Efficacy of bevacizumab (Bev) plus chemotherapy (CT) compared to CT alone in previously untreated locally advanced or metastatic non-small cell lung cancer (NSCLC): systematic review and meta-analysis

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CRD summary
The authors concluded that chemotherapy plus bevacizumab increased the response rate and progression-free survival of patients with non-small cell lung cancer. The benefit of bevacizumab remained uncertain for overall survival. The uncertain quality of included trials precludes judgement about the reliability of the review.

Authors’ objectives
To compare the efficacy of chemotherapy plus bevacizumab versus chemotherapy alone in patients with previously untreated locally advanced or metastatic non-small cell lung cancer.

Searching
EMBASE, LILACS, MEDLINE, Science Citation Index, Cochrane Central Register of Controlled Trials (CENTRAL), The National Cancer Institute Clinical Trials Service, and the Clinical Trials Register of Trials Central were searched. Abstracts of four conference proceedings were scanned. Search terms were reported, but search dates were not.

Study selection
Eligible for inclusion were parallel-design randomised controlled trials (RCTs) that compared chemotherapy regimens with or without the use of bevacizumab (7.5mg/kg and 15mg/kg). Patients were included if they had locally advanced or metastatic (IIIB, with supraclavicular lymph node metastasis or malignant pleural or pericardial effusion or IV) non-small cell lung cancer that was previously untreated.

In included trials, chemotherapy regimens contained either carboplatin and paclitaxel, or gemcitabine and cisplatin. The primary outcomes measured were overall survival and progression-free survival (time from randomisation to either death or disease progression). Other outcomes assessed were overall response rate and adverse events (grade 3 or more) which were haematological (neutropenia, thrombocytopenia, anaemia, febrile neutropenia) and non-haematological (haemoptysis, hypertension, proteinuria, venous thromboembolic events, vomiting, rash or desquamation, epistaxis, and bleeding events).

Two reviewers selected the trials for inclusion.

Assessment of study quality
Trial quality was assessed on randomisation and allocation concealment, blinding, use of intention-to-treat analysis, sample size definition, loss to follow-up, reporting of adverse events, whether the trial was multi-centre, and sponsorship.

Two reviewers carried out the quality assessment.

Data extraction
Intention-to-treat data were extracted or calculated to present risk ratios (RR) or hazard ratios (HR) and corresponding 95% confidence intervals (CI).

Two reviewers independently extracted the data.

Methods of synthesis
Effect sizes were pooled in a fixed-effect (inverse-variance method), or a random-effects (DerSimonian and Laird) meta-analysis; the latter was used when statistical heterogeneity was present.

Heterogeneity was assessed using $I^2$ (25% was considered low heterogeneity, 25 to 50% moderate, and over 50% high).
Subgroup analysis was planned for patients with squamous cell histology.

The calculation of number needed to treat (NNT) was intended where significant publication bias was present. Publication bias was investigated with a funnel plot and Egger's test.

**Results of the review**

Four RCTs (2,200 patients) were included in the review. Three trials used double-blind design and one trial used open-label design. No other aspects of trial quality were reported.

Overall survival was longer in patients who received chemotherapy plus bevacizumab at 15mg/kg (HR 0.89, 95% CI 0.80 to 1.00; four trials; I²=41%; NNT=9), but statistical significance disappeared when the random-effects model was applied; the removal of one trial of patients with squamous cell histology failed to explain the heterogeneity. No statistically significant difference was reported in the analysis of chemotherapy versus chemotherapy plus bevacizumab at 7.5mg/kg.

Statistically significant improvements in progression free survival were reported for combination therapy using bevacizumab at 7.5mg/kg (HR 0.78, 95% CI 0.68 to 0.90; two trials; I²=30%; NNT=4) and 15mg/kg (HR 0.72, 95% CI 0.65 to 0.80; four trials; I²=60%; NNT=3).

Overall response rate was significantly higher using bevacizumab at 7.5mg/kg (RR 0.58, 95% CI 0.46 to 0.74; two trials; I²=0%; NNT=7) and 15mg/kg (RR 0.53, 95% CI 0.45 to 0.63; four trials; I²=30%; NNT=6).

Haematological toxicities were significantly higher at the 7.5mg/kg dose for neutropenia (two trials) and at the 15mg/kg dose for neutropenia and febrile neutropenia (four trials each). Non-haematological toxicities were significantly higher at the 7.5mg/kg dose for hypertension and bleeding events (two trials each), and at the 15mg/kg dose for haemoptysis, hypertension, proteinuria, vomiting, rash or desquamation, and bleeding (four trials each).

There was no evidence of publication bias (results not reported).

**Authors’ conclusions**

The combination of chemotherapy plus bevacizumab increased the response rate and progression-free survival of patients with non-small cell lung cancer. The benefit of chemotherapy with bevacizumab for overall survival remained uncertain.

**CRD commentary**

The review question was clear. Inclusion criteria were stated for all aspects apart from outcomes. A range of data sources, including unpublished material, were accessed. Publication bias was assessed using appropriate methods. The review process was conducted with some attempts to minimise error and bias, although the extent to which study selection and quality assessment were performed independently by the reviewers was unclear.

Quality assessment criteria were clearly stated, but their results and how trial quality impacted on the review findings was unclear. Trial details were presented. Heterogeneity was assessed. The chosen methods of synthesis appeared to be appropriate.

The authors’ conclusion reflects the evidence presented, but the uncertain quality of included trials precludes judgement about the reliability of the review.

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

**Practice:** The authors stated that the potential toxic effects of bevacizumab should be considered when dealing with patients at increased risk of bleeding, recent or current use of aspirin, or oral and/or parenteral anticoagulants. Patients with central nervous system metastasis, active infection, radiation therapy within 21 days or major surgery within 28 days of enrolment should not be given bevacizumab.

**Research:** The authors stated that future research should aim to clarify the role of bevacizumab in patients with advanced lung cancer. Incremental costs of the drug should also be evaluated.
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