Thymosin plus cisplatin with vinorelbine or gemcitabine for non-small cell lung cancer: a systematic review and meta-analysis of randomized controlled trials

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CRD summary
The review concluded that thymosin plus chemotherapy, when compared with chemotherapy alone, can improve overall response rate, tumour control rate quality of life and immune system function in patients with non-small cell lung cancer. The reliability of the authors' conclusions is uncertain as they did not incorporate the considerable uncertainty relating to the quality of the included trials.

Authors' objectives
To evaluate the efficacy and safety of thymosin given as an addition to chemotherapy in patients with non-small cell lung cancer.

Searching
PubMed, EMBASE, The Cochrane Library, Web of Knowledge and Chinese Biomedical Database were searched to December 2010 without language restrictions; search terms were reported. Reference lists, Google Scholar and Medical Matrix and (unspecified) conference abstracts and unpublished material on the Internet were searched.

Study selection
Randomised controlled trials (RCT) that compared thymosin plus chemotherapy against chemotherapy alone in adults with non-small cell lung cancer (diagnosed by pathology or cytology) were eligible for inclusion. Patients had to have a Karnofsky performance score of at least 60 and their expected survival time had to be at least three months. Chemotherapy had to be vinorelbine with cisplatin or gemcitabine with cisplatin. Patients must not have received prior surgery or radiotherapy.

Most patients in the included studies were male and mean ages ranged from 50 to 68 years. Patients had either stage III or IV disease. Karnofsky scores ranged from 60 to 90 (where reported). Thymosin was given subcutaneously at a dose of 200mg; it was described as thymosin alpha 1 (at a dose of 1.6mg) or thymopentin (at a dose of 1mg or 10mg) in some trials. Half of the studies used vinorelbine with cisplatin as control treatment and the other half used gemcitabine with cisplatin. Results for 15 different outcomes or time points were reported.

Two reviewers independently selected studies for inclusion. Disagreements were resolved by a third reviewer.

Assessment of study quality
Risk of bias was evaluated using the Cochrane Risk of Bias tool to assess sequence generation, allocation concealment, blinding, incomplete outcome data, selective outcome reporting and other threats to validity. GRADE criteria (high, moderate, low and very low) were used to assess the quality of evidence.

Two reviewers independently assessed risk of bias. Disagreements were resolved by a third reviewer.

Data extraction
Data were extracted in order to calculate odds ratios or mean differences, with 95% confidence intervals (CI).

Two reviewers independently extracted data. Disagreements were resolved by a third reviewer.

Methods of synthesis
Meta-analyses were performed to calculate pooled odds ratios (OR), weighted mean differences or standardised mean differences. Where no statistical heterogeneity was found ($I^2<50\%$) a fixed-effect model was used; otherwise a random effects model was used.

Results of the review
Ten RCTs (724 patients, range 42 to 200) were included. All studies were classed as having an unclear risk of bias for sequence generation and blinding. Eight had an unclear rating for allocation concealment and two studies used sealed envelopes. It appeared that all studies had complete outcome data. None selectively reported outcomes.

Addition of thymosin to vinorelbine chemotherapy significantly increased overall response rate (OR 1.86, 95% CI 1.08 to 3.20; four RCTs), tumour control rate (OR 3.06, 95% CI 1.36 to 6.88; four RCTs) and one-year survival rate (OR 3.05, 95% CI 1.34 to 6.96; two RCTs) but not survival rates at two, three and four years. It also significantly improved quality of life (OR 3.39, 95% CI 1.54 to 7.47; two RCTs) and results for two measures of immune function (CD4 in three RCTs and NK cells in two RCTs). There was a significant decrease in thrombocytopenia.

Addition of thymosin to gemcitabine chemotherapy significantly increased overall response rate (OR 1.67, 95% CI 1.09 to 2.55; four RCTs), tumour control rate (OR 2.38, 95% CI 1.01 to 5.62; four RCTs). It also significantly improved quality of life (OR 3.84, 95% CI 1.97 to 7.48; three RCTs) and results for two measures of immune function (CD4 in three RCTs and NK cells in three RCTs). There were no significant differences for adverse effects.

No statistically significant differences were reported for any other outcomes. All evidence was rated as being of moderate quality according to GRADE criteria. Heterogeneity was indicated for some of the five different immune function outcomes but precise details were not presented.

**Authors' conclusions**
Thymosin plus chemotherapy, when compared with chemotherapy alone, can improve overall response rate, tumour control rate and quality of life and can increase immune system function.

**CRD commentary**
The review addressed a clear question and was supported by reproducible eligibility criteria. Electronic databases were searched for relevant studies in any language. Unpublished studies were searched for specifically. Suitable methods were employed to reduce the risks of reviewer error and bias throughout the review.

Sufficient population and treatment details were provided. It appeared that appropriate methods were used to pool data and assess heterogeneity. The absence of forest plots meant that individual trial results were not presented and made it difficult to interpret the basic heterogeneity reporting. Several analyses had relatively small sample sizes, so the possibility of chance results could not be ruled out. Study quality was assessed and the limitations of the trial reporting were acknowledged in the discussion.

The reliability of the authors' conclusions is uncertain as they did not incorporate the considerable uncertainty relating to the quality of the included trials.

**Implications of the review for practice and research**
The authors did not state any implications for practice or further research other than a need for better reporting in studies.

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