No study left behind: a network meta-analysis in non-small-cell lung cancer demonstrating the importance of considering all relevant data

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CRD summary
This review used network analysis to evaluate four drugs as second-line therapy for non-small cell lung cancer. It found erlotinib, docetaxel and gefitinib were significantly effective compared to placebo. There were no significant effect differences between docetaxel and erlotinib, gefitinib or pemetrexed. Given potential limitations in the review process and study quality, the reliability of the authors’ conclusions is unclear.

Authors' objectives
To evaluate the efficacy of erlotinib, docetaxel, gefitinib and pemetrexed as second-line therapy for non-small cell lung cancer using a network analysis.

Searching
MEDLINE and EMBASE were searched from January 1997 to October 2007 for publications in English. Search terms were not reported, but were available from the authors. Presentations at recent oncology conferences were searched for unpublished studies. Bibliographies of each retrieved article were handsearched.

Study selection
Randomised controlled trials (RCTs) that evaluated erlotinib, docetaxel, gefitinib or pemetrexed as second-line therapy for stage III/IV patients with non-small cell lung cancer were eligible for inclusion. Eligible trials had to include at least some patients with stage III/IV disease who had received previous chemotherapy. The included trials had to use the drugs at their licensed doses: erlotinib 150mg/day; docetaxel 75mg/m$^2$ every 21 days; gefitinib 250 mg/day; and pemetrexed 500mg/m$^2$ every 21 days. Trials using concomitant radiotherapy were excluded. The eligible outcome was the hazard ratio for overall survival.

In included trials, treatment duration (where given) ranged from 2.7 to four months. The included trials either compared drug with placebo or compared two different drugs. Most included patients had received one previous course of chemotherapy, but a significant minority had received more. The median age range of patients was 57 to 63 years; the proportion of females ranged from 25% to 36%; their performance status was mostly Eastern Cooperative Oncology Group status 1 or 2 (details of disease stage were provided).

Two reviewers performed the selection.

Assessment of study quality
Methodological quality was assessed using the method of Jadad and Schulz. Quality scores were reported, with a maximum of 5 points for criteria including randomisation, blinding, and treatment of withdrawals and drop-outs.

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

Data extraction
The number of events for each outcome was extracted in order to calculate hazard ratios (HR) and 95% confidence intervals (CI).

The authors did not report how many reviewers performed the extraction.

Methods of synthesis
A network analysis was performed in order to compare treatments using indirect evidence; this meta-analysis used mean
log-hazard ratios plus the standard errors of the mean. The results of this review were compared with those of another limited network analysis (NICE 2007, see Other Publications of Related Interest), concentrating on the comparison between docetaxel and erlotinib.

A sensitivity analysis was performed excluding one trial with a low Jadad score, which was a conference presentation published in abstract form only. Pair wise meta-analyses were also performed. Relative treatment effects were also synthesised using a Bayesian hierarchical model with a regression structure.

**Results of the review**
Six relevant RCTs were identified (n=4,672 patients, range 104 to 1,692). Jadad scores were relatively low (four trials scored less than 3 points, and the remaining two trials scored 3 and 4), partly because three trials used an open-label design and one provided little relevant information; two RCTs were double-blind.

The network analysis found a significant effect for docetaxel (HR 0.85, 95% CI 0.72 to 1.00), erlotinib (HR 0.71, 95% CI 0.58 to 0.85), and gefitinib (HR 0.88, 95% CI 0.78 to 0.99) versus placebo but no significant effect for pemetrexed versus placebo (HR 0.85, 95% CI 0.65 to 1.08), with one RCT for each comparison. There was no significant difference in effect for gefitinib versus docetaxel (two RCTs) or pemetrexed versus docetaxel (one RCT) or for an estimated hazard ratio for erlotinib versus docetaxel (mean HR 0.83, 95% CI 0.65 to 1.06). A pairwise meta-analysis was possible for gefitinib versus docetaxel, but the result was not significant.

The limited network analysis found a stronger significant effect for docetaxel versus placebo (HR 0.51, 95% CI 0.24 to 0.96) and a similar significant effect for erlotinib versus placebo (HR 0.71, 95% CI 0.58 to 0.85).

Network meta-analysis results were also displayed as probability of treatment occupying different rankings; there was an 85% probability that erlotinib was the most effective treatment.

**Authors’ conclusions**
All potentially relevant data should be considered when comparing treatments. Erlotinib, docetaxel and gefitinib were significantly effective compared to placebo. There were no significant effect differences between docetaxel and erlotinib, gefitinib or pemetrexed. Some of the estimated treatment effects from the network were highly correlated.

**CRD commentary**
The review addressed a well-defined question in terms of participants, interventions, study design and relevant outcomes. Relevant databases were searched and unpublished studies were considered, but only studies published in English were included, so some relevant studies may have been missed. Publication bias was not assessed. Efforts were made to reduce error and bias in study selection but it was not clear whether this process applied to quality assessment or data extraction.

Study quality was assessed using suitable criteria. Relevant study details were reported. The review performed a network meta-analysis and compared it with direct evidence.

In view of some potential limitations arising from the review process and the relatively low quality of the studies identified, the reliability of the authors’ conclusions is unclear.

**Implications of the review for practice and research**
**Practice:** The authors did not state any implications for practice.

**Research:** The authors identified a need for further work using regression analysis of both study and individual level data in order to identify and adjust for confounding factors.

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