Addition of bevacizumab to chemotherapy in advanced non-small cell lung cancer: a systematic review and meta-analysis

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CRD summary
This review of five trials found that the addition of bevacizumab to chemotherapy increased overall and progression-free survival and the response rate for patients with advanced non-small cell lung cancer. The authors suggested that the small absolute benefit and toxicities should be discussed with patients, but their conclusions did not fully incorporate the uncertainty in the evidence.

Authors' objectives
To evaluate and quantify the effectiveness and safety of bevacizumab given with chemotherapy for patients with non-small cell lung cancer.

Searching
PubMed, EMBASE, LILACS, ClinicalTrials.gov and Cochrane Central Register of Controlled Trials (CENTRAL) were searched using specified search terms (dates not reported). References and meeting websites were checked.

Study selection
Published parallel randomised controlled trials (RCTs) were eligible if they evaluated chemotherapy with and without bevacizumab in patients with advanced non-small cell lung cancer. Specified outcomes were overall survival, progression-free survival, response rate, toxicities and treatment-related mortality, notably from bleeding. Trials of drugs targeting the epidermal growth factor receptor were excluded.

Most of the trials evaluated first-line palliative therapy. Chemotherapy regimens included paclitaxel plus carboplatin for up to six cycles, cisplatin plus gemcitabine for up to six cycles, and docetaxel or pemetrexed alone until disease progressed. Bevacizumab dose was 7.5 or 15mg per kg on day one of each cycle.

Two reviewers independently assessed eligibility.

Assessment of study quality
Some trial methods that could introduce bias were explored (trial phase, blinding, description of withdrawals, alpha and beta error rates, intention-to-treat analysis, number of centres, and funding source).

Two reviewers assessed trial quality.

Data extraction
Time to event data were extracted as presented or were calculated, and expressed as hazard ratios. Binary data were extracted as odds ratios. Associated 95% confidence intervals were extracted.

Two reviewers extracted the data, with reference to a third to resolve discrepancies.

Methods of synthesis
Random-effects models were used to derive overall estimates of effect. Heterogeneity was quantified using $I^2$ and tested using the Cochran Q.

Results of the review
Five phase II or III RCTs (2,252 patients) were included.

The addition of bevacizumab to platinum-based chemotherapy prolonged overall survival slightly (HR 0.89, 95% CI 0.79 to 0.99; four trials), increased progression-free survival (HR 0.73, 95% CI 0.66 to 0.82; all trials) and response rates (OR 2.34, 95% CI 1.89 to 2.89; three trials). However hypertension (OR 5.51, 95% CI 3.17 to 9.55; all trials), febrile neutropenia (OR 2.12, 95% CI 1.19 to 3.81; three trials), and bleeding events (OR 3.16, 95% CI 1.82 to 5.48; all
trials) all increased, with large effects for hypertension and bleeding. There was a small, but statistically significant, increase in deaths with bevacizumab (OR 1.82, 95% CI 1.04 to 3.18; all trials). There was minimal heterogeneity between trials.

Authors’ conclusions
The addition of bevacizumab to chemotherapy increased overall and progression-free survival and the response rate for patients with advanced non-small cell lung cancer. The toxicities and small absolute benefit should be discussed with patients prior to decision making.

CRD commentary
This review had an appropriate search and inclusion strategy to minimise bias in treatment effectiveness, but it might not have been sensitive enough to retrieve all relevant data on adverse events. Trials were assessed for the usual sources of bias, except for the method of randomisation. The data extraction and the synthesis were appropriate and minimised potential biases. The small number of studies, lack of information on randomisation and combination of phase II and III trials result in uncertainty around the reliability of the estimates. The increases in overall survival and progression-free survival were statistically significant, but they were small and might not have been clinically significant. The effects of adverse events were larger, but also uncertain as the search was not designed to identify adverse events. Failure to detect publication bias does not mean that there was no bias, particularly as the number of trials was low and adverse events were not sought.

The authors’ conclusions reflect the evidence and are likely to be reliable, but they do not fully represent the uncertainty in the evidence particularly for the relative harms and benefits of treatment.

Implications of the review for practice and research
Practice: Bevacizumab plus a platinum-based chemotherapy should be considered for selected patients with advanced non-small cell lung cancer. The risks and benefits should be discussed with the patients before a decision is taken.

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

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Record Status
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