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Review

Oral Chinese herbal medicine (CHM) as an adjuvant treatment during chemotherapy for non-small cell lung cancer: A systematic review

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ABSTRACT

Background: Non-small cell lung cancer (NSCLC) remains a major global health problem because of its prevalence and poor prognosis. Treatment options are limited and there is a need to explore alternatives. This systematic review evaluates the role of Chinese herbal medicine (CHM) in association with chemotherapy for NSCLC.

Methods: English and Chinese databases were searched for RCTs comparing CHM with conventional biomedical treatment or placebo. Papers were reviewed systematically and data were analysed using standard Cochrane software Revman 5.

Results: Fifteen Chinese trials involving 862 participants met the inclusion criteria. All trials were of poor quality with a considerable risk of bias. There was a significant improvement in quality of life (QoL) (increased Karnofsky Performance Status) (RR 1.83, 95% CI 1.41–2.38, $p < 0.00001$ for both stages III, IV only NSCLC and all stages NSCLC) and less anaemia (RR 0.37, 95% CI 0.15–0.91, $p = 0.03$ for stages III, IV only NSCLC; $p = 0.005$ for all stages NSCLC) and neutropenia (RR 0.42, 95% CI 0.22–0.82, $p = 0.01$ for stages III, IV only NSCLC; $p < 0.00001$ for all stages NSCLC) when CHM is combined with chemotherapy compared to chemotherapy alone. There was no significant difference in short term effectiveness and limited inconclusive data concerning long term survival. Five promising herbs have been identified.

Conclusion: It is possible that oral CHM used in conjunction with chemotherapy may improve QoL in NSCLC. This needs to be examined further with more rigorous methodology.

1. Introduction

Lung cancer is a major worldwide health problem and accounts for approximately one sixth of all cancer deaths globally. In the UK lung cancer accounts for around 1 in 7 of new cancer cases, that is, 38,313 new patients diagnosed in 2004 [1]. It is the most common cause of death from cancer for both men and women, and was responsible for 33,465 UK deaths in 2007 accounting for a quarter (24%) of all male and a fifth (19%) of all female cancer deaths [2].

Lung cancer classification describes two broad histological types that account for the majority of diagnosed cases; non-small cell lung cancer (NSCLC 80%) and small cell lung cancer (SCLC 20%). NSCLC can be further sub-divided into squamous cell cancers, adenocarcinoma and large cell carcinoma; these account for approximately 35%, 27% and 10% of all UK lung cancers respectively [3]. The most up to date internationally accepted staging, the Tumour, Node, Metastasis (TNM) of therapeutic interventions by ascribing an accurate prognosis. This staging for lung cancers is described elsewhere [4].

Whilst surgical resection before spread can affect a cure the majority of patients with lung cancer present with disease that is beyond remedial surgical intervention. Consequently surgical resection rates remain low [5,6] in the UK. Although survival has improved for most cancers this is not the case for lung cancer where 5-year survival rates remain low for decades and are at 6% [7–9]. Some chemotherapeutic (platinum based) and radiotherapeutic interventions (CHART) have begun to show promise in

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controlling disease progression. However they are onerous forms of therapy where toxicity and morbidity limit the completion of the recommended number of dose cycles. Adjuvant therapies that might allow patients to complete the full number of dose cycles could therefore have a significant therapeutic impact. For instance Traditional Chinese Medicine (TCM) based interventions such as acupuncture have been utilised to manage adverse reactions to chemotherapy such as nausea [10] Chinese Herbal Medicine (CHM) may also reduce the occurrence of adverse reactions such as anaemia and neutropenia and may offer cheaper and safer options for such strategies than current conventional medication [11]. This systematic review focuses on the use of CHM as an adjuvant treatment for patients receiving chemotherapy for NSCLC.

Our primary research question is

- Does CHM plus chemotherapy show a different survival time when compared to chemotherapy alone for NSCLC patients?

Our secondary research questions are

- What effect does CHM have on the side effect profile of chemotherapeutic interventions in matched patient groups?
- Does CHM have recorded adverse effects?
- Does the addition of CHM improve quality of life (QoL) among those receiving conventional chemotherapy for NSCLC?

2. Methods

2.1. Types of studies and participants

Patients were included if they were receiving treatment for NSCLC and were using adjuvant oral CHM to reduce side effects and increase survival. Three types of randomized controlled trials (RCT's) trials were reviewed; CHM versus an inactive placebo group; a comparison of different CHM regimes; and CHM versus conventional biomedical treatment. Studies using intravenous CHM were not considered because these preparations are not available or licensed in the EU. Studies which used interventions such as radiotherapy, acupuncture, or a complicated sequence of treatment such as various vitamin supplementations were also not included in this systematic review and we considered the outcomes uninterpretable.

Primary outcomes
- Improvement in response rates.
- Improvement in survival rates.

Secondary outcomes
- Improvement in known subjective and objective side effects from chemotherapy.
- Improvement in validated QoL measures.
- Adverse events from CHM.
- Improvement in compliance to chemotherapy regimes.
- Identifying key herbs used in CHM adjuvant treatment.

2.2. Search methods for identification of studies

The Cochrane Central Register of Controlled Trials (CENTRAL) English databases: MEDLINE, EMBASE, AMED, CINAHL, NLH and Chinese language databases: Chinese BioMedical Literature Database (CBM), Chinese Medical Current Contents (CMCC), China Academic Journals (CNKI), Chinese Sci &Tech Journals (VIP) were searched using the following terms: non-small cell lung cancer, traditional medicine, adjuvant treatment, Chinese medicine, herbal medicine, plant extract, complementary medicine. The references of all included studies and relevant reviews were scanned to identify further relevant articles. All searches ended at June 2008.

2.3. Trial characteristics

2.3.1. To minimize selection, attrition and performance bias

We required clear inclusion and exclusion criteria, appropriate data for demographic characteristics included such as age, duration of illness, comparable treatment and control groups at entry and a clear and acceptable method of randomisation. We defined acceptable randomisation as no more than a 10% variation between the number of participants in the treatment and control group. This suggested it is likely that a proper blinded randomisation procedure may have been employed should the randomisation procedure be inadequately described in the trial methodology. Quality of allocation concealment was also recorded (allocation concealment will be scored as adequate (A), unclear (B), or inadequate (C)). We included details of the duration, timing and the location of the study, confirmation of the care programmes and the types of CHM and placebos used along with their methods of administration, the number of randomized participants excluded or lost to follow up, treatment compliance and the presence of an intention to treat analysis.

2.3.2. To minimize detection bias

We evaluated whether the outcome assessors were blind to the assessment and whether the outcome measures used were clearly defined and clearly and consistently reported. If all quality criteria were met the study was categorised as low risk of bias (A), one or more criteria were only partly met as a moderate risk of bias (B), one or more criteria not met as a high risk of bias (C).

2.4. Analysis

At the protocol stage, a mutually agreed, standardised data extraction form was generated and used for all published trials.

Statistical analysis was performed using the Review Manager (*RevMan 5*) software and meta-analyses were performed if more than two trials were identified with the same outcome. The effect estimates were presented as relative risk (RR) and associated 95% confidence intervals (CI) for binary data, and mean difference (MD) and 95% CI for continuous data. Data were analysed by the fixed-effect model. If there was significant heterogeneity (defined as when $I^2 > 50\%$), the data were analysed and presented using a random-effects model.

3. Results

3.1. Description of studies

A total of 209 trials were identified; all of these trials took place in China and were reported in Chinese. Fifteen trials are included in this review (Fig. 1), involving a total of 862 participants [12–27]. One trial was presented in two papers [23–24], therefore this has been considered as one study. All the trials took place in hospitals in China among in-patients. Participants, diagnostic criteria and types of herbal invention and chemotherapeutic drugs (where relevant) are all described in Table 1 and are divided into the various types of interventions.

3.2. Comparisons and control groups

There were no placebo only groups in any of the included studies. The studies can be conveniently grouped as follows:

Table 1
Characteristics of included studies.

Study	Risk of bias	Sample size	Method of diagnosis	Staging criteria, method and distribution	Intervention	Duration of the study	Outcome measures
Chinese herbal medicine plus chemotherapy versus chemotherapy alone							
Jie et al. [12] [a]	C	60 (30 CHM plus chemotherapy; 30 chemotherapy only) Dropout: 1	Cytology/histology	UICC criteria: Unclear systematic scanning method Stages: IIIb – 10 IV – 50	1. NP regimen (Navelbine and cisplatin) plus Chinese herbs 2. NP regimen only	9 weeks	1. Short term effective rate 2. Increase in quality of life (KPS scale) 3. Decrease in natural killer cell count 4. Anaemia 5. Thrombocytopenia 6. Decrease in white blood cell count
Liu et al. [15] [a]	C	60 (30 CHM plus chemotherapy; 30 chemotherapy only)	Cytology/histology	UICC criteria: CT/Chest X-ray Stage distribution IIIb – 18 IV – 19	1. Chinese herbs plus NP regimen 2. NP regimen only	At least 2 months	1. Short term curative effect 2. Increase in quality of life (KPS scale)
Yang et al. [17] [a]	C	40 (20 CHM plus chemotherapy; 20 chemotherapy only)	Cytology/histology	Chinese criteria CT/MRI Stage distribution: IIIB – 13 IV – 27	1. Chinese herbs (pills), plus GP regimen (gemcitabine and cisplatin) 2. GP regimen only	2–3 months	1. Short term effective rate 2. Increase in quality of life (KPS scale) 3. Nausea 4. Vomiting 5. Diarrohea 6. White blood cell decrease 7. Thrombocytopenia 8. Abnormal ECG 9. Abnormal liver function test
Feng et al. [19] [a]	C	60 (30 chemotherapy only; 30 chemotherapy plus CHM)	Cytology/histology	UICC criteria CT/Chest X-ray Stage distribution: IIIa – 15 IIIb – 23 IV – 22	1. Paclitaxel, gemicitabine, or GP regimen 2. Paclitaxel, gemcitabine, or GP regimen plus Chinese herbs	3 weeks for chemotherapy, 3 months for Chinese herbs	1. Short term effective rate 2. Increase in quality of life (KPS scale) 3. Increase in quality of life (weight stability)
Zhang et al. [20] [a]	C	60 (30 chemotherapy plus CHM; 30 chemotherapy only)	Cytology/histology	Staging criteria unclear CT/Chest X-ray Stage distribution: III – 16 IV – 44	1. MVP regimen (mitomycin, vindesine and cisplatin) plus Chinese herbs 2. MVP regimen only	Unclear chemotherapy treatment duration, Chinese herbs treated for 2 weeks after chemotherapy stops	1. Short term effective rate 2. Survival rate at one year 3. Increase in quality of life (KPS scale) 4. White blood cell decrease
Zhang et al. [21] [a]	C	70 (36 CHM plus chemotherapy; 34 chemotherapy only)	Cytology/histology	Staging criteria unclear CT/Chest X-ray Stage distribution: III – 34 IV – 36	1. Chinese herbs plus NP regimen 2. NP regimen only	Chemotherapy continue for 3 weeks and then Chinese herbs continue for 3 weeks	1. increase in quality of life (ECOG performance status grades) 2. Anaemia, thrombocytopenia, white blood cell decrease on days seven and fourteen after treatment 3. Abnormal liver function test (ALT/AST) 4. Abnormal urea and creatinine 5. Nausea, decrease in appetite

Table 1 (*Continued*)

Study	Risk of bias	Sample size	Method of diagnosis	Staging criteria, method and distribution	Intervention	Duration of the study	Outcome measures
Yi et al. [22] [a]	C	62 (32 CHM plus chemotherapy; 30 chemotherapy only)	Cytology/histology	UICC criteria CT Stages: IIIa – 13 IIIb – 26 IV – 23	1. NP, MVP or CAP (cyclophosphamide, doxorubicin, cisplatin) regimen plus Chinese herbs 2. NP, CAP or MVP regimen Chinese herbs are individually tailored	2 months	1. Short term effective rate 2. Increase in quality of life (KPS scale)
Ma [25] [a]	C	53 (28 CHM plus chemotherapy; 25 chemotherapy only)	Cytology/histology	UICC criteria CT/Chest X-ray Unclear staging distribution	1. CAP or MFP (melphalan, 5-fluorouracil, medroxyprogesterone acetate) regimen plus, Chinese herbs (capsules) 2. CAP or MFP regimen	2 months	1. Short term effective rate
Wang et al. [27] [a]	C	93 (48 CHM plus chemotherapy; 45 chemotherapy)	Cytology/histology	Staging criteria unclear CT/Chest X-ray Stages: IIIa – 44 IIIb – 33 IV – 16	1. MVP regimen, Chinese herbs 2. MVP regimen Chinese herbs are individually tailored	4–6 weeks	1. Short term effective rate 2. Survival rate at one year 3. Survival rate at two years 4. Survival rate at three years 5. Increase in quality of life (KPS scale)
Chinese herbal medicine plus chemotherapy versus chemotherapy alone versus Chinese herbal medicine alone							
Liu et al. [13] [a,b]	C	51 (18 CHM; 16 chemotherapy; 17 CHM plus chemotherapy)	Cytology/histology	UICC criteria: CT/Chest X-ray Stage distribution IIIa – 11 IIIb – 13 IV – 27	1. Chinese herbs 2. MVP regimen 3. Chinese herbs plus MVP regimen	2 months	1. Short term effectiveness rate 2. Increase in quality of life (KPS)
Xu et al. [18] [a,b]	C	91 (31 chemotherapy; 32 chemotherapy plus CHM; 28 CHM only)	Cytology/histology	UICC criteria: CT/Chest X-ray Stage distribution unclear	1. MVP or NP regimen 2. MVP or NP regime plus Chinese herbs 3. Chinese herbs Chinese herbs are modified according to specific symptoms	3–4 months	1. Short term effective rate 2. Increase in quality of life (KPS scale) 3. Increase in quality of life (weight stability)
Li et al. [23] [a]Zhang et al. [24] [a,b]	C	100 (34 CHM; 33 chemotherapy; 33 CHM plus chemotherapy)	Cytology/histology	UICC criteria Unclear systematic scanning method Stages: I – 10 II – 22 III – 58 IV – 10	1. Chinese herbs (capsules) 2. CAP or MVP regimen 3. CAP or MVP regimen plus Chinese herbs (capsules)	2 months	1. Short term effective rate 2. Increase in quality of life (KPS scale) 3. Increase in quality of life (weight stability) 4. Anaemia 5. Decrease in white blood cell 6. Abnormal liver function test 7. Abnormal kidney function
Chinese herbal medicine alone versus chemotherapy alone							
Liu et al. [26] [b]	C	122 (60 CHM; 62 chemotherapy	Cytology/histology	UICC criteria Unclear systematic scanning method Stages: III – 70 IV – 52	1. Chinese herbs 2. COF (cyclophosphamide, 5 – fluorouracil, vincristine) regimen for squamous cell carcinoma, MOF (mitomycin, vincristine, 5 – fluorouracil) regimen for adenocarcinoma Chinese herbs are individually tailored	3 months	1. Short term effective rate 2. Survival rate at one year 3. Increase in quality of life (KPS scale) 4. Increase in quality of life (weight stability)

Chinese herbal medicine versus Chinese herbal medicine							
Sun et al. [14]	C	51 (26 CHM; 25 CHM)	Pathology	Unclear staging criteria CT/Chest X-ray Stage distribution IA – 3 IB – 9 IIA – 9 IIB – 30	1. Chinese herbs (Gao) 2. Chinese herbs (capsules)	6 months	1. Increase in quality of life (KPS 2. Increase in quality of life (weight stability)
Chinese herbal medicine plus chemotherapy versus Chinese herbal medicine plus chemotherapy							
Huang et al. [16]	C	40 (20 CHM plus chemotherapy; 20 CHM plus chemotherapy)	Pathology	Chinese criteria Unclear systematic scanning method Stages: IIIb – 23 IV – 17	1. Chinese herbs plus GP regimen 2. Chinese herbs (differ to that in intervention 1) plus GP regimen Chinese herbs are individually tailored	6 weeks	1. Short term effective rate 2. Increase in quality of life (FACT-L scores) 3. Overall objective chemotherapy side effects in terms of anaemia, thrombocytopenia, liver function tests

[a] Trials used in Chinese herbal medicine plus chemotherapy versus chemotherapy alone analysis.
[b] Trials used in Chinese herbal medicine alone versus chemotherapy therapy alone analysis.

- CHM + chemotherapy versus chemotherapy (9 trials involving 558 participants).
- CHM + chemotherapy versus chemotherapy versus CHM (3 trials involving 242 participants)[1]
- CHM versus CHM (1 trial involving 51 participants).
- CHM + chemotherapy versus other CHM + chemotherapy (1 trial involving 40 participants).
- CHM versus chemotherapy (1 trial involving 112 participants).

In total, seven different chemotherapy regimens were used (see Table 1), or alternatively paclitaxel or gemcitabine was used alone. A single regimen or agent may have been used for the whole trial or a combination of the regimens may be have been used, depending on the clinical status of the individual participants. It was not possible to analyse the data to compare the effect of any single chemotherapy regimen.

3.3. Outcomes measures

Eleven [12,13,16–20,22,25–27] out of thirteen trials evaluating the short term effect of the lung cancer treatment used the internationally validated WHO criteria for complete response (CR), Partial response (PR), stable disease (SD) and progressive disease (PD) [28].

Eleven trials [12–15,17–20,22–24,27] used the Karnofsky Performance Status (KPS) scale to measure QoL (0–100) [29], three [14,18,23] of which also recorded weight changes. All trials defined a 10-point change in KPS scale or a $\geq$1 kg change in weight as clinically significant. One trial [20] using KPS reported total group score that could not be interpreted. Two trials used functional assessment of cancer therapy-lung (FACT-L) [16] and Eastern Cooperative Oncology Group (ECOG) performance status [20] to assess QoL but the data could not be properly interpreted or extracted so these three trials were excluded.

Six trials [12,16,17,20–23] reported objective side effects of chemotherapy such as anaemia, thrombocytopenia and neutropenia, one trial [16] reported incomplete haematological data that could not be analysed. The other trials recorded the results either as actual levels [12,17,21] or in terms of grades (0 to IV) using the WHO criteria for acute and subacute response to tumour treatment [30]. Subsequent analysis of chemotherapy side effects includes those classified as WHO grade I and above or the equivalent in raw values.

Long term follow up (up to 3 years) was generally not available in these studies; only three trials [20,26–27] were found to contain this information.

3.4. Risk of bias in included studies

All trials claimed to have randomly assigned participants into different treatment groups; however there was no record of any randomisation method or any method of blinding. Consequently all the trials included in this review have been assigned a 'C' status with a high risk of bias.

3.5. Effects of interventions

All but three of the trials analysed were performed exclusively with stages III and IV non-small cell lung cancer participants. Those three trials consisted of participants with either early stage (I and II) or a mixture of all four stages. Therefore in order to aid accurate interpretation of the results by disease stage two risk ratios and

[1] These trials were analysed by dividing the interventions into two groups: CHM versus CHM plus chemotherapy; CHM versus chemotherapy. Therefore the results may appear to include more than 15 trials as there will be a sum of 12 trials for the former intervention and 4 trials for the latter intervention.

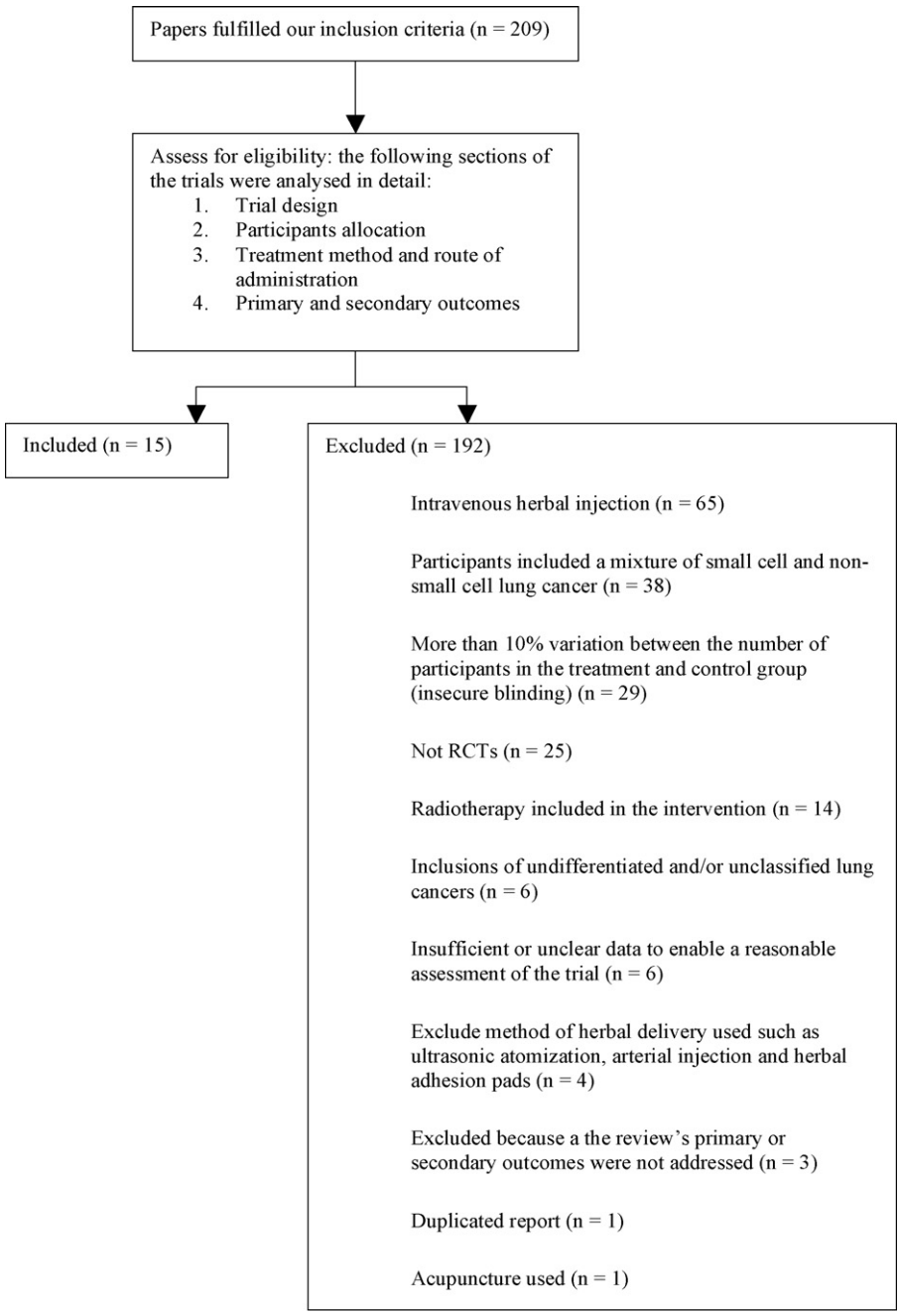

Fig. 1. A flow chart to demonstrate trial selection criteria used for review analysis.

confidence intervals are given where appropriate. Table 2 summarises the risk ratio, confidence interval and p values for the different intervention categories: CHM plus chemotherapy versus CHM (response rate and long term survival; QoL; objective and subjective chemotherapy side effects); CHM versus chemotherapy (response rate and long term survival; QoL; anaemia).

3.5.1. *Response and survival rates*

The combined treatment (chemotherapy plus CHM) demonstrated borderline non-significant difference for short term effectiveness compared to chemotherapy alone for NSCLC (RR 1.29, 95% CI 1.00–1.67, $p = 0.05$, 8 trials, for stages III, IV only NSCLC; RR 1.27, 95% CI 1.00–1.61, $p = 0.05$, 9 trials for all stages NSCLC). Two trials looked at long term survival of patients and these showed no significant difference for improved rates of survival at 1, 2 and 3 years (RR 1.25, 95% CI 0.94–1.65, $p = 0.12$, 2 trials; RR 1.31, 95% CI 0.72–2.40, $p = 0.38$, 1 trial; RR 1.31, 95% CI 0.59–2.90, $p = 0.50$, 1 trial respectively). Similarly, CHM alone showed no significant difference for short term effectiveness compared to chemotherapy alone (RR 0.86, 95% CI 0.30–2.42, $p = 0.77$, 3 trials). The results regarding long term survival comparing CHM alone to chemotherapy alone were not consistent: one trial suggested some significant improvement in the CHM only group for survival rate at 1 year (RR 2.16, 95% CI 1.35–3.46, $p = 0.001$, 1 trial) but another trial suggested non-significant improvement at two and a half years RR 3.10, 95% CI 0.12–79.23, $p = 0.49$, 1 trial respectively). Overall CHM does not significantly improve either short term or long term survival, although the evidence for the latter is sparse. Importantly, it does not appear to compromise survival which makes it possible to consider its use as an adjuvant therapy to chemotherapy.

Table 2
Summary of relative risk and confidence intervals for Chinese herbs combined with chemotherapy or Chinese herbs alone versus chemotherapy alone.

Outcome measures	Relative risk (RR)	95% Confidence intervals	*P* values	Total number of trials	Total number of participants
Chinese herbal medicine plus chemotherapy versus chemotherapy alone					
Short term effectiveness	1.29	1.00–1.67	0.05	8	470
	1.27[a]	1.00–1.61	0.05	9	523
Rates of survival at 1 year	1.25	0.94–1.65	0.12	2	150
Rates of survival at 2 years	1.31	0.72–2.40	0.38	1	90
Rates of survival at 3 years	1.31	0.59–2.90	0.50	1	90
Improvement in quality of life (KPS)	1.83	1.41–2.38	<0.00001	8	469
	1.83[a]	1.42–2.36	<0.00001	9	535
Improvement in quality of life (weight)	1.57	1.08–2.30	0.02	1	63
	1.40	1.11–1.76	0.004	2	129
Anaemia	0.37	0.15–0.91	0.03	1	59
	0.42[a]	0.23–0.77	0.005	2	125
Neutropenia	0.42	0.22–0.82	0.01	3	169
	0.34[a]	0.20–0.57	<0.00001	5	295
Thrombocytopenia	0.56	0.18–1.78	0.33	2	99
Abnormal urea and creatinine levels	0.19	0.02–1.54	0.12	1	70
Abnormal liver function test	0.33	0.08–1.28	0.11	2	110
Nausea	0.67	0.22–2.01	0.47	2	110
Vomiting	0.50	0.10–2.43	0.39	1	40
Diarrhoea	0.67	0.12–3.57	0.64	1	40
Chinese herbal medicine alone versus chemotherapy alone					
Improvement in quality of life (KPS)	2.65	1.56–4.48	0.0003	3	156
	2.71[a]	1.69–4.33	<0.00001	4	222
Improvement in quality of life (weight)	1.59	1.09–2.33	0.02	1	60
	1.46[a]	1.17–1.82	0.0008	2	126
Short term effectiveness	0.86	0.30–2.42	0.77	3	216
Rates of survival at 1 years	2.16	1.35–3.46	0.001	1	103
Rates of survival at two and half years	3.10	0.12–79.23	0.49	1	60
Anaemia	0.15[a]	0.04–0.61	0.008	1	67

[a] Include all NSCLC stages.

3.5.2. Effects on the side effects of chemotherapeutic interventions

There was significantly less anaemia (RR 0.37, 95% CI 0.15–0.91, $p = 0.03$, 1 trial for stages III, IV only NSCLC; RR 0.42, 95% CI 0.23–0.77, $p = 0.005$, 2 trials for all stages NSCLC) and less neutropenia (RR 0.42, 95% CI 0.22–0.82, $p = 0.01$, 3 trials for stages III, IV only NSCLC; RR 0.34, 95% CI 0.20–0.57, $p < 0.00001$, 5 trials for all stages NSCLC) in the combined treatment group (CHM plus chemotherapy). In the CHM only treatment group, there were significantly lower rates of anaemia (RR 0.15, 95% CI 0.04–0.61, $p = 0.008$, 1 trial). However, this was the outcome of one trial [23] which included a mixture of lung cancer participants with all four disease stages. CHM, used either as an adjuvant therapy or alone appears to significantly decreased the rates of anaemia and neutropenia. Although the number of trials analysed is small involving a total of 230 and 330 participants respectively. The poor quality of these trials makes it impossible to come to any definitive conclusions but this significant result is worthy of more detailed investigations utilising more rigorous research methods.

3.5.3. Effects on quality of life

The combined treatment demonstrated improvement in QoL (compared to chemotherapy alone) measured either by an increase in KPS scale (RR 1.83, 95% CI 1.41–2.38, $p < 0.00001$, 8 trials for stages III, IV only NSCLC; RR 1.83, 95% CI 1.42–2.36, $p < 0.00001$, 9 trials for all stages NSCLC) or by weight stability over the study period (RR 1.57, 95% CI 1.08–2.30, $p = 0.02$, 1 trial for stages III, IV only NSCLC; RR 1.40, 95% CI 1.11–1.76, $p = 0.004$, 2 trials for all stages NSCLC). CHM alone was also significantly better at improving quality of life compared with chemotherapy alone as measured by improvement in KPS (RR 2.65, 95% CI 1.56–4.48, $p = 0.003$, 3 trials for stages III, IV only NSCLC; RR 2.71, 95% CI 1.69–4.33, $p < 0.00001$, 4 trials for all stages NSCLC); weight stability (RR 1.59, 95% CI 1.09–2.33, $p = 0.02$, 1 trial for stages III, IV only NSCLC; RR 1.46, 95% CI 1.17–1.82, $p = 0.0008$, 2 trials for all stages NSCLC). These results demonstrated that CHM can significantly improve quality of life using internationally validated tools. This important finding suggests we should consider the potential for CHM use in NSCLC.

Table 3
Common TCM diagnostic categories and the pharmacology of representative Chinese herbs used.

TCM diagnosis	Representative herb	Pharmacology
Qi deficiency	Huang Qi (*Radix Astragali membranaceus*)	Activates NK and macrophage cells [32,33] Inhibits T-helper cell type 2 cytokines [33] May increase cancer cell apoptosis [34]
Blood deficiency	Dang Gui (*Radix Angelica sinensis*)	Increases macrophage, lymphocyte and NK cell activity [31,35]
Yin deficiency	Mai Men Dong (*Radix Ophiopogon japonicus*)	Induces apoptosis [36] Stimulates lymphocyte proliferation [37]
Blood stagnation	E Zhu (*Radix Curcuma zedoaria*)	Increases macrophage activity Cytotoxic against several cancer cell lines Inhibits platelet aggregation [38]
Fire poison	Bai Hua She She Cao (Herba *Oldenlandia Diffusa*)	Inhibits protein tyrosine kinases and induces cancer cell apoptosis [39,40]

3.5.4. Adverse effects of CHM

Two trials reported the outcome of adverse effects from CHM: one trial [17] reported none; the other trial [13] reported the onset of dry mouth and feeling anxious in a few participants in one of the CHM only group, which was relieved by adequate water and fruit intake. The overall incidence of adverse effects appeared to be much less than with conventional chemotherapy treatment.

3.6. Herb frequency

Although the included trials exhibited considerable variability in the constituents of the herbal formulae used there was a broad consensus in both diagnosis and in the selection of key herbs underlying this heterogeneity. Within the rather archaic but descriptive language of TCM, herbs are targeted therapeutically to deal with the TCM syndromes associated with NSCLC. The common TCM syndromes involve nourishing Qi and Yin, two syndromes most commonly associated with improvement in QoL and neutropenia within the trials, invigorating the Blood and clearing Fire-Poison, associated with improvement in anaemia. The single most commonly used herb across all TCM diagnostic categories is Huang Qi (*Astragali membranaceus*). Additional herbs that are most commonly used within each of the TCM syndromes are presented in Table 3 together with the pharmacological data on some of the possible mechanisms that may underlie the effects described in this review. This data describes 5 herbs which are worthy of more detailed investigation ideally designed to evaluate their active chemical components, the mechanism of the actions as well as providing specific therapeutic and clinical indications for their use.

4. Discussion

This systematic review utilises standardised methodology and describes the potential for CHM to improve quality of life and mitigate the toxicity associated with chemotherapeutic interventions for the treatment of NSCLC. CHM in conjunction with chemotherapy demonstrated significant improvements in quality of life and a reduction in anaemia and neutropenia. When Chinese herbal medicine is used alone quality of life is better than that reported with chemotherapy alone without apparently compromising survival. There appear to be fewer adverse events associated with CHM than with chemotherapy in the treatment of NSCLC. CHM does not appear to significantly improve long term survival rate. Many of the studies were underpowered and all were open to significant bias so the results of this systematic review must be interpreted with great caution.

This meta-analysis evaluates TCM as a whole system in the treatment of NSCLC. Despite the heterogeneity of the trials there is a consistency of conventional and TCM diagnosis, treatment principle and a common core of individual herbs that makes it appropriate to evaluate their impact as an adjuvant therapy for NSCLC thus justifying the pooling of the data and subsequent meta-analytical approach. It is possible that an evaluation of the active chemical components of commonly used CHM could potentially lead to the discovery of novel therapeutic compounds. However this approach may neglect the complex synergy within the whole system of TCM that arises from combining several herbs together. The impact of CHM on quality of life is also supported by a recent trial looking at the intravenous delivery of CHM as an adjuvant to chemotherapy for NSCLC. The use of intravenous herbs falls outside the scope of this review but the positive result of this study, in relieving chemotherapy induced nausea and vomiting [41] is consistent with our findings. This indicates that further assessment of the effect(s) of CHM may be worthy of more detailed investigation particularly in NSCLC where conventional medicine has little to offer this common and fatal condition.

The mechanisms through which CHM may operate remain open to speculation although we have presented some evidence that might underpin the pharmacological action of these specific herbal remedies. Another possible explanation for the non-significant improvement in the CHM only group for long term survival could be that the toxicity and morbidity associated with chemotherapy actually impairs long term survival, rather than CHM having a direct effect on survival. This data also suggests that CHM may offer a cheap, safe alternative to erythropoietin and granulocyte colony stimulating factor in the treatment of cancer related neutropenia and anaemia [42,43].

The Karnofsky performance status scale was used to assess quality of life consistently across all trials. It is a uni-dimensional functional status scale which gives a global measure of activity [44]. Its acceptability, reliability and validity have been established in both clinical practice and research [44]. The only disadvantage associated with KPS is its lack of sensitivity with respect specific activities. This, however, is not a substantial concern with regard to this review where the main aim is to assess the overall improvement in QoL.

No placebo trials have been found for this review and this poses major problems when trying to interpret the specific effects of CHM. It is technically, and in some cases culturally difficult, to generate blinded placebo treatments for CHM due to the strong taste and smell of the herbal medicine decoction. The only method which could make placebo treatment and blinding easier is if treatment was given in the form of capsules. This makes it complex to modify the treatment on an individualised basis and this process of individualisation may be one of the great strengths of TCM. There is no information about the randomisation methods employed including the generation and concealment of allocation sequences for treatment and blinding in any of the trials included. Therefore there is a very high risk of bias and consequently these trials and their outcomes should be interpreted with great caution. No power calculation was performed in any of the included trials to establish sample size. Twelve [12,13,15,17,19–23,25–27] out of fifteen trials were unclear about their exclusion criteria, two [26,27] of which were also unclear about the inclusion criteria. Five trials [13,20,21,25,26] did not provide appropriate baseline data for comparison despite of the fact that they claimed groups were comparable at baseline. There is also an absence of data regarding compliance to treatment and dropout rates and there are no CONSORT diagrams for any of these studies. Many trials were unclear about the length of treatment given during the trial. For example, when there is a difference between the length of CHM treatment and the length of chemotherapy treatment, it is unclear whether the two groups are assessed at the same time or before and after treatment. Our reported results indicate that there are a limited number of trials using validated international criteria to assess chemotherapy side effects. Two trials [15,23] used Chinese criteria to assess short term effective rate but these criteria are not clearly explained. The results therefore only give an overview of how CHM may be affecting QoL. Overall the primary data is of poor quality. A more general review of CHM and cancer has also recently been published which came to similar conclusions about the methodological quality of clinical trials in this area [45].

This review raises the possibility that CHM could be used as an adjuvant to chemotherapy for the treatment of non-small cell lung cancer to improve QoL and reduce rates of anaemia and neutropenia thus improving compliance to chemotherapy. These tentative conclusions need further detailed investigations with high quality rigorous studies that are designed to focus on the promising herbs that we have identified while overcoming the poor methodology that has been employed to date when investigating CHM.

Conflict of interest statement

None declared.

Contributions

LJP and YH searched the Chinese language database to identify trials that could be considered for inclusion in this review. AF and SC did do the same in the English language database. AF and SC reviewed and identified studies for inclusion and any differences of opinion were resolved through discussion between AF, SC and GL. All authors were involved in drafting the final paper.

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