 0.0002$]. Matrine injection combined with first-line chemotherapy regimen for lung cancer has a certain synergistic effect, but it needs to be further confirmed through a large sample of clinical studies.

KEYWORDS matrine injection, lung cancer, chemotherapy, RCTs, meta-analysis

INTRODUCTION

Lung cancer is one of the malignant tumors with a fastest growing incidence and mortality. It is a serious threat to people's health and life. Over the past 50 years, many countries have reported a significant increase in the incidence and mortality of lung cancer.The statistics from American Cancer Society showed that 224,390 new lung cancer cases and 158,080 lung cancer deaths were projected to occur in the US in 2016. The mortality rate of lung cancer ranks first in all tumors" could be revised to "The statistics from American Cancer Society showed that 222,500 new lung cancer cases and 155,870 lung cancer deaths were projected to occur in the US in 2017[1]. According to annual report on the status of cancer from the National Central Cancer Registry (NCCR) of China in 2011, lung cancer was considered as the leading cause of death in China. The total new lung cancer incident cases and lung cancer deaths were 651,053 and 529,153 in 2011, with an incidence rate of 48.32/100,000, and mortality rate of 39.27/100,000, respectively[2]. Lung cancer can be divided into small cell lung cancer (SCLC) and non-small cell lung cancer (NSCLC), the most common of which is non-small cell lung cancer, accounting for about 85%. The main clinical treatments of lung cancer were chemotherapy, intervention, surgery, gene, immunotherapy, and so on. However, the majority of patients diagnosed when the disease has been developed to the late, they failed to take the advantage of surgery, so that chemotherapy became the primary means. At present, platinum-based combination therapy is still the main first-line treatment regimen recommended by the NSCLC Clinical Practice Guidelines developed by the National Comprehensive Cancer Network (NCCN). The chemotherapy drugs play cytotoxic effect on tumor cells, but meanwhile, they can also make the body proliferating active normal cell damage with varying degrees, causing side effects, which seriously affect the quality of life of patients, and even many patients discontinue treatment as they cannot tolerate serious adverse reactions. Therefore, exploring attenuated therapy against the

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adverse reactions caused by chemotherapy has become a top priority for the treatment of cancer[3].

Matrine injection (MI) is one kind of traditional Chinese medicine preparations with matrine as its main component. Matrine can play an anti-tumor effect by inhibiting tumor cell proliferation, inducing tumor cell differentiation and apoptosis, inhibiting tumor cell metastasis and other pathways in lung cancer cells[4–5]. In addition, matrine injection can also benefit and strengthen the body resistance, and enhance the body immune function[6]. Studies have shown that matrine injection combined with first-line chemotherapy in the treatment of lung cancer can improve the efficacy of chemotherapy drugs and reduce the toxicity. However, the samples of the current trials were mostly small, lacking of certain persuasion.

In this study, a meta-analysis method was conducted to systematically evaluate the efficacy and safety of matrine injection combined with first-line chemotherapy in the treatment of lung cancer. We hope to provide a true and reliable basis for clinical medication of lung cancer.

METHODS

Search strategy and inclusion criteria

According to the PRISMA statement guidelines for the meta-analysis of RCTs[7], we searched Cochrane Library, EMBASE, PubMed, Web of Science, CNKI, WANFANG DATA, VIP and CBM database to identify RCTs of MI combining first-line chemotherapy versus chemotherapy alone in the treatment of lung cancer in English and Chinese from January 2006 to December 2016, using the following Medical Subject Headings (MeSH) and keywords as search strategy: (matrine, OR matrine injection) AND (lung cancer, OR NSCLC, OR SCLC) AND (TP, OR DP, OR GP, OR NP) AND (random* OR clin* OR study* OR trial*). The reference lists of articles were scanned to identify potential additional relevant studies. For articles published in Chinese, we translated the titles into English and added the DOI address in reference part. Two reviewers (Y.Z. and H.G) screened the articles independently based on the inclusion and exclusion criteria and then crosschecked to reach a consensus. Details of search and selection process are shown in Fig. 1.

All the randomized clinical trials were included. Participants of older than 18 years with a clear pathology, imaging or clinical diagnosis of lung cancer and required chemotherapy, KPS score ≥60, expected survival ≥3 months were considered. This meta-analysis was limited to studies focused on short-term clinical effect, complete response (CR) rate, quality of life, side effects including leukopenia and gastrointestinal reactions, comparing MI combining first-line chemotherapy to chemotherapy alone, with an observation cycle of three treatment cycles.

Exclusion criteria

Studies met any of the following criteria were excluded: (1) non-randomized controlled trials; (2) non-conventional

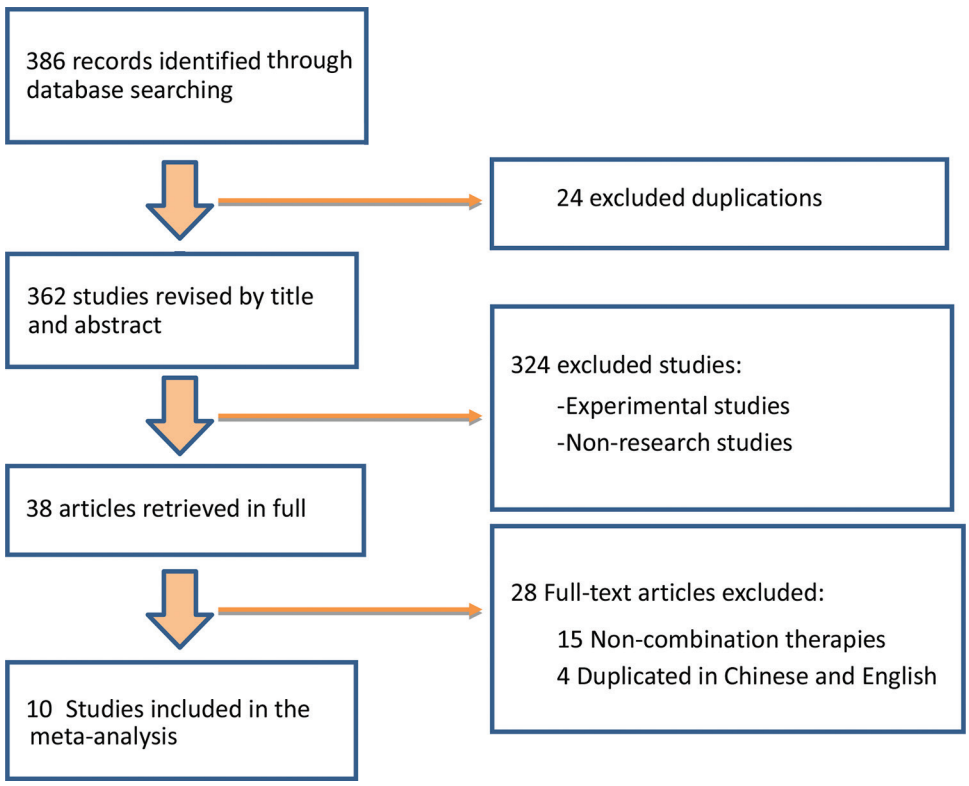

Fig. 1 Article selection process for meta-analysis.

first-line chemotherapy treatment; (3) combined surgery, radiotherapy or other treatment; (4) medication contraindications or use drugs similar to MI; (5) repeated published literature; (6) cannot get the full text or cannot extract the data of literature; (7) no outcome of this study; (8) the samples of control group or the experimental group less than 30.

Quality assessment

Two reviewers (Y.Z. and H.G) conducted a risk-of-bias assessment independently according to the standardized manner recommended in the *Cochrane Handbook for Systematic Reviews of Intervention*[8] and then crosschecked. Jadad Scale[9] was used to evaluate the quality of included studies, which consists of the following items: random sequence generation, allocation concealment, blindness, the completeness of the outcome data, selective reporting of results, and other possible bias, scored 1 to 2 were regarded as low-quality research, while 3 to 5 were high. There were no disagreements between reviewers.

Data extraction and outcome measures

On the basis of pre-designed data extraction sheet, two reviewers (Y.Z. and H.G) extracted the data from each included studies independently. The extracted information include: (1) name of the first author; (2) year of publication; (3) type of trial design; (4) characteristics of trial participants (including age, number); (5) type of intervention; (6) type of outcome measure (including the total number of effective cases, number of complete response cases, number of KPS score increased by 10 points or more cases, incidence rate of adverse drug reaction).

Primary outcome was the improvement of short-term clinical efficacy, counted by the number of participants who got complete response (CR) and partial response (PR)[10]. In addition, the improvement in quality of life, assessed by the Karnofsky performance scale (KPS)[11] and the number of patients got CR were regarded as secondary outcomes. We determined the quality of life improved when KPS score increased by 10 points or more. Side effects such as leukocyte, nausea and vomiting were also included and counted for the incidence rate of adverse drug reaction.

State description of efficacy

Complete response (CR): The lesions completely disappeared for more than 4 weeks.

Partial response (PR): The product of the maximum diameter and the maximum vertical diameter of the lesions reduced by 50%, other lesions did not increase, lasting more than 4 weeks.

Stable disease (SD): The product of the maximum diameter and the maximum vertical diameter of the lesions reduced by less than 25% or increased by no more than 25%, lasting more than 4 weeks. No new lesions appear.

Progressive disease (PD): The product of the maximum diameter and the maximum vertical diameter of the lesions increased by more than 25% or new lesions appear.

Effective rate: The number of cases with CR and PR.

Improvement in quality of life: KPS score increased 10 or more.

Statistical analysis

This meta-analysis was performed using RevMan 5.3 software. The relative outcome (RR) was used as the statistical data, and the effect was expressed as 95% confidence intervals (95% CI). The heterogeneity test between the included studies was based on the I^2 test. If there was no statistical heterogeneity ($I^2 \leq 50\%$), the fixed effect model was used, whereas the random effect model was used or not, hypothesis test would be used as a statistical significance analysis of the final outcome. According to the statistical P value of Z(u), the final outcome can be analyzed whether there was statistical significance, $P \leq 0.05$ for the difference was statistically significant, otherwise, the difference was not statistically significant. At the same time, the study also used the 95% CI method for analysis. In the forest plots, the the 95% CI didn't contain the ineffective line that combined statistics were statistically significant.

RESULTS

Characteristics of studies in the meta-analysis

Totally, the search of Chinese and English databases provided 386 literatures. After removing duplicates, 362 remained, of which 324 studies were excluded after reading the title and abstract. It indicated that these articles did not meet the criteria (experimental studies, non-research studies or cannot get the full text), and then examined the full text of the remaining 38 studies. 15 trials were excluded for non-combination therapy, 4 trials for duplication, 5 trials for outcome couldn't be judged, and 4 trials were case reports. A total of 10 studies, involving 906 patients were included in the meta-analysis finally. Details of literature screening process are shown in Table 1.

These 10 included studies were randomized controlled trials comparing the matrine injection combined with first-line chemotherapy regimen versus first-line chemotherapy alone in the treatment of lung cancer[12–21]. All of the trials were conducted between 2006 and 2016. The main characteristics of 10 included trials and the quality of them assessed by the Jadad score are shown in Table 1. All the included studies referred to the word "random", one of which[12] was grouped by random number table method, and none of the other studies referred to the specific randomized method. All of the included studies did not mention the allocation of concealment and blindness. Only one of the literatures[15] mentioned cases of withdrawal.

Table 1 Characteristics of included trails.

Reference	Year	Trial design	Age of patients (years)	No. of patients (Control/ treatment)	Intervention		Outcome	Group balance	Randomized method	Blind	Jadad score
					Control group	Treatment group					
Zhang JW[12]	2015	RCT	18 – 75	60/60	GP	GP + MI	①②③	Better	Random number	NM	4
Zhang ZY[13]	2011	RCT	18 – 65	30/30	NP	NP + MI	①②④	Better	NM	NM	3
Liu JL[14]	2011	Retrospection	18 – 75	36/36	GP	GP + MI	①②③④	Better	NM	NM	3
Zhou L[15]	2009	RCT	18 – 75	32/32	NP	NP + MI	①②③④	Better	NM	NM	2
Xu W[16]	2005	RCT	50 – 75	30/30	NP	NP + MI	①②③④	Better	NM	NM	2
Yan J[17]	2001	RCT	18 – 75	97/106	CC	CC + MI	①②③⑤	Better	NM	NM	2
Shi LH[18]	2001	Observation	18 – 75	59/62	CC	CC + MI	①②④	Better	NM	NM	2
Su SY[19]	2014	RCT	18-75	24/26	TP	TP + MI	①②④	Better	NM	NM	2
Tao YJ[20]	2007	Observation	18 – 75	64/62	NP/DP/GP	NP/DP/GP + MI	④	Better	NM	NM	2
Zhu L[21]	2016	RCT	18 – 75	15/15	DP/GP/TP	DP/GP/TP + MI	①②③④	Better	NM	NM	2

GP: Gemcitabine combined with the platinum-based chemotherapy, NP: Vinorelbine (NVB) combined with the platinum-based chemotherapy, TP: Taxol combined with the platinum-based chemotherapy, DP: Docetaxel combined with the platinum-based chemotherapy, CC: Conventional chemotherapy, MI: Matrine Injection, NM: non-mentioned, ① CR: complete response, ② Effective rate = (CR+PR)/(control group + treatment group) × 100%, ③ KPS, ④ ADR rate = ADR patients/(control group + treatment group) × 100%, ⑤ Pain relief rate.

The short-term clinical efficacy

Nine studies reported a short-term clinical efficacy, including 906 patients, of which 397 were in the treatment group and 383 in the control group. There was no statistical heterogeneity ($I^2 = 16\%$, $P = 0.30$), we used fixed effect model (Mantel–Haenszel model) to analyze. Meta-analysis showed that the short-term efficacy of the MI group was higher than that of the control group [RR = 1.17, 95% CI (1.02, 1.34), $P = 0.02$], suggested that matrine injection combined with the first-line chemotherapy could have a significant improvement in short-term clinical efficacy than chemotherapy alone of lung cancer after three treatment cycle (Fig. 2).

A funnel plot was applied to represent the publication bias (Fig. 3). The shape of the funnel was basically symmetrical and the literature was concentrated, indicating that the potential bias of the nine studies was less. Consolidated statistics were stable and reliable.

Complete response

There were six articles, 289 patients in the MI group and 286 in the control group, reporting the complete response rate. As shown in Fig. 4, statistical heterogeneity wasn't observed ($I^2 = 0\%$, $P = 0.99$), using the fixed effect model (Mantel–Haenszel model) as a meta-analysis method. The results tended to indicate that MI combined with first-line chemotherapy could get a higher CR rate than chemotherapy alone after three treatment cycles [RR = 1.46, 95% CI (0.99, 2.15)].

Z-curse test (Z(u) = 1.91, $P > 0.05$) showed that the results were not statistically significant.

Quality of life

Of the studies included, there were three trials reporting the improvement of quality of life evaluated by KPS score, a total of 252 patients, of which 126 cases of MI group and 126 of control group. There was no signif-

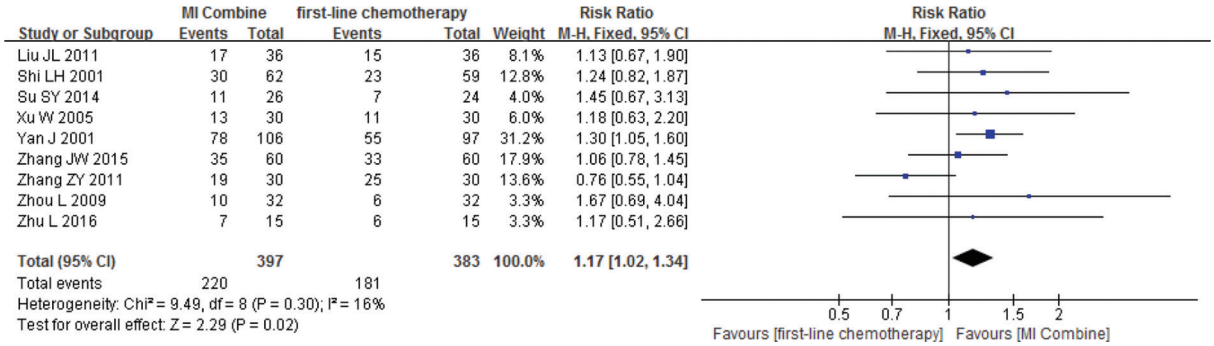

Fig. 2 The meta-analysis of total efficacy about MI combined with first-line chemotherapy and chemotherapy alone for lung cancer.

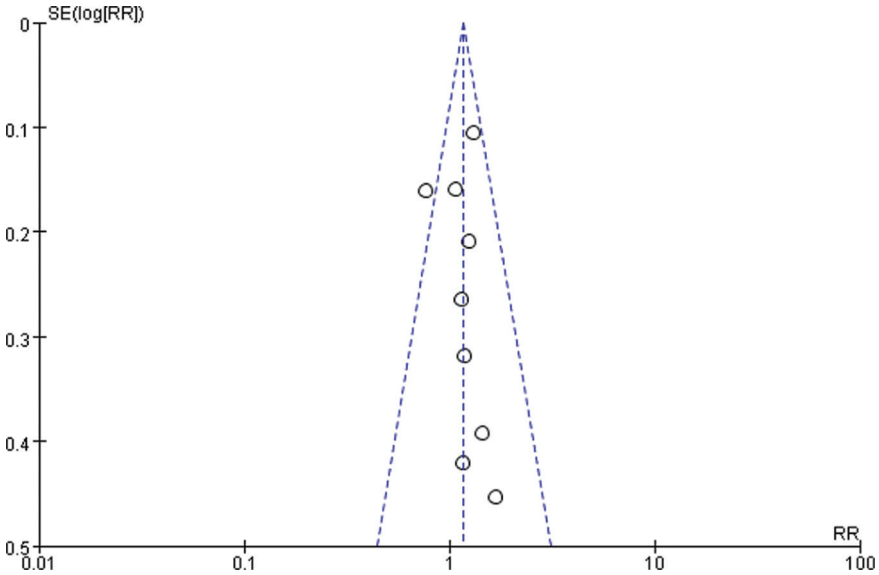

Fig. 3 The funnel plot of meta-analysis of total efficacy about MI combined with first-line chemotherapy and chemotherapy alone for lung cancer.

icant heterogeneity between the studies [I^2 = 0%, P = 0.05], so meta-analysis was performed by fixed effect model. As shown in Fig. 5, the results indicated that MI combined with first-line chemotherapy could make patients with better quality of life than chemotherapy alone in the treatment of lung cancer [RR = 1.62, 95% CI (1.19, 2.20)], and Z(u) test showed that the results were statistically significant [Z = 3.06, P = 0.002] .

Leukocyte decrease

Among 10 included studies, 8 observed a decrease of leukocyte, including 360 patients in MI group and 348 in control group. Mantel–Haenszel was used as a meta-analysis method as the data showed no significant heterogeneity between studies [I^2 = 0%, P = 0.79]. Meta-analysis showed that MI combined with first-line chemotherapy made the number of cases that caused leukocyte to decrease above grade III less than that of the control group after three treatment cycles [RR = 0. 39, 95% CI (0.27, 0.55)]. Z(u) test showed that the results were statistically significant [Z = 5.30, P < 0.00001] (Fig. 6).

Nausea and vomiting

Eight studies evaluated the adverse reactions in nausea and vomiting. A total of 575 patients (287 in MI group and 288 in control group) were included. There was statistically significant heterogeneity between studies [I^2 = 63%, P = 0.008]. Meta-analysis showed that comparing to chemotherapy alone, MI combined with first-line chemotherapy for lung cancer would like to reduce the number of cases caused by nausea and vomiting grade III or more [RR = 0.52, 95% CI (0.37, 0.73). Z(u) test demonstrated that the results were statistically significant [Z = 3.76, P = 0.0002], even though heterogeneity between studies was obvious.

DISCUSSION

In the comprehensive treatment of lung cancer, chemotherapy is an important treatment. However, the cytotoxic effect of chemotherapy drugs can also make the body's normal cell damage.

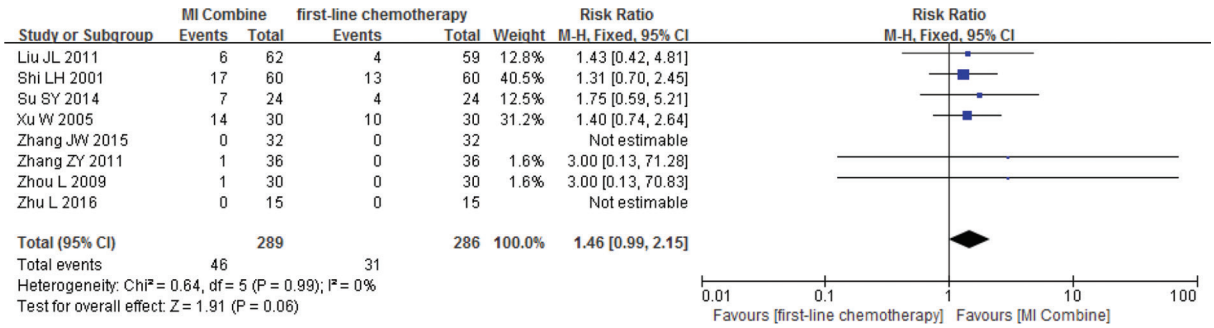

Fig. 4 The meta-analysis of CR rate about MI combined with first-line chemotherapy and chemotherapy alone for lung cancer.

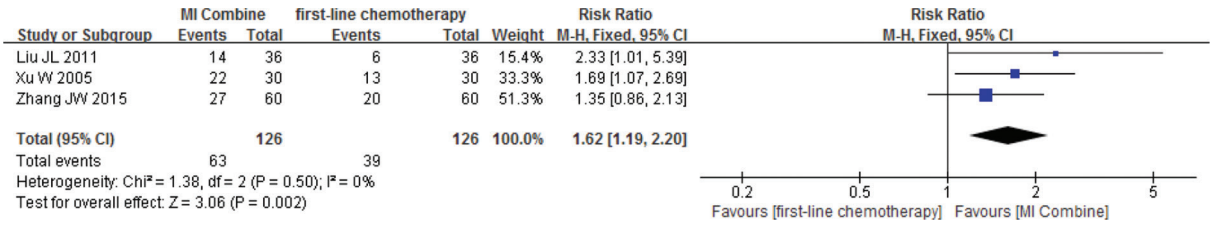

Fig. 5 The meta-analysis of quality of life about MI combined with first-line chemotherapy and chemotherapy alone for lung cancer.

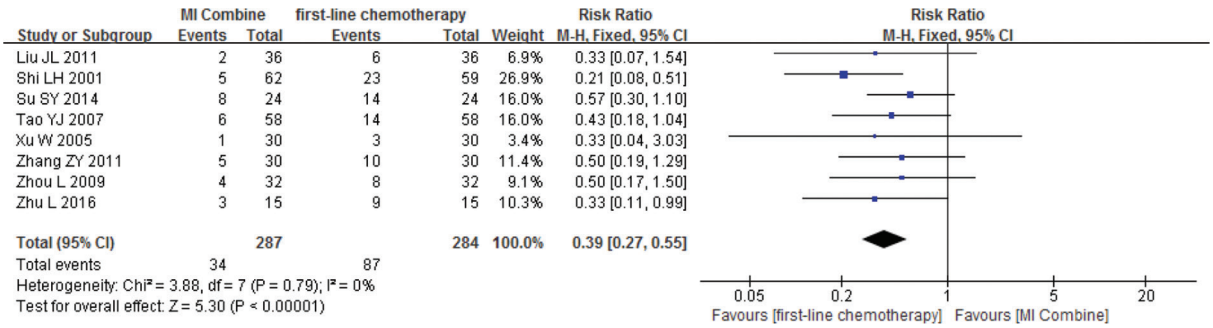

Fig. 6 The meta-analysis of leukocyte decrease about MI combined with first-line chemotherapy and chemotherapy alone for lung cancer.

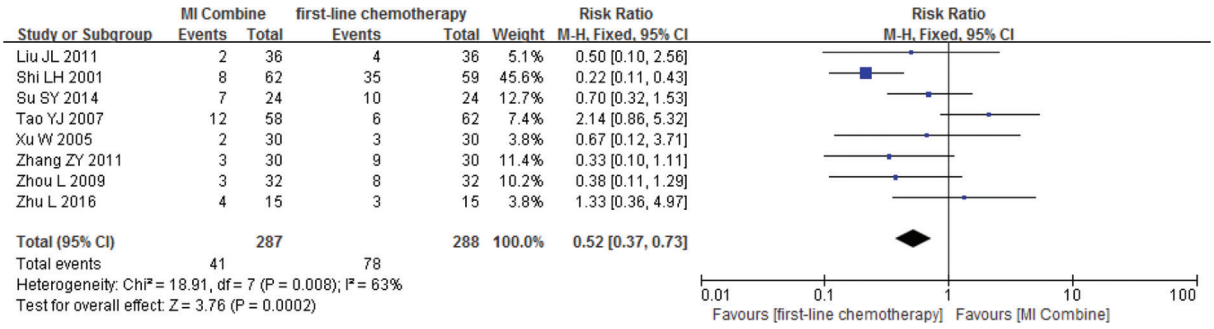

Fig. 7 The meta-analysis of nausea and vomiting about MI combined with first-line chemotherapy and chemotherapy alone for lung cancer.

Matrine is the effective components extracted from the traditional Chinese medicine *Sophora flavescens* Ait., containing more than 98% of oxymatrine and a small amount of horseradish. Matrine has a significant inhibitory effect on the proliferation of human lung cancer A549 cells, may be related to activation of caspase 3/7 activity, promote apoptosis[22]. Besides, matrine can enhance the body's immune function, especially the cellular immune function so that the inhibition of chemotherapy on immune function could be slowed down. It was still able to treat chemotherapy-induced leukopenia[23].

When comparing the result of the total effect of matrine injection combined with first-line chemotherapy to chemotherapy alone, the statistics of 9 studies including 780 patients showed that the short-term clinical efficacy after three treatment cycles is significantly better in the MI group, and its total effective rate is 55.4% (220/397), higher than control group (47.3%, (181/383)). In 252 cases of 3 studies, MI combined with first-line chemotherapy made 50% (63/126) of patients have the improvement in quality of life, while chemotherapy alone group got 31% (39/126), which indicated that in the conventional treatment of lung cancer, matrine injection does have a role in improving efficacy.

In terms of safety, the incidence of leukopenia decrease over grade III was more frequent in chemotherapy alone group (30.6% versus 11.8%), so nausea and vomiting (27.1% versus 14.3%), suggesting matrine injection may have a positive effect on reducing the common and serious adverse effects of chemotherapy.

The results of this meta-analysis showed that the short-term clinical efficacy, complete response rate and KPS score of the observation group treated with matrine injection combined with first-line chemotherapy were significantly better than those of first-line chemotherapy alone group, In terms of safety, the incidence of leukopenia, nausea and vomiting in the observation group, were significantly lower than the control group.

CONCLUSION

In conclusion, matrine injection combined with first-line chemotherapy regimen in the treatment of lung cancer not only improves the short-term clinical efficacy, complete response rate, and quality of life of patients, but also reduces the incidence of serious side effects caused by chemotherapy. These results require a large sample of randomized controlled trials to further prove.

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