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

CRD summary
This review assessed the efficacy and safety of oral Chinese herbal medicine as adjuvant treatment during chemotherapy for non-small cell lung cancer; it found that Chinese herbal medicine may improve quality of life. The authors noted that further, more rigorous research is needed. These cautious conclusions were appropriate, given the limitations of the review and weaknesses in the underlying trials.

Authors' objectives
To assess the efficacy and safety of oral Chinese herbal medicine as an adjuvant treatment during chemotherapy for non-small cell lung cancer.

Searching
MEDLINE, EMBASE, AMED, CINAHL, National Library of Guidelines (NHS Evidence NHL), Cochrane Central Register of Controlled Trials (CENTRAL) and four Chinese language databases were searched to June 2008. Search terms were reported. Bibliographies of included studies and reviews were screened for additional articles.

Study selection
Randomized controlled trials (RCTs) that compared adjuvant Chinese herbal medicine with inactive placebo, different adjuvant Chinese herbal medicine regimes, or adjuvant Chinese herbal medicine versus conventional biomedical treatment, in patients receiving treatment for non-small cell lung cancer, were eligible for inclusion. Trials using intravenous Chinese herbal medicine, interventions such as radiotherapy, acupuncture, or a complicated sequence of treatment (such as various vitamin supplementations) were excluded.

Primary outcome measures were response rate and survival rate. Secondary outcomes were side effects from chemotherapy, quality of life measures, adverse events associated with Chinese herbal medicine, and compliance to chemotherapy regimes.

All the trials took place in hospitals in China among in-patients. All but three of the included trials were performed exclusively in patients with stages III and IV non-small cell lung cancer. Types of Chinese herbal medicine and chemotherapy regimes varied (details reported). One trial was included that compared Chinese herbal medicine alone with chemotherapy alone (not Chinese herbal medicine as an adjuvant treatment, as specified by the inclusion criteria). Trial duration appeared to range from four weeks to six months.

Two reviewers assessed studies for inclusion; any disagreements were resolved through discussion.

Assessment of study quality
The authors did not apply a validated quality assessment tool, but recorded a number of aspects of methodological quality including: reporting of clear inclusion and exclusion criteria and appropriate participant characteristics; comparable treatment and control groups at baseline; acceptable method of randomization (no more than a 10% variation between the number of participants in the treatment and control group); allocation concealment; the number of randomized participants excluded or lost to follow-up; use of intention to treat analysis; and blinding of outcome assessors. Details of the duration, timing and the location of the trial, confirmation of the care programmes, and the types of Chinese herbal medicine and placebos used along with their methods of administration, also appeared to form part of the quality assessment.

The authors stated that if all quality criteria were met, the trial was categorised as low risk of bias (A); if one or more criteria were only partly met, the trial was at moderate risk of bias (B); if one or more criteria not met, the trial was at high risk of bias (C).
The authors did not state how many reviewers performed the quality assessment.

**Data extraction**
The details and outcome measures assessed were extracted for each included trial. The authors reported that a standardized data extraction form was used.

The authors did not state how many reviewers performed the data extraction.

**Methods of synthesis**
Pooled estimates of relative risk (RR), with 95% confidence intervals (CIs), were calculated for any outcome measure reported by two or more trials. Where significant heterogeneity was identified ($I^2$ over 50%), a random-effects model was used, otherwise a fixed-effect model was applied.

**Results of the review**
Fifteen trials were included in the review (n=862 patients). All trials were of poor quality (classified as at a high risk of bias).

The comparisons assessed were: Chinese herbal medicine plus chemotherapy versus chemotherapy (nine trials; n=558 patients); Chinese herbal medicine plus chemotherapy versus chemotherapy versus Chinese herbal medicine (three trials; n=242 patients); Chinese herbal medicine versus another Chinese herbal medicine (one trial; n=51 patients); Chinese herbal medicine plus chemotherapy versus other Chinese herbal medicine plus chemotherapy (one trial; n=40 patients); and Chinese herbal medicine versus chemotherapy (one trial; n=112 patients).

**Chinese herbal medicine plus chemotherapy versus chemotherapy alone**: Adjuvant therapy with Chinese herbal medicine showed no significant improvements in survival compared with chemotherapy alone for studies of patients at all stages of non-small cell lung cancer. Adjuvant Chinese herbal medicine was associated with an improvement in quality of life (as measured on the Karnofsky Performance Scale, KPS) compared with chemotherapy alone (RR 1.83, 95% CI 1.42 to 2.36; nine trials) and with increased weight stability (RR 1.40, 95% CI 1.11 to 1.76; two trials). Adjuvant Chinese herbal medicine was also associated with a reduction in the risk of anaemia (RR 0.42, 95% CI 0.23 to 0.77; two trials) and a reduction in the risk of neutropenia (RR 0.34, 95% CI 0.20 to 0.57; five trials). Results were similar for trials that included only non-small cell lung cancer stage III and IV patients. No other outcome measures showed significant differences between Chinese herbal medicine and chemotherapy and chemotherapy alone.

**Chinese herbal medicine alone versus chemotherapy alone**: Chinese herbal medicine alone was associated with an improvement in quality of life (KPS scores) compared with chemotherapy alone (RR 2.71, 95% CI 1.69 to 4.33; four trials) for all stages of non-small cell lung cancer; it was also associated with increased weight stability (RR 1.46, 95% CI 1.17 to 1.82; two trials) for all stages of non-small cell lung cancer. In addition, one trial showed an increase in the one year survival rate, (RR 2.16, 95% CI 1.35 to 3.46; n=103 patients) for Chinese herbal medicine alone compared with chemotherapy alone, and one trial showed a decrease in the risk of anaemia (RR 0.15, 95% CI 0.04 to 0.61; n=67 patients). No other outcome measures showed significant differences between Chinese herbal medicine alone and chemotherapy alone.

No measures of statistical heterogeneity were reported.

**Authors’ conclusions**
It was possible that oral Chinese herbal medicine used in conjunction with chemotherapy may improve quality of life in non-small cell lung cancer. This needs to be examined further with more rigorous methodology.

**CRD commentary**
The review applied well defined inclusion criteria to a clearly stated research question. The inclusion of one trial which compared Chinese herbal medicine alone with chemotherapy alone and had no Chinese herbal medicine adjuvant therapy group, appeared to be outside the inclusion criteria defined. A range of sources were searched for relevant
trials. Measures to minimise error and/or bias were applied to the study selection process, but it was unclear whether similar measures were used throughout the review.

Although a validated quality assessment tool was not used, the authors reported relevant aspects of the methodological quality and highlighted the poor quality of all included trials. The meta-analytic methods applied were broadly appropriate, although interpretation of the overall findings was hindered by the lack of results for individual trials. In addition, it was unclear which meta-analytic model was actually used (fixed-effect or random-effects model) as no statistical heterogeneity data were reported.

The authors' cautious conclusions were appropriate, given the limitations of the review and the weakness of the underlying trials.

Implications of the review for practice and research

Practice: The authors made no recommendations for practice.

Research: The authors stated that further, high quality studies are needed to investigate the possible effects of adjuvant Chinese herbal medicine on quality of life in non-small cell lung cancer.

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