Endostar combined with chemotherapy versus chemotherapy alone for advanced NSCLCs: a meta-analysis

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CRD summary
The authors concluded that recombinant human endostatin combined with platinum-based chemotherapy can improve response rate without increasing side effects in patients with advanced non-small cell lung cancer. The authors' conclusions reflect the findings for vinorelbine plus cisplatin in combination with recombinant human endostatin but insufficient evidence on other combination therapies means their reliability is unclear.

Authors' objectives
To assess the clinical efficacy and safety of recombinant human endostatin combined with chemotherapy in the treatment of patients with advanced non-small cell lung cancers.

Searching
MEDLINE, EMBASE, The Cochrane Library, Science Citation Index, Chinese Biomedical Literature and Chinese National Knowledge Infrastructure were searched to December 2011; search terms were reported. No language restrictions were applied. Four oncology journals were searched manually from 1995 to 2011. Google was searched. Authors were contacted directly.

Study selection
Eligible for inclusion were parallel design randomised controlled trials (RCTs) and quasi-RCTs that compared the efficacy and safety of recombinant human endostatin (Endostar) alone or combined with chemotherapy with or without radiotherapy versus chemotherapy with or without radiotherapy. Trials had to include at least 40 patients with confirmed advanced non-small cell lung cancers. The outcomes of interest were survival, median time to progression, median survival time, response rate (complete and partial), quality of life and adverse events (severe leucopenia, severe thrombocytopenia, nausea and vomiting). Patients with serious medical illness, infections or metastatic cancer with additional tumour diseases were excluded from the review.

Most patients were males. Chemotherapy regimens included vinorelbine plus oxaliplatin or cisplatin, gemcitabine plus cisplatin and paclitaxel plus carboplatin or cisplatin.

The authors did not state how many reviewers selected studies for inclusion.

Assessment of study quality
Methodological quality was assessed according to the Cochrane Handbook criteria for randomisation, blinding, follow-up and drop-outs and intention-to-treat analysis. Trials were classified as having low bias (A), moderate bias (B) and high bias (C).

The authors did not clearly state how many reviewers performed the quality assessment.

Data extraction
Two reviewers independently extracted data using a standardised form. Discrepancies were resolved by consensus. Count data were extracted to calculate relative risks (RRs) and odds ratios (ORs), and 95% confidence intervals. Continuous data were extracted to calculate mean differences and 95% confidence intervals.

Methods of synthesis
A fixed-effect model (no evidence of statistical heterogeneity) or random-effects model (evidence of statistical heterogeneity) was used to combine relative risks or odds ratios, and 95% confidence intervals (CIs). Mean differences were combined to calculate weighted mean differences (WMDs) and 95% CIs. Statistical heterogeneity was assessed using the X² test.
**Results of the review**

Twenty-two RCTs (1,884 participants reported; calculated as 1,878) were included in the review. Two RCTs were considered to have low risk of bias, seven moderate risk of bias and 13 high risk of bias.

Recombinant human endostatin in combination with vinorelbine plus cisplatin showed statistically higher response rates compared to vinorelbine plus cisplatin (OR 2.22, 95% CI 1.62 to 3.03; eight RCTs). There were no statistically significant differences in adverse events between recombinant human endostatin in combination with vinorelbine plus cisplatin compared to vinorelbine plus cisplatin.

There were no statistically significant differences between recombinant human endostatin in combination with vinorelbine plus oxaliplatin plus radiotherapy versus vinorelbine plus oxaliplatin plus radiotherapy for any outcomes measured.

Paclitaxel plus cisplatin in combination with recombinant human endostatin showed a statistically significant higher response rate than compacted paclitaxel combination (OR 2.22, 95% CI 1.32 to 3.75; four RCTs). Similarly for gemcitabine plus cisplatin combined with recombinant human endostatin compared to gemcitabine plus cisplatin alone (OR 2.02, 95% CI 1.11 to 3.68; three RCTs).

Paclitaxel plus carboplatin in combination with recombinant human endostatin showed a statistically significant higher response than paclitaxel plus carboplatin alone (OR 2.49, 95% CI 1.30 to 4.74; two RCTs).

There was no evidence of statistical heterogeneity for any outcome ($I^2=0\%$).

**Authors’ conclusions**

Recombinant human endostatin combined with platinum-based chemotherapy can improve the response rate without increasing side effects in patients with advanced non-small cell lung cancer.

**CRD commentary**

The review question and inclusion criteria were clearly stated. Several sources were searched for relevant literature. There were no language restrictions, which reduced potential for language bias. Risk of bias was assessed and most studies were considered to be at high risk of bias. Data extraction was undertaken in duplicate, but it was unclear whether this was true for study selection and quality assessment so reviewer error and bias could not be ruled out.

Very limited patient and study details were reported. Therefore it was unclear whether it was appropriate to pool the trials. There was no evidence of statistical heterogeneity. Different chemotherapy combinations were reported for the same results in the abstract and main body of the review and this made it difficult to determine which were the correct combinations used. Only a small number of RCTs were used to assess some outcomes. Results were not reported for quality of life. Confidence intervals were wide for some outcomes and this reduced the reliability of these findings.

The authors’ conclusions seem to reflect the findings for vinorelbine plus cisplatin in combination with recombinant human endostatin but the evidence may be insufficient for other combination therapies and should be interpreted cautiously as their reliability is unclear.

**Implications of the review for practice and research**

**Practice:** The authors stated that recombinant human endostatin should be added to platinum-based chemotherapy for the treatment of patients with advanced non-small cell lung cancer to improve effect and quality of life.

**Research:** The authors did not state any implications for research.

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