A trial-based assessment of the cost-utility of bevacizumab and chemotherapy versus chemotherapy alone for advanced non-small cell lung cancer

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Record Status
This is a critical abstract of an economic evaluation that meets the criteria for inclusion on NHS EED. Each abstract contains a brief summary of the methods, the results and conclusions followed by a detailed critical assessment on the reliability of the study and the conclusions drawn.

CRD summary
The study investigated the cost-effectiveness of adding bevacizumab to first-line chemotherapy (carboplatin and paclitaxel) for the palliative treatment of patients with advanced non-squamous non-small cell lung cancer. The authors concluded that adding bevacizumab to first-line chemotherapy was not cost-effective from the US health payers’ perspective. The methods, analyses and results of the study were clear and comprehensive. The authors’ conclusions appear to be a sound assessment of the findings.

Type of economic evaluation
Cost-effectiveness analysis, cost-utility analysis

Study objective
The aim was to examine the cost-effectiveness of adding bevacizumab to chemotherapy for the palliative treatment of advanced non-small cell lung cancer in adult patients (average age 63 years) with stage IIIB/IV non-small cell lung cancer.

Interventions
Bevacizumab (an anti-vascular endothelial growth factor monoclonal antibody) was added to chemotherapy (carboplatin plus paclitaxel) and compared with chemotherapy alone (carboplatin and paclitaxel) alone. Six cycles of carboplatin (area under the curve=6) and paclitaxel 200mg/m$^2$ were given intravenously every three weeks with the same regimen plus bevacizumab (15mg/kg). If patients did not experience disease progression or intolerable toxicity, they received maintenance bevacizumab treatment every three weeks. Infusion times were five hours with bevacizumab and four hours with usual chemotherapy.

Location/setting
USA/Secondary care

Methods
Analytical approach:
A Markov model was developed to synthesise evidence from published studies, epidemiological data and one key clinical trial (the ECOG 4599 trial, Ramalingam, et al. 2008, see ‘Other Publications of Related Interest’ for bibliographic details). The model time horizon was four years. The authors stated a US health care payer perspective was adopted.

Effectiveness data:
The key clinical outcome was overall survival; this was based on results from the ECOG (Eastern Cooperative Oncology) 4599 trial. Other end-points were progression-free survival, response rates and toxicity. The ECOG 4599 was a phase III randomised controlled trial (RCT) with 850 participants. The median follow-up was 19 months; an intention-to-treat analysis was undertaken. The trial showed a median two-month survival benefit for bevacizumab.

Monetary benefit and utility valuations:
Utility estimates were taken from two published reports of utilities for the health states (stable disease on therapy; stable disease off therapy; fever and neutropenia; severe bleeding; and progressive disease) in the model (Doyle, et al. 2008, and Nafees, et al. 2008, see ‘Other Publications of Related Interest’ for bibliographic details).
Measure of benefit:
The measures of benefit used were life-years saved (future years of life expectancy) and quality-adjusted life years (QALYs). These were discounted at an annual rate of 3%.

Cost data:
Direct medical costs included the drugs, drug administration and monitoring, outpatient visits, progressive disease (per month) and side effects. No drug wastage was assumed. The drug costs came from the Centers of Medicare and Medicaid Services; published sources were used to estimate the cost of side effects. All costs were in US $ for 2010 and adjusted for inflation. Costs were discounted at an annual rate 3%.

Analysis of uncertainty:
One-way sensitivity analyses were performed on key parameters (hazard ratios for death; tumour progression; utilities; unit costs and number of bevacizumab cycles; dosage; and discount rates) using 95% confidence intervals or ±20%. Probabilistic sensitivity analysis using 1,000 simulations were run with beta, Dirichlet and gamma distributions assigned to model parameters. Sensitivity analyses results were illustrated using tornado diagrams, a cost-effectiveness plane and a cost-effectiveness acceptability curve.

Results
The total discounted costs were $115,910 for carboplatin-paclitaxel plus bevacizumab compared with $44,290 for carboplatin-paclitaxel alone. Drug use costs were the key cost driver ($70,285) for carboplatin-paclitaxel plus bevacizumab, while disease progression costs were the main cost for the carboplatin-paclitaxel regimen ($41,501). The QALYs for carboplatin-paclitaxel plus bevacizumab were 0.66 compared with 0.53 QALYs for carboplatin-paclitaxel alone. The incremental cost per QALY ratio for carboplatin-paclitaxel plus bevacizumab versus carboplatin-paclitaxel alone was $559,610; the incremental cost per life-year saved was $308,982.

One-way sensitivity analyses showed that the base results were most sensitive to survival in stable disease on treatment state, the number of bevacizumab cycles, and utility of the stable disease on treatment state. The cost of bevacizumab would have to be $885 for bevacizumab to be cost-effective at $100,000 per QALY gained. Bevacizumab (plus carboplatin and paclitaxel) had a 0.2% likelihood of being cost-effective at a willingness-to-pay threshold of $100,000 per QALY gained, 1.2% at a threshold of $150,000 and 4.1% at a threshold of $200,000.

Authors' conclusions
The authors concluded that for patients with non-squamous non-small cell lung cancer, bevacizumab added to first-line chemotherapy (carboplatin and paclitaxel) was not cost-effective from the US health payers’ perspective. Their analyses suggested that there was a very small likelihood that bevacizumab offered good value for money.

CRD commentary
Interventions:
The therapeutic agents compared were briefly described. The selection of bevacizumab and the first-line chemotherapy comparators (carboplatin and paclitaxel) appeared to be appropriate for the study setting (USA), but may not be relevant for other settings.

Effectiveness/benefits:
The clinical effectiveness estimates were based on a pivotal RCT that directly compared bevacizumab plus carboplatin and paclitaxel versus carboplatin and paclitaxel alone. The authors appropriately used the overall survival plot (Kaplan-Meier) for both arms directly from the trial outcomes for the economic model. Only a few details of the ECOG 4599 trial were reported, so it was not possible to assess its validity. Subgroup analyses were not undertaken on certain clinical characteristics, but the authors stated that none of the subgroup analysis in the ECOG 4599 trial suggested a patient characteristic that predicted a survival benefit of over one year. The analysis did not raise the issue of medication adherence, participant withdrawals due to treatment, whether these were adequately addressed in the trial, or the implications outside trial conditions. QALYs and life years were appropriate measures of benefit as they allowed comparisons with other disease interventions.

Costs:
The resource quantities and unit costs were clearly presented. The categories of the included costs in the analysis...
reflected the perspective of the study. The measurement of these resources and the sources appeared reasonable and comprehensive. The sources for the costs, the price year, time horizon, discount rate, and currency were reported.

**Analysis and results:**
The evidence on costs and outcomes was synthesised in a Markov model. Details of the model were given with a diagram. An appropriate incremental approach was used to synthesise the costs and benefits of the two treatments. The authors discussed their findings with other pharmacoeconomic studies. Two studies showed similar incremental cost per life years saved of over $300,000, while a third Italian study concluded bevacizumab was cost-effective. The latter findings were attributed to relative drug prices, currency differences and smaller dosage of bevacizumab. The one-way sensitivity results were well-illustrated (with tornado diagrams), clearly showing the extent of variation in changes to key variables. The authors acknowledged limitations in their study including the omission of imaging and blood tests, and not considering second-line treatments as they would not significantly impact on the results.

**Concluding remarks:**
The methods, analyses and results were clear and comprehensive. The conclusions reached by the authors appear to be a sound assessment of the findings.

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