

Is the traditional Chinese medicine helpful for patients with hematologic malignant diseases? A meta-analysis of randomized controlled trials

Cheng-Liang Qian, Fei Yan, Yan-Zhi Song, Dong Li, Ke-Zhou Dong, Yi-Min Zhu

Cheng-Liang Qian, Department of Traditional Chinese Medicine, Nanjing BenQ Medical Center, Nanjing Medical University, Nanjing 021000, Jiangsu Province, China
Fei Yan, Department of Medical Oncology, Jiangsu Cancer Hospital, Nanjing 021000, Jiangsu Province, China
Yan-Zhi Song, Dong Li, Department of Hematology, Nanjing BenQ Medical Center, Nanjing Medical University, Nanjing 021000, Jiangsu Province, China
Ke-Zhou Dong, Yi-Min Zhu, Department of Respiration, the 2st Jiangsu Province Hospital of TCM, Nanjing University of Chinese Medicine, Nanjing 021000, Jiangsu Province, China

Author contributions: Song YZ conceived and designed the study, searched and selected trials for inclusion, assessed methodological quality of included trials, extracted data, performed the statistical analysis and wrote the review; Qian CL searched trials, selected trials for inclusion, assessed methodological quality of included trials and extracted data; Yan F searched and selected trials for inclusion and wrote the review; Li D, Dong KZ and Zhu YM wrote and revised the review.

Supported by The Six Peak Talent Program of Jiangsu Province, No. 2009-47-D.

Conflict-of-interest: There is no conflict of interest reported.
Data sharing: No.

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Correspondence to: Dr. Yan-Zhi Song, Department of Hematology, Nanjing BenQ Medical Center, Nanjing Medical University, 71st Hexi Street, Jianye District, Nanjing 021000, Jiangsu Province, China. yandgics@126.com
Telephone: +86-25-52238800
Fax: +86-25-52238800

Received: October 19, 2014
Peer-review started: October 21, 2014
First decision: December 26, 2014
Revised: April 13, 2015
Accepted: May 5, 2015
Article in press: May 6, 2015
Published online: June 26, 2015

Abstract

AIM: To evaluate the efficacy of traditional Chinese medicine (TCM) for the treatment of hematologic malignant diseases.

METHODS: We searched the Cochrane CENTRAL, PubMed, Embase, Web of Science, AMED, CNKI, Wanfang Platform; China Sinomed and the clinical trial registry web sites and Google Scholar electronically up to June 19th, 2014 and hand searched related publications. Only randomized controlled trials (RCTs) researching on whether TCM as the adjuvant treatment improved the effect for hematologic malignant diseases were included. Two reviewers extracted data and evaluated the studies independently. Pooled risk ratios (RR) were calculated as outcome measures. Our primary outcomes were the overall response (OR) rate.

RESULTS: We retrieved 13143 references and included 11 RCTs involved 891 participants after screening. Because the non-significant heterogeneity we used the fixed effect model to combine data and TCM had a significantly higher OR and CR (complete response) rates than the control [RR = 1.17, 95%CI: (1.10, 1.25), $P < 0.00001$; RR = 1.24, 95%CI: (1.11, 1.37), $P < 0.0001$, respectively]. Only three studies included in the survival rate analysis. We combined them with random effects model and there was no significant difference between the TCM and control arms. Because

of the low heterogeneity we used the fixed effect model to combine the non-hematologic adverse effects (AEs) data. Our results showed that TCM significantly decreased non-hematologic AEs rates we researched, the gastrointestinal reaction [RR = 0.50, 95%CI: (0.37, 0.68), $P < 0.0001$], liver and/or kidney injury [RR = 0.37, 95%CI: (0.26, 0.53), $P < 0.00001$] and heart injury [RR = 0.24, 95%CI: (0.09, 0.68), $P = 0.007$]. Additionally, TCM had a trend to decrease the infection rate [RR = 0.16, (0.02, 1.12), $P = 0.07$], but not statistically significantly.

CONCLUSION: TCM increases OR and CR rates for hematologic malignances and reduces treatment associated serious non-hematologic AEs. Therefore, TCM should be included in the treatment of hematologic malignances.

Key words: Hematologic malignant disease; Leukemia; Lymphoma; Chinese medicine

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Core tip: We pooled all the studies complied to our inclusion criteria that were retrieved by extensively searching the related databases, journals and websites. Our result suggested that adding traditional Chinese medicine (TCM) increased overall response and complete response rates for malignant hematologic diseases treatment. Although it was based on the evidence of low level of GRADE quality, our result demonstrated that TCM reduced treatment associated serious non-hematologic adverse effects (AEs). Furthermore, considering the rare AEs and drugs interactions, TCM should be included in the hematologic malignances treatment, at least for adult acute leukemia.

Qian CL, Yan F, Song YZ, Li D, Dong KZ, Zhu YM. Is the traditional Chinese medicine helpful for patients with hematologic malignant diseases? A meta-analysis of randomized controlled trials. *World J Meta-Anal* 2015; 3(3): 163-180 Available from: URL: <http://www.wjgnet.com/2308-3840/full/v3/i3/163.htm> DOI: <http://dx.doi.org/10.13105/wjma.v3.i3.163>

INTRODUCTION

The incidence and mortality of malignant tumors have increased greatly in recent years^[1]. Albeit the treatment methods of malignant diseases progress quickly the general prognosis of this kind of diseases is poor^[1]. Whereby the hematologic malignancies have a particular high-grade malignancy and are systemic diseases that are common to involve multiple systems and organs. Hence, the systemic chemotherapy with western medicine becomes the standard treatment of these kind of diseases^[2]. However, the same as other malignant diseases, even in nowadays, the response and survival

rates are still not ideal^[3,4]. As well as the chemotherapy always causes serious adverse effects (AEs), such as III-IV grade bone marrow suppression, serious nausea and vomiting, hepatic and renal dysfunction and heart injury etc. Attempts to improve therapy by intensifying the number of chemotherapeutic agents or their doses lead only to increase side effects^[5]. Even the targeted molecular therapy developed in recent years also causes obvious side effects. For example, the rituximab increases the response rate and survival time for B cell lymphoma^[6,7], alternatively, it will obviously suppress the bodies' normal immune response to pathogens for a long period of more than one year. As a result of it, patients who received it are sensitive to infection and sometimes it is fatal^[8,9]. And furthermore, in most conditions, these new medicines need to be administered with chemotherapy together not to mention the tumor cells will become resistant to the therapy after treated for a period^[10].

On the other hand, many studies reported that adding traditional Chinese medicine (TCM) into the malignant diseases treatment strategy not only increased the response rate but also significantly lowered the treatment associated AEs rate^[11-14]. There are a variety of herbs being used in different combinations and forms, such as oral administration and intravenous injection for hematologic malignancies yet. Many randomized controlled studies have shown that TCM as the adjuvant agent improved the malignant hematologic diseases response and reduced the AEs associated with chemotherapy^[15]. But most of the published studies were small sample sized and the results were not consensus. So we wrote the meta-analysis to evaluate the efficacy of TCM for the treatment of hematologic malignant diseases.

MATERIALS AND METHODS

This meta-analysis followed the Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) Statement issued in 2009 (Table 1).

Inclusion criteria

We only included randomized controlled trials (RCTs) that researched on whether TCM as the adjuvant treatment improved the effect for malignant hematologic diseases. There was no age, sex, race, complicated diseases or language limits of the study. Our primary outcomes were the overall response (OR) rate calculated by summing the complete response (CR), partial response and stable disease rates. The survival and serious AEs rates and the change of quality of life were our secondary outcomes. The diagnosis must be confirmed by pathological sections or bone marrow smears.

Since some TCMs for acute promyelocytic leukemia treatment, such as the compound Huang Dai Tablets, have been administered as the primary maintenance treatment, not the adjuvant treatment and their active ingredients has been recognized as Tetraarsenic tetra-

Table 1 The Preferred Reporting Items for Systematic Review and Meta-Analysis checklist

Section/topic	<i>n</i>	Checklist item	Reported on page
Title			
Title	1	Identify the report as a systematic review, meta-analysis, or both	1
Abstract			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number	2
Introduction			
Rationale	3	Describe the rationale for the review in the context of what is already known	3
Objectives	4	Provide an explicit statement of questions being addressed with reference to PICOS	3-4
Methods			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (<i>e.g.</i> , Web address), and, if available, provide registration information including registration number	
Eligibility criteria	6	Specify study characteristics (<i>e.g.</i> , PICOS, length of follow-up) and report characteristics (<i>e.g.</i> , years considered, language, publication status) used as criteria for eligibility, giving rationale	5
Information sources	7	Describe all information sources (<i>e.g.</i> , databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched	5
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated	5-6, Table 2
Study selection	9	State the process for selecting studies (<i>i.e.</i> , screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis)	6-7
Data collection process	10	Describe method of data extraction from reports (<i>e.g.</i> , piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators	7
Data items	11	List and define all variables for which data were sought (<i>e.g.</i> , PICOS, funding sources) and any assumptions and simplifications made	7
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis	6-7
Summary measures	13	State the principal summary measures (<i>e.g.</i> , risk ratio, difference in means)	7
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (<i>e.g.</i> , I^2) for each meta-analysis	7

PICOS: Participants, interventions, comparisons, outcomes, and study design.

sulfide we did not include these studies. The efficacy and safety of this kind of TCM is the focus of our next study.

Searching method

YS and CQ searched the following databases independently, the Cochrane Central Register of Controlled Trials (CENTRAL) in The Cochrane Library, PubMed, Embase, Web of Science, Allied and Alternative Medicine (AMED), Google Scholar, China National Knowledge Infrastructure (CNKI), Wanfang Data Knowledge Service Platform; China biomedical literature service system (Sinomed); and the well-known clinical trial registry sites (<http://www.clinicaltrial.gov/>; <http://apps.who.int/trialsearch/>). The electronic search was up to June 19th, 2014. The detailed searching strategy for PubMed was recorded in Table 2.

We specified three searching themes: First, we searched TCM related words, we used the terms "complementary medicine", and the free words "tradition or tradition* or china or chinese or herb or herbal or complement* or tcm or 'zhong yi' or chm or ethno* or folk or home or indigenous or primitive or materia* or nosod* or east or eastern or orient or oriental or Asian or Korea* or Tibet* or herbaceous or plant or

plants or botan* or kampo or mongol* or phytogetic or phytotherapy or alternative"; Second, we searched hematologic diseases related words, we used the terms "leukemia" or "lymphoma" or "multiple myeloma", and the free words "hemotolog* or anemia or thrombocytopen* or pancytopen* or 'bone marrow' or transplant or 'stem cell' or 'leukemia or lymphoma' or cancer or dysplas* or malignant or hyperplas* or hypoplas* or myelom* or Hodgkin or non-Hodgkin or blast or blasts or 'progression free survival (PFS)' or 'disease free survival (DFS)' or 'overall survival (OS)' or OS or PFS or DFS or chemotherapy or (chemical treatment) or radiotherapy or irradiat* or oncolog* or monoclon*"; and third, we used the Cochrane highly sensitive search filters to retrieve randomized trials in Medline and Embase^[16].

We also hand searched other journals that might publish relative clinical trials, PubMed related articles, reference lists of retrieved articles. Considering there might be some ongoing studies which did not register in the clinical trial registry sites and some finished studies which did not published, we contacted some researchers, relative manufacturers and specialists for further information of unpublished trials. Our study did not set limits of ages, sexes, races, published languages and

Table 2 The PubMed searching strategy

- (1) "Complementary therapies" (Mesh)
- (2) Tradition or tradition* OR china or chinese OR herb or herbal OR complement* or tcm or "zhong yi" or chm or ethno* or folk or home or indigenous or primitive or materia* or nosod* or east or eastern or orient or oriental or asian or Korea* or Tibet* or herbaceous or plant or plants or botan* or kampo or mongol* or phytogetic or phytotherapy or alternative
- (3) Medicine or medicinal or medical or remed* or therapy or therapies or therapeutic or therapeutics or therapist or treat or treatment or drug or drugs
- (4) (2) and (3)
- (5) (1) or (4)
- (6) Leukemia or lymphoma or "multiple myeloma" (mesh)
- (7) Hemotolog* or anemia or thrombocytopen* or pancytopen* or "bone marrow" or transplant or "stem cell"
- (8) Leukemia OR lymphoma OR cancer OR dysplas* OR malignant OR hyperplas* OR hypoplas* or myelom* or Hodgkin or non-hodgkin or blast or blasts or "progression free survival" or "disease free survival" or "overall survival" or OS or PFS or DFS or chemotherapy or (chemical treatment) or radiotherapy or irradiat* or oncolog* or monoclon*
- (9) (7) and (8)
- (10) (6) or (9)
- (11) (((((Randomized controlled trial [Publication type]) OR controlled clinical trial [Publication type]) OR (randomized or placebo[Title/ Abstract]))) OR drug therapy [MeSH Subheading]) OR (randomly or groups or trial [Title/Abstract])) OR rct
- (12) Animals [mh] NOT humans [mh]
- (13) (11) not (12)
- (14) (5) and (10) and (13)
- (15) (Cancer or carcinoma or sarcoma)[ti]
- (16) Carcinoma[mesh] or sarcoma[mesh]
- (17) (14) not (15) or (16)

Table 3 Characteristics of Dian Rong 2009 study

Methods	A randomized double blind placebo controlled I multicenter study
Participants	Refractory acute leukemia patients
Interventions	TCM group: Combine Chinese interventions with standard chemotherapy of western medicine Control group: Standard chemotherapy with western medicine
Outcomes	The primary outcome: the response rate

TCM: Traditional Chinese medicine.

regions.

Data extraction, evaluation and analysis

YS and CQ extracted data from the retrieved studies. Then they independently used the Cochrane Collaboration tool for assessing risk of bias^[17] to assess the quality of the trials (Tables 3-24). The tool comprised of seven specific domains (named sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective outcome reporting and other issues). We only included studies in "low risk" of bias in the randomization sequence generation and did not show high risks in any other domains. We used the funnel plot to detect the publication bias. If it was symmetrical we considered there was no publication bias, or else, we considered there was publication bias. If there was some disagreement between the two authors, they would resolve it by discussion.

We analyzed the included data with the Revman software (Version 5.2. Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2012). We used the relative risk (RR) to evaluate the outcomes. If there was not significant heterogeneity between the included studies (detected by the *P* value of the

χ^2 test over 0.10 and $I^2 \leq 25\%$) we used the Mantel-Haenszel fixed effect model to analyze data. If there was significant heterogeneity (detected by the *P* value was less than 0.10 and/or $I^2 \geq 50\%$) we detected if there was clinical heterogeneity. In the condition of absence of clinical heterogeneity we pooled data with random effects model. If $P \geq 0.10$ and $25\% \leq I^2 \leq 50\%$, we decided to choose the fixed effect or random effects models to combine data by discussion. Considering there might be clinical heterogeneity between different diseases we performed subgroup analyses (studies were divided into four subgroups: the adult acute leukemia, chronic myelogenous leukemia, lymphoma and pediatric acute myeloid leukemia subgroups). We also used sensitivity analyses to assess the association of the quality of included studies and the clinical characteristics. A two-sided *P* value of less than 0.05 was considered as a significant difference. We also used the GRADE grid to evaluate the quality of evidence on the primary outcome.

Statistical analysis

Technical appendix, statistical code, and dataset available from the corresponding author at yandgics@126.com. The article was reviewed by the statistician Xiaoxiao Wang. In her opinion, the RR rate was suitable, the heterogeneity of the included articles was effectively detected and the appropriate pooling methods (the random effects model or fixed effect model) was chosen for the systematic review. He also supported using the funnel plot to detect the publication bias.

RESULTS

We searched 13143 references in total. There were 367 papers retained after we examined the titles and abstracts. We excluded 347 references in the further assessment with the reason of that focused on the solid

Table 4 Risk assessment of Dian Rong 2009 study

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: Central randomized Comment: Probably done. Several studies published by this research group reported reliable randomization method
Allocation concealment (selection bias)	Unclear	Quote: Not mentioned Comment: Unclear
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: A double-blind and placebo controlled Comment: Probably done. Several studies published by this research group reported reliable method to warrant the double blindness
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: Not mentioned Comment: Mortality and survival time are objective parameter. Subjective judgement can not influent the result
Incomplete outcome data (attrition bias) All outcomes	Unclear	Quote: Not mentioned Comment: Unclear
Selective reporting (reporting bias)	Low risk	The primary outcome listed in the method section are all reported Comment: Probably done
Other bias	Unclear	The study did not use the intention to treat strategy to analyze the result

Table 5 Characteristics of Xiu Mei 1997 study

Methods	A randomized controlled study
Participants	Non-Hodgkin lymphoma patients
Interventions	TCM group: Standard chemotherapy + traditional Chinese medicine Control group: Standard chemotherapy
Outcomes	The primary outcome: The overall response rate

TCM: Traditional Chinese medicine.

tumors but not the hematologic malignancies, were not real RCTs, did not report the primary outcome of our study or clearly described the randomization methods, and had other reasons that did not conform our inclusion criteria^[18-20]. Finally all the reviewers agreed 11 studies^[15,21-35] involved 891 participants should be included for meta-analysis (Figure 1).

Characteristics of included trials

The 11 included studies all compared the OR rate between the addition of TCM or not in the treatment of hematologic malignant diseases, such as acute leukemia, lymphoma, *etc.* Seven studies^[15,21,24-31,33,34] researched the effect of adding TCM to the standard treatment for adult acute leukemia patients. Among the 7 studies, Mao Sheng 2007, Chuan Xin 2013, Ji Hong 2011, Rui Rong 2004 and Wen Jiang 2010^[26,27,29,30,32,34] focused on acute myeloid leukemia. [Wang, 2007 #18; Wang, 2007 #9; Xu, 2010 #11; Zhu, 2011 #21]. The rest two studies did not restrict the type of the acute leukemia (lymphoblastic or non-lymphoblastic). Only one study Chuan Xin 2013^[32] focused on pediatric acute myeloid leukemia patients while no study focused on pediatric acute lymphoblastic leukemia patients. Also only one study Xiu Mei 1997^[35] focused on lymphoma patients. Two studies (sHai Yan 2007 and sWei Hong 2013)^[22,23] focused on chronic myelogenous leukemia patients. But the basic treatment of the two studies were the hydroxyurea and/or α -interferon treatment but not

the tyrosine kinase inhibitors which was the standard treatment recently^[36]. Hence we did a sensitivity analysis of excluding the two studies. There was not study included was about the multiple myeloma (MM) or myelodysplastic syndrome (MDS). Only the study Dian Rong 2009^[15] published one article in English, all of the rest studies were published in Chinese. Only one study reported the quality of life hence we did not analyze this outcome. There was not significant difference in the demographic characteristics of the two treatment groups in the 11 included studies (Table 25).

Quality of included trials

Five studies (Dian Rong 2009; Ying Fei 2005; Su Juan 2005; Mao Sheng 2007; Rui Rong 2004)^[15,21,24-29,31,33] were multi-center double-blind RCT studies. The rest six studies^[22,23,30,32,34,35] were single center studies and did not use the blind method. All of the included studies were not large sampled with the largest sample size (Xiu Mei 1997)^[35] was 167 and the smallest sample size was 18 (sHai Yan 2007)^[22]. All of the included studies did not use the intention to treat strategy to analyze results. There was no other factors influenced the quality of included studies. The funnel plot of the primary outcome was symmetric (Figure 2 and Tables 3-24, 26).

Efficacy analysis

Studies in both the OR and CR meta-analyses did not show significant heterogeneity so we combined data with the fixed effect model. The efficacy analyses showed the TCM arm had a significantly higher OR rate than the control arm (RR = 1.17 with a 95%CI: (1.10, 1.25), $P < 0.00001$) (Figure 3). The higher response rate was also statistically significant in the sensitivity analysis of excluding the two chronic myelogenous studies (RR = 1.17, 95%CI: (1.09, 1.26), $P < 0.00001$). As for the CR rate, the TCM arm was significantly higher than the control group as well [RR = 1.24, 95%CI: (1.11, 1.37), $P < 0.0001$] (Figure 4). And also it was

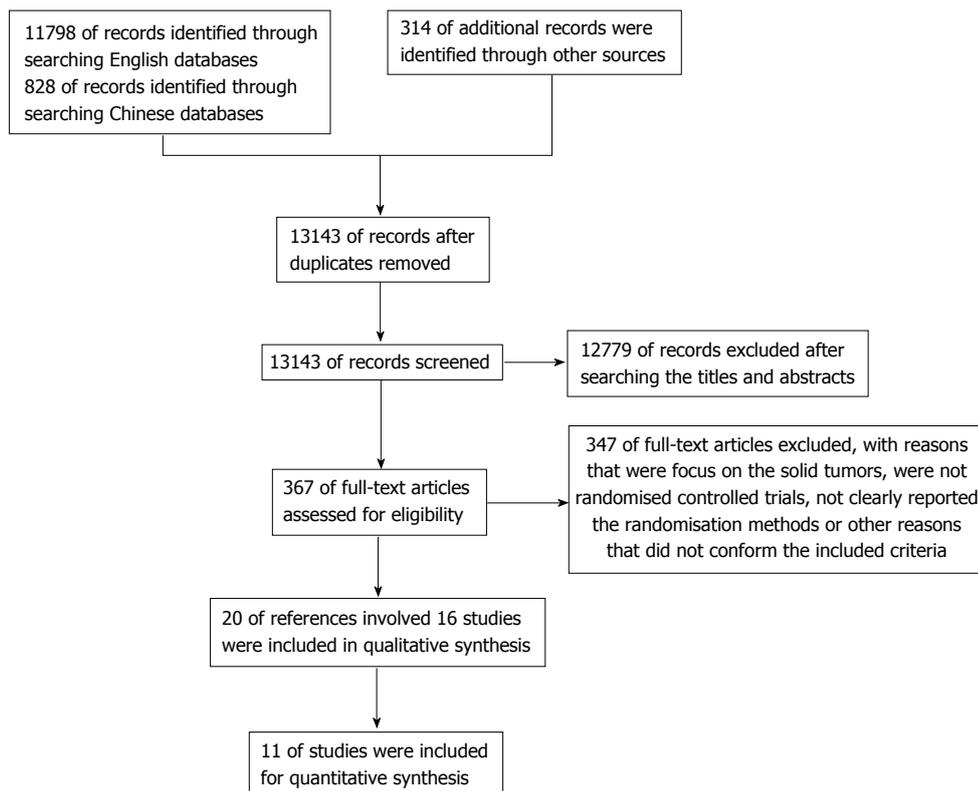


Figure 1 Study selection.

Table 6 Risk assessment of Xiu Mei 1997 study

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: The random sequence produced by rolling the dice Comment: Probably done
Allocation concealment (selection bias)	Unclear	Quote: Not mentioned Comment: Unclear
Blinding of participants and personnel (performance bias) All outcomes	Unclear	Quote: Not mentioned Comment: Unclear
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: Not mentioned Comment: Mortality and survival is an objective parameter. Subjective judgement can not influent the result
Incomplete outcome data (attrition bias) All outcomes	Unclear	Quote: Not mentioned Comment: Unclear
Selective reporting (reporting bias)	Low risk	The primary outcome listed in the method section are all reported Comment: Probably done
Other bias	Unclear	The study did not use the intention to treat strategy to analyze the result

Table 7 Characteristics of Ji Hong 2011 study

Methods	A randomized controlled study
Participants	Initial treat old AML patients
Interventions	TCM group: HAG + TCM Control group: HAG
Outcomes	The primary outcome: The overall response rate

TCM: Traditional Chinese medicine; AML: Acute myeloid leukemia; HAG: Homoharringtonine + cytoarabine + granulocyte colony stimulating factor.

not changed in the sensitivity analysis that excluded

the two chronic myelogenous leukemia studies [RR = 1.21, 95%CI: (1.08, 1.35), P = 0.0007]. However, the Summary of findings (SoF) table showed the quality of the evidence was low (Table 27). There were three studies^[15,21,25-27,35] reported the survival rate. The pooled results of the three studies did not show significant difference between the TCM arm and the control arm [RR = 1.22, 95%CI: (0.77, 1.94), P = 0.40] (Figure 5). Studies included in this analysis reported the survival rate of different period and the heterogeneity was significant. As a result of it, we used the random effects model to pool data.

Table 8 Risk assessment of Ji Hong 2011 study

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: Use the random number table to get the allocation sequence Comment: Probably done
Allocation concealment (selection bias)	Unclear	Quote: Not mentioned Comment: Unclear
Blinding of participants and personnel (performance bias) All outcomes	Unclear	Quote: Not mentioned Comment: Unclear
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: Not mentioned Comment: The response rate is an objective parameter. Subjective judgement can not influent the result
Incomplete outcome data (attrition bias) All outcomes	Low risk	Quote: 7 participants in 53 randomized lost to follow-up Comment
Selective reporting (reporting bias)	Low risk	The primary outcome listed in the method section are all reported Comment: Probably done
Other bias	Unclear	The study did not use the intention to treat strategy to analyze the result

Table 9 Characteristics of Ying Fei 2005 study

Methods	A multicenter double-blinded randomized controlled study
Participants	Initial treat leukemia patients
Interventions	TCM group: standard chemotherapy + Shen Qi Fu Zheng Ye Control group: Standard chemotherapy
Outcomes	The primary outcome: The overall response rate

TCM: Traditional Chinese medicine.

Serious AEs analysis

Our study demonstrated the TCM arm had a significantly less non-hematologic serious AEs rates in the gastrointestinal reaction [RR = 0.50, 95%CI: (0.37, 0.68), $P < 0.0001$], liver and/or kidney injury [RR = 0.37, 95%CI: (0.26, 0.53), $P < 0.00001$] and heart injury [RR = 0.24, 95%CI: (0.09, 0.68), $P = 0.007$] analyses (Figure 6). Additionally, the TCM showed a trend of reducing the infection rate [RR = 0.16, 95%CI: (0.02, 1.12), $P = 0.07$] but it was not statistically significant (Figure 7). The rates of III-IV grade agranulocytosis and thrombocytosis were not different between adding TCM in the treatment method and not adding it [RR = 0.52, 95%CI: (0.14, 1.84), $P = 0.31$; RR = 0.52, 95%CI: (0.14, 1.91), $P = 0.33$, respectively] (Figure 7). Most of the included studies did not report the myelosuppression recovery time. So we did not analyze this outcome. In the non-hematologic serious AEs analyses, studies were pooled with the fixed effect model while in the hematologic AEs analyses, studies were pooled with the random effects model because of the significant heterogeneity. Because there were only two to three studies included in the serious AEs meta-analyses, we did not perform subgroup analysis to detect the clinical heterogeneity.

DISCUSSION

Oncologists begin to pay attention to the effect of TCM for the malignant diseases treatment in nowadays.

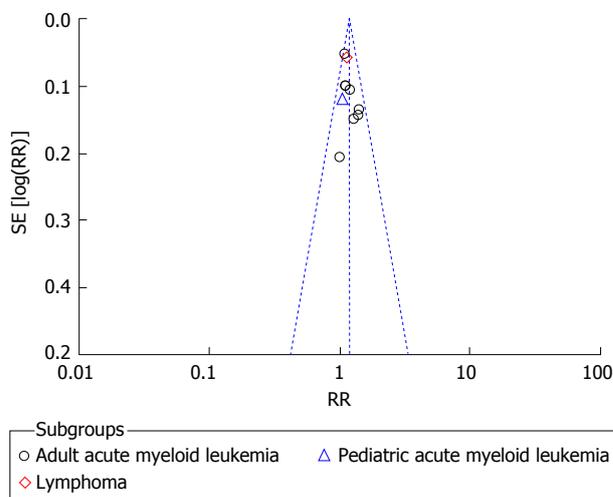


Figure 2 Funnel plot of the overall response meta-analysis. RR: Risk ratios.

Several meta-analyses revealed that TCM could improve response rate for some kinds of solid tumors^[11-13]. There were also several RCTs showed that some TCM could increase the OR rate and decrease the AEs rate for hematologic malignancies. But the results published were not consistent^[15,34]. At the same time there is not large sample sized RCT reported. As is generally accepted, meta-analysis attempts to identify all studies that would meet the eligibility criteria, subjectively assess the validity of the findings of the included studies and systematically present and synthesize the characteristics and findings of the included studies^[37]. Therefore, it increases the sample size and reports a more reliable result. In The Oxford 2011 Levels of Evidence Table, meta-analysis of RCT has become the highest level of evidence^[38]. In consequence, meta-analysis is a good method to evaluate the efficacy and safety of TCM for hematologic malignancies.

Response rate of TCM

Our results showed that TCM significantly increased the OR and CR rates. Although the GRADE SoF tables (Table

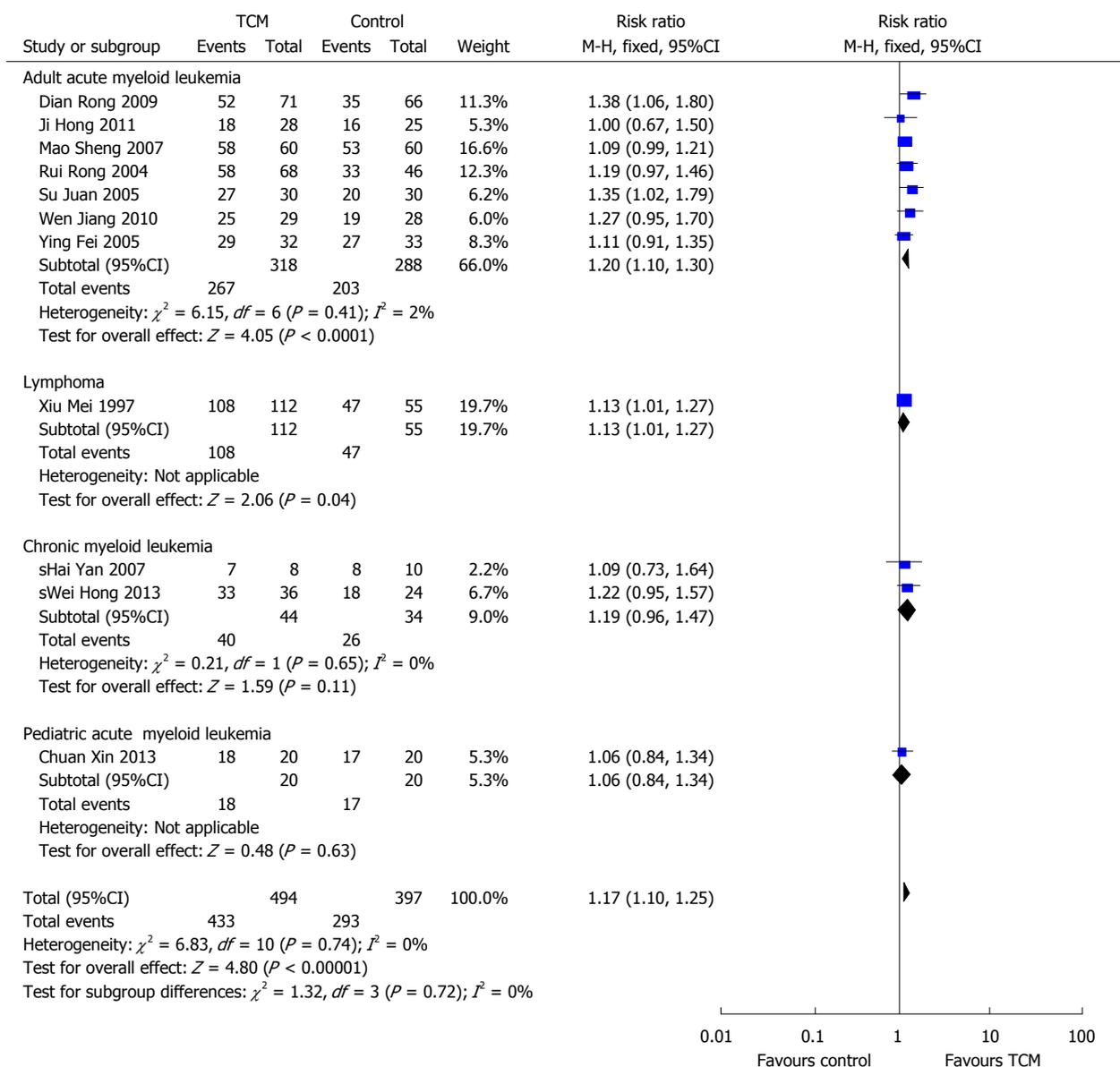


Figure 3 Overall response meta-analysis. TCM: Traditional Chinese medicine.

Table 10 Risk assessment of Ying Fei 2005 study

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: Generate randomization sequence by drawing lots Comment: Probably done
Allocation concealment (selection bias)	Unclear	Quote: Not mentioned Comment: Unclear
Blinding of participants and personnel (performance bias) All outcomes	Unclear	Quote: Not mentioned Comment: Unclear
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: Not mentioned Comment: The response rate is an objective parameter subjective judgement can not influence the result
Incomplete outcome data (attrition bias) All outcomes	Unclear	Quote: Not mentioned Comment: Unclear
Selective reporting (reporting bias)	Low risk	The primary outcome listed in the method section are all reported Comment: Probably done
Other bias	Unclear	The study did not use the intention to treat strategy to analyze the result

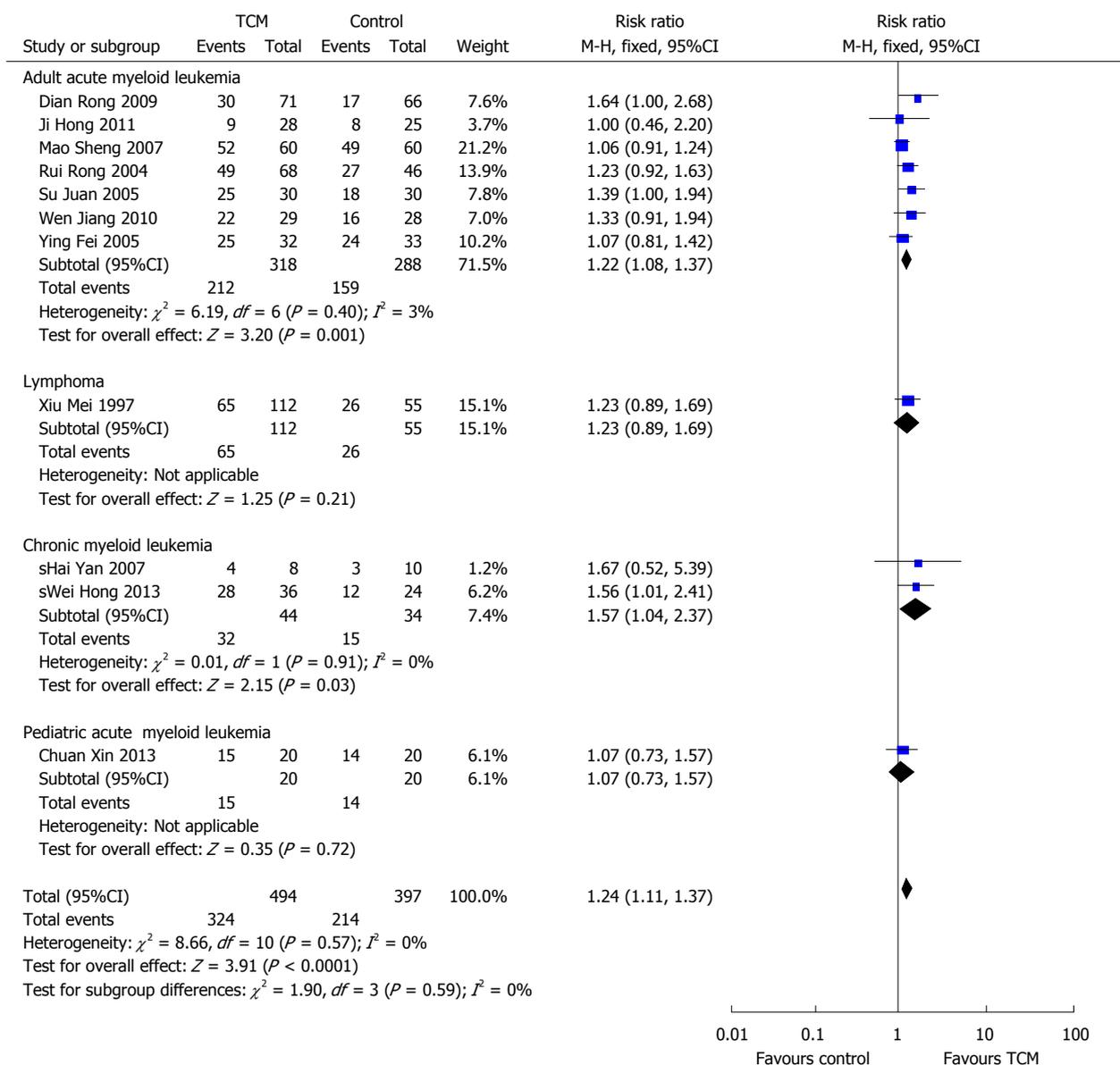


Figure 4 Complete response meta-analysis. TCM: Traditional Chinese medicine.

Table 11 Characteristics of Wen Jiang 2010 study	
Methods	A randomized placebo controlled study
Participants	Initial treat acute leukemia patients
Interventions	TCM group: Standard chemotherapy + Shen Qi Qing Re Ke Li Control group: Standard chemotherapy
Outcomes	The primary outcome: The overall response rate

TCM: Traditional Chinese medicine.

27) showed the evidence quality of the two meta-analyses was low and the recommendation strength was weak (data not show), the TCM causes little side effects and it is economical. Furthermore, even though we included studies of different diseases there was not significant heterogeneity in the meta-analyses. So we could pooled data with the fixed effect model which made the result more reliable. Subsequently, it is

suggested that TCM, as an adjuvant treatment method, can improve the efficacy of hematologic malignant diseases treatment.

However, there were two studies included in the chronic myelogenous leukemia subgroup prescribed the hydroxyurea or interferon as the fundamental treatment rather than the tyrosine kinase inhibitors which should be the first choice^[36] nowadays. We excluded the two studies in the sensitivity analyses and then we got the same result that the TCM arm had significantly higher response rates (both OR and CR) than the control arm. The results of the sensitivity analyses strengthened the evidence that the response rate could be increased by adding TCM for hematologic malignancies. But there was only one study included in the pediatric acute myeloid leukemia and lymphoma subgroups and no studies on MM and MDS. As it was shown in the efficacy forest, the better effect of the TCM was mainly contributed by

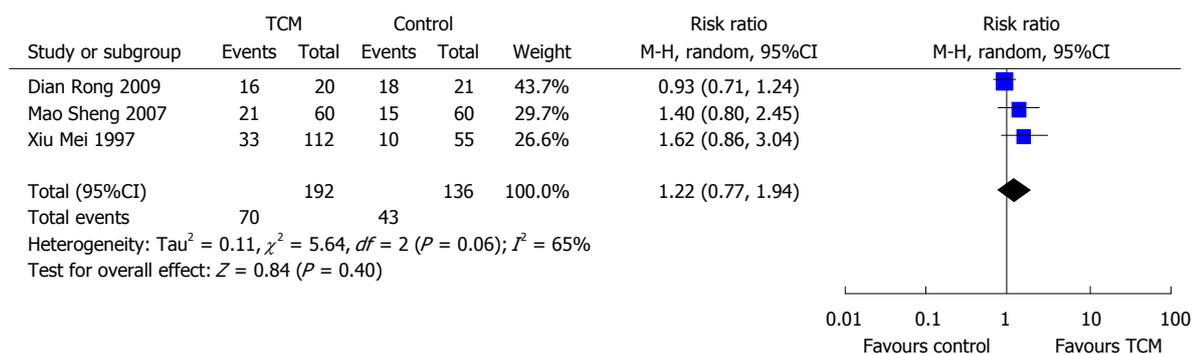


Figure 5 Survival rate meta-analysis. TCM: Traditional Chinese medicine.

Table 12 Risk assessment of Wen Jiang 2010 study

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: Use the random number table to get the allocation sequence Comment: Probably done
Allocation concealment (selection bias)	Unclear	Quote: Not mentioned Comment: Unclear
Blinding of participants and personnel (performance bias) All outcomes	Unclear	Quote: Not mentioned Comment: Unclear
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: Not mentioned Comment: The response rate is an objective parameter. Subjective judgement can not influent the result
Incomplete outcome data (attrition bias) All outcomes	Unclear	Quote: Not mentioned Comment: Unclear
Selective reporting (reporting bias)	Low risk	The primary outcome listed in the method section are all reported Comment: Probably done
Other bias	Unclear	The study did not use the intention to treat strategy to analyze the result

Table 13 Characteristics of Su Juan 2005 study

Methods	A multicenter randomized controlled study
Participants	Acute leukemia
Interventions	TCM group: Standard chemotherapy + TCM Qing Re Jie Du Kang Bai Fang Control group: Standard chemotherapy
Outcomes	The primary outcome: The overall response rate

TCM: Traditional Chinese medicine.

Table 14 Risk assessment of Su Juan 2005 study

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: Use the random number table to get the allocation sequence Comment: Probably done
Allocation concealment (selection bias)	Unclear	Quote: Not mentioned Comment: Unclear
Blinding of participants and personnel (performance bias) All outcomes	Unclear	Quote: Not mentioned Comment: Unclear
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: Not mentioned Comment: The response rate is an objective parameter. Subjective judgement can not influent the result
Incomplete outcome data (attrition bias) All outcomes	Unclear	Quote: Not mentioned Comment: Unclear
Selective reporting (reporting bias)	Low risk	The primary outcome listed in the method section are all reported Comment: Probably done
Other bias	Unclear	The study did not use the intention to treat strategy to analyze the result

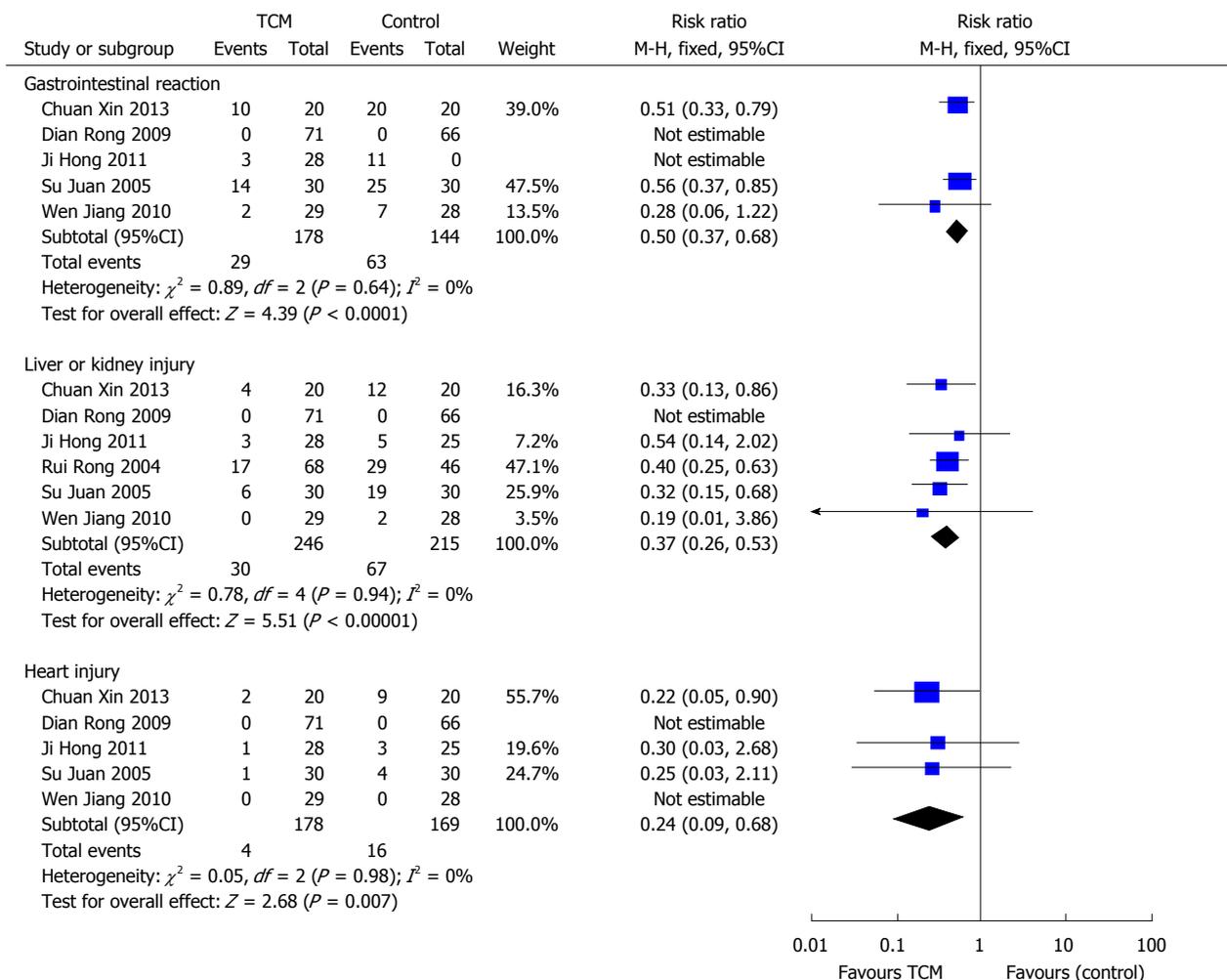


Figure 6 Non-hematologic serious adverse effects meta-analysis. TCM: Traditional Chinese medicine.

Table 15 Characteristics of Mao Sheng 2007 study	
Methods	A multicenter double-blinded randomized placebo controlled study
Participants	Acute myeloid leukemia patients with micro residual disease
Interventions	TCM group: Standard chemotherapy + Yi Qi Jie Du Huo Xue Fang Control group: Standard chemotherapy
Outcomes	The primary outcome: The overall response rate

TCM: Traditional Chinese medicine.

the adult acute leukemia subgroup. For this reason we concluded TCM can be used as the adjuvant treatment for acute myeloid leukemia and there was in lack of studies on other hematologic malignant diseases, including chronic myelogenous leukemia.

Survival rate of TCM

There were only three studies with significantly heterogeneity involved 328 participants included in the survival rate meta-analysis. We did not show the difference between adding the TCM or not for treatment of malignant hematologic diseases. The result might because the small number of included studies was not enough to show a statistical significance or the addition of TCM can not change the survival rate. We need more

high quality studies to clarify the problem. As a result of it, the data included was not enough to draw a conclusion of besides increasing the response rates, whether the addition of TCM can further improve patients survival rate.

Serious AEs rate of TCM

It is well known in the solid tumors treatment, TCM can decrease the AEs of chemotherapy^[39], our results also showed that TCM significantly decreased the serious non-hematologic AEs and had a trend to reduce the serious infection rate. The result enhanced the role of TCM for hematologic malignant diseases treatment. Decreasing the serious non-hematologic AEs makes the chemotherapy safer and improves patients' tolerance

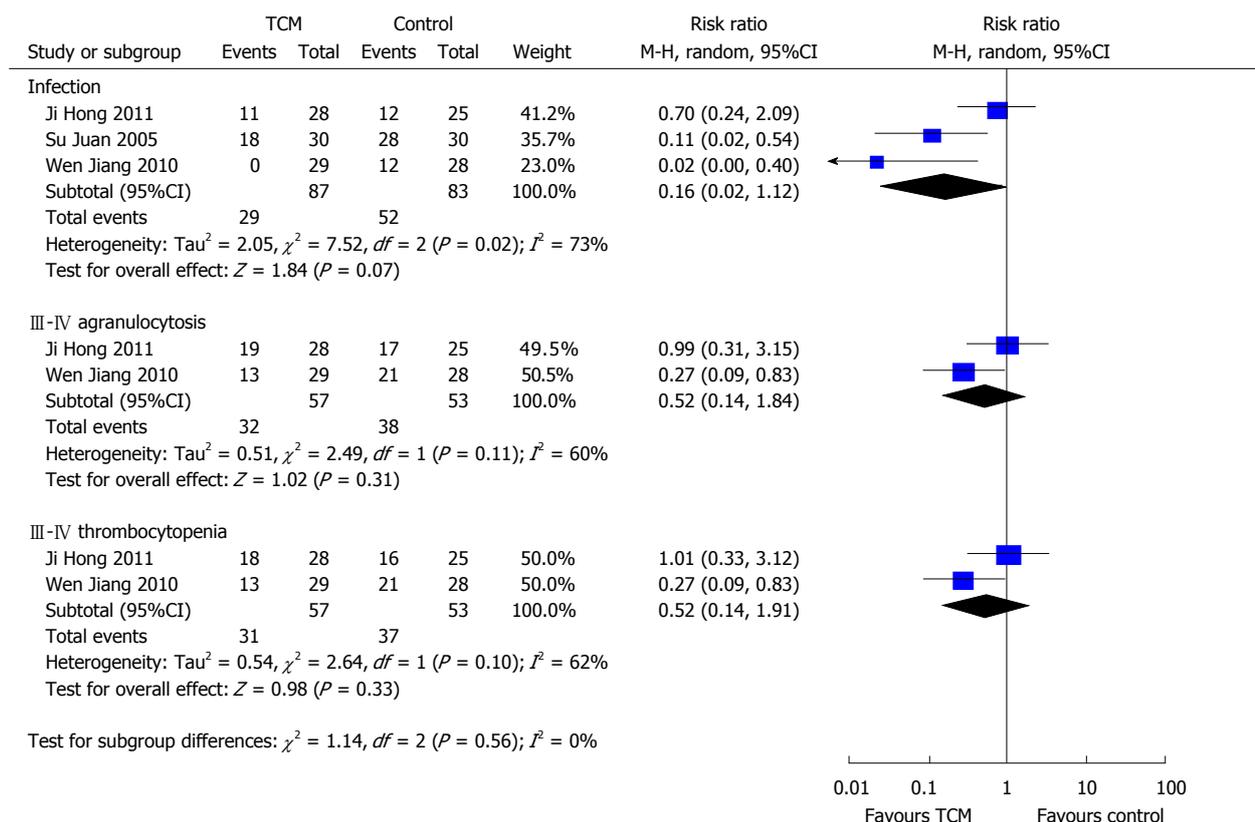


Figure 7 Hematologic serious adverse effects meta-analysis. TCM: Traditional Chinese medicine.

Table 16 Risk assessment of Mao Sheng 2007 study

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: Use the random number table to get the allocation sequence Comment: Probably done
Allocation concealment (selection bias)	Unclear	Quote: Not mentioned Comment: Unclear
Blinding of participants and personnel (performance bias) All outcomes	Unclear	Quote: Not mentioned Comment: Unclear
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: Not mentioned Comment: The response rate is an objective parameter. Subjective judgement can not influence the result
Incomplete outcome data (attrition bias) All outcomes	Unclear	Quote: Not mentioned Comment: Unclear
Selective reporting (reporting bias)	Low risk	The primary outcome listed in the method section are all reported Comment: Probably done
Other bias	Unclear	The study did not use the intention to treat strategy to analyze the result

Table 17 Characteristics of Rui Rong 2004 study

Methods	A multicenter double-blinded randomized placebo controlled study
Participants	Acute myeloid leukemia
Interventions	TCM group: Standard chemotherapy + Yi Qi Yang Yin Qing Re Fa Control group: Standard chemotherapy
Outcomes	The primary outcome: The overall response rate

TCM: Traditional Chinese medicine.

and adherence. This point is especially important for

hematologic malignant diseases because most of such patients do not have the opportunity of surgical operation and rely on chemotherapeutic treatment. Additionally, the chemotherapy usually has better effect for hematologic malignant diseases than solid tumors. Infection is the most common cause of death among patients with acute leukemia accounting for up to 75% of mortality^[40]. In our study, we showed a trend of reducing infection rate but it was not statistically significant. Since the three included studies all showed better effect of TCM and two were statistically significant we inferred the reason might be there were not enough studies included. More data was

Table 18 Risk assessment of Rui Rong 2004 study

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: Use the random number table to get the allocation sequence Comment: Probably done
Allocation concealment (selection bias)	Unclear	Quote: Not mentioned Comment: Unclear
Blinding of participants and personnel (performance bias) All outcomes	Unclear	Quote: Not mentioned Comment: Unclear
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: Not mentioned Comment: The response rate is an objective parameter. Subjective judgement can not influent the result
Incomplete outcome data (attrition bias) All outcomes	Unclear	Quote: Not mentioned Comment: Unclear
Selective reporting (reporting bias)	Low risk	The primary outcome listed in the method section are all reported Comment: Probably done
Other bias	Unclear	The study did not use the intention to treat strategy to analyze the result

Table 19 Characteristics of Chuan Xin 2013 study

Methods	A randomized controlled study
Participants	Child acute myeloid leukemia patients
Interventions	TCM group: Standard chemotherapy + traditional Chinese medicine Control group: Standard chemotherapy
Outcomes	The primary outcome: The overall response rate

TCM: Traditional Chinese medicine.

Table 20 Risk assessment of Chuan Xin 2013 study

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: Use the random number table to get the allocation sequence Comment: Probably done
Allocation concealment (selection bias)	Unclear	Quote: Not mentioned Comment: Unclear
Blinding of participants and personnel (performance bias) All outcomes	Unclear	Quote: Not mentioned Comment: Unclear
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: Not mentioned Comment: The response rate is an objective parameter. Subjective judgement can not influent the result
Incomplete outcome data (attrition bias) All outcomes	Unclear	Quote: Not mentioned Comment: Unclear
Selective reporting (reporting bias)	Low risk	The primary outcome listed in the method section are all reported Comment: Probably done
Other bias	Unclear	The study did not use the intention to treat strategy to analyze the result

Table 21 Characteristics of sWei Hong 2013 study

Methods	A randomized controlled study
Participants	Chronic myeloid leukemia patients
Interventions	TCM group: A-interferon or hydroxyurea + TCM Control group: A-interferon or hydroxyurea
Outcomes	The primary outcome: The response rate

TCM: Traditional Chinese medicine.

Comparison with other studies

Our study result was consistent with several meta-analyses on the solid tumors^[11-14]. In the studies, the authors showed that the Chinese herbal medicine (CHM) can increase the response and survival more than one year rates. Among the diseases studied, the non small cell lung cancer (NSCLC) is also sensitive to chemotherapeutic agents that is something like the hematologic malignancies. Our study also showed that TCM increased the response rate but failed to show that TCM increased the survival rate. This might be because there were not enough participants involved in our meta-analysis or the different clinical features of the diseases we researched. In the NSCLC study, authors

needed to confirm whether it was the truth. There were only two studies included in the serious hematologic AEs meta-analyses and we were in need of more studies to clarify this question.

Table 22 Risk assessment of sWei Hong 2013 study

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: The random number table was used to generate the allocation sequence Comment: Probably done
Allocation concealment (selection bias)	Unclear	Quote: Not mentioned Comment: Unclear
Blinding of participants and personnel (performance bias) All outcomes	Unclear	Quote: Not mentioned Comment: Unclear
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: Not mentioned Comment: Mortality and survival is an objective parameter. Subjective judgement can not influence the result
Incomplete outcome data (attrition bias) All outcomes	Unclear	Quote: Not mentioned Comment: Unclear
Selective reporting (reporting bias)	Low risk	The primary outcome listed in the method section are all reported Comment: Probably done
Other bias	Unclear	The study did not use the intention to treat strategy to analyze the result

Table 23 Characteristics of sHai Yan 2007 study

Methods	A randomized controlled study
Participants	Chronic myeloid leukemia patients
Interventions	Traditional Chinese medicine group: Hydroxyurea + traditional Chinese medicine Control group: Hydroxyurea
Outcomes	The primary outcome: The response rate

Table 24 Risk assessment of sHai Yan 2007 study

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: The random number table was used to generate the allocation sequence Comment: Probably done
Allocation concealment (selection bias)	Unclear	Quote: Not mentioned Comment: Unclear
Blinding of participants and personnel (performance bias) All outcomes	Unclear	Quote: Not mentioned Comment: Unclear
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: Not mentioned Comment: Mortality and survival is an objective parameter. Subjective judgement can not influence the result
Incomplete outcome data (attrition bias) All outcomes	Unclear	Quote: Not mentioned Comment: Unclear
Selective reporting (reporting bias)	Low risk	The primary outcome listed in the method section are all reported Comment: Probably done
Other bias	Unclear	The study did not use the intention to treat strategy to analyze the result

demonstrated the CHM decreased the morbidity of serious agranulocytosis and thrombocytosis which was not revealed in our study. As well, this might be caused by the lack of studies included or the different clinical features of the diseases. The consistency of our study with other studies strengthened our results.

Limitation of the meta-analysis

We have tried our best to make our research more reliable but we still have some limitation. First, none of included studies were performed out of China and all of the included studies except one were published in Chinese. As the funnel plot was symmetric, the publication bias was unavoidable. Second, six of the included studies were

small sample sized and did not mention any blindness methods that had the risk of compromising concealment allocation^[41]. Third, except the acute leukemia subgroup, there were rare studies of other hematologic malignant diseases included in the meta-analyses. Thus the efficacy result mainly reflected the efficacy of TCM for acute leukemia. According to our result, it was not clear whether the TCM usage had the same efficacy for other hematologic malignant diseases. Finally, all of the included studies were not large sample sized. Only 5 studies used the central randomization method. As a result of it, the quality of evidence of our study was compromised and the GRADE recommendation level was low. Because of these limitations the reliability might be influenced and the

Table 25 Characteristics of included studies

Studies	Age	Sex (male:female)	Race	Disease	No. of participants (TCM:control)	Intervention		Published language
						TCM	Control	
Dian Rong 2009 ^[53,21,25,31,33]	TCM 39.52 ± 18.87 Control 37.94 ± 18.55	TCM 50:21 Control 39:27	Chinese	Acute leukemia	71:66	Compound Zhe Bei granule + standard chemotherapy	Placebo + standard chemotherapy	English
Mao Sheng 2007 ^[56,27]	TCM 35.63 ± 6.46 Control 36.57 ± 7.38	TCM 33:27 Control 31:29	Chinese	Acute myeloid leukemia	60:60	Yi Qi Jie Du Huo Xue decoction + standard western medicine	Standard western medicine	Chinese
sHai Yan 2007 ^[22]	TCM 18-65 Control 19-63	TCM 5:3 Control 7:3	Chinese	Chronic myelogenous leukemia	8:10	Qu Du Hua Yu decoction + hydroxyurea	Hydroxyurea	Chinese
sWei Hong 2013 ^[23]	TCM 25-60 Control 17-7	TCM 22:14 Control 17:7	Chinese	Chronic myelogenous leukemia	22:17	TCM + interferon-α	Interferon-α	Chinese
Chuan Xin 2013 ^[23]	TCM 4.30 ± 1.81 Control 4.95 ± 2.04	TCM 12:8 Control 10:10	Chinese	Pediatric acute myeloid leukemia	20:20	TCM + standard chemotherapy	Standard chemotherapy	Chinese
Ji Hong 2011 ^[54]	TCM 60-71 Control 61-72	TCM 16:16 Control 15:13	Chinese	Elderly acute myeloid leukemia	32:28	TCM + HAG chemotherapy	HAG chemotherapy	Chinese
Rui Rong 2004 ^[29]	TCM 12-78 Control 11-76	TCM 40:28 Control 27:19	Chinese	Acute myeloid leukemia	68:46	TCM + standard chemotherapy	Standard chemotherapy	Chinese
Su Juan 2005 ^[24]	TCM 32.5 ± 12.45 Control 31.53 ± 12.41	TCM 16:14 Control 17:13	Chinese	Acute leukemia	30:30	Qing Re Jie Du kang Bai decoction + standard chemotherapy	Standard chemotherapy	Chinese
Wen Jiang 2010 ^[30]	TCM 47-78 Control 46-79	TCM 17:12 Control 15:13	Chinese	Acute myeloid leukemia	29:28	Shen Qi Qing Re Ke Li + HAG chemotherapy	HAG chemotherapy	Chinese
Xiu Mei 1997 ^[35]	TCM 6-73 Control 6-71	TCM 72:40 Control 36:19	Chinese	Non-Hodgkin lymphoma	112:55	TCM + standard chemotherapy	Standard chemotherapy	Chinese
Ying Fei 2005 ^[28]	TCM 13-72 Control 15-71	TCM 22:10 Control 25:8	Chinese	Acute leukemia	32:33	Shen Qi Fu Zheng injection + standard chemotherapy	Standard chemotherapy	Chinese

TCM: Traditional Chinese medicine; HAG: Homoharringtonine + cytarabine + granulocyte colony stimulating factor.

Table 26 Quality assessment of included studies

Studies	Random sequence generation (selection bias)	Allocation concealment (selection bias)	Blinding of participants and personnel (performance bias)	Blinding of outcome assessment (detection bias)		Incomplete outcome data (attrition bias)	Selective reporting (reporting bias)	Other bias
				All outcomes	All outcomes			
Dian Rong 2009 ^[53,21,25,31,33]	Low risk	Unclear	Low risk	Low risk	Unclear	Unclear	Low risk	Unclear
Mao Sheng 2007 ^[56,27]	Low risk	Unclear	Unclear	Low risk	Unclear	Unclear	Low risk	Unclear
sHai Yan 2007 ^[22]	Low risk	Unclear	Unclear	Low risk	Unclear	Unclear	Low risk	Unclear
sWei Hong 2013 ^[23]	Low risk	Unclear	Unclear	Low risk	Unclear	Unclear	Low risk	Unclear
Chuan Xin 2013 ^[23]	Low risk	Unclear	Unclear	Low risk	Unclear	Unclear	Low risk	Unclear
Ji Hong 2011 ^[54]	Low risk	Unclear	Unclear	Low risk	Unclear	Low risk	Low risk	Unclear
Rui Rong 2004 ^[29]	Low risk	Unclear	Unclear	Low risk	Unclear	Unclear	Low risk	Unclear
Su Juan 2005 ^[24]	Low risk	Unclear	Unclear	Low risk	Unclear	Unclear	Low risk	Unclear
Wen Jiang 2010 ^[30]	Low risk	Unclear	Unclear	Low risk	Unclear	Unclear	Low risk	Unclear
Xiu Mei 1997 ^[35]	Low risk	Unclear	Unclear	Low risk	Unclear	Unclear	Low risk	Unclear
Ying Fei 2005 ^[28]	Low risk	Unclear	Unclear	Low risk	Unclear	Unclear	Low risk	Unclear

Table 27 Summary of findings of the overall response and complete response outcomes

Outcomes	Illustrative comparative risks ¹ (95%CI)		Relative effect (95%CI)	No. of participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk Control	Corresponding risk Overall response rate				
Overall response rate	Study population		RR = 1.14 (1.03-1.26)	974 (12 studies)	++-- Low	
	761 per 1000 Moderate 775 per 1000	867 per 1000 (784-959) 883 per 1000 (798-976)				
Complete response rate	Study population		RR = 1.21 (1-1.46)	974 (12 studies)	++-- Low ^{2,3}	
	579 per 1000 Moderate 579 per 1000	701 per 1000 (579-846) 701 per 1000 (579-845)				

Overall response rate for malignant hematologic disease
Patient or population: Patients with malignant hematologic disease
Settings:
Intervention: Overall response rate

¹The basis for the assumed risk (*e.g.*, the median control group risk across studies) is provided in footnotes. The corresponding risk (and its 95%CI) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95%CI); ²Not all studies included were high quality randomized controlled trial; ³Most studies showed better effect when traditional Chinese medicine was added while some studies did not show statistically significant better effect. GRADE Working Group grades of evidence. High quality: Further research is very unlikely to change our confidence in the estimate of effect; Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate; Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate; Very low quality: We are very uncertain about the estimate.

results should be interpreted with caution. As there were some limitations, we extensively searched the related databases, publications and websites, strictly screened and evaluated retrieved articles and analyzed the pooled data. Our study assessed the evidence available recently so it is still significant for evaluating the role of TCM for hematologic malignancies.

Because TCM causes little AEs, has little interaction with other drugs or treatment methods it can be safely prescribed in most of the malignant diseases treatment. It is especially popular among the complementary and alternative medicine usage in the palliative care of cancer patients^[42]. But recently, it plays more important role in the tumor treatment. Our meta-analysis demonstrated that TCM not only had the advantage of reducing the chemotherapy associated serious non-hematologic AEs and had a trend to reduce the serious infection rate, but also significantly increased the response rate. Our result suggests TCM is helpful for hematologic malignant diseases treatment. Although we failed to show a better survival rate of TCM compared with control, we believed to recommend adding TCM to the hematologic malignancies treatment as an adjuvant therapy is reasonable, at least for adult acute leukemia.

Conclusion and implications for research

TCM increases the OR and CR rate for acute leukemia treatment and reduced the treatment associated serious non-hematologic AEs. Therefore, we recommend including TCM in the hematologic malignancies treatment, at least for adult acute leukemia treatment.

Except adult acute leukemia, we need more high quality studies on other hematologic malignant diseases, pediatric patients and in other regions apart from China. We are also in need of studies of TCM on the survival, infection and hematologic AEs rates for hematologic

malignancies treatment.

COMMENTS

Background

Albeit as the standard treatment, the chemotherapy always causes serious adverse effects (AEs) and its efficacy is still not satisfactory. Recently, many studies showed that traditional Chinese medicine (TCM) can improve the effect of the standard treatment and reduce the AEs.

Research frontiers

In recent years, more and more researchers begin to pay attention to the effect of TCM for malignant diseases. Many studies showed that TCM can increase the efficacy of the standard treatment and decrease the AEs.

Innovations and breakthroughs

Although there were many clinical studies published on the TCM for hematologic malignances, as far as we know, there was no systematic review published on this issue. As far as we know, the authors first summarized the evidence now available on it with systematic review and demonstrated a subjective result. The result confirmed the effectiveness of TCM for hematologic malignances and could be used in the clinical practice.

Applications

The result showed that TCM can increase the overall response and complete response rates. In addition, TCM also reduced the non-hematologic serious AEs. The authors consider TCM should be used for hematologic malignances treatment.

Peer-review

The manuscript is quite interesting.

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P- Reviewer: Alshehabi Z, Romero MR **S- Editor:** Ji FF
L- Editor: A **E- Editor:** Liu SQ





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