Gefitinib versus docetaxel in previously treated advanced non-small-cell lung cancer: a meta-analysis of randomized controlled trials


CRD summary
The review found that gefitinib and docetaxel were associated with similar progression-free and overall survival rates in previously treated advanced non-small cell lung cancer. Gefitinib was associated with increased response rates and improved quality of life and tolerability. These conclusions require cautious interpretation due to the small number of studies, suboptimal trial quality and unexplained statistical heterogeneity.

Authors' objectives
To compare the efficacy and toxicity of gefitinib versus docetaxel for advanced previously treated non-small cell lung cancer.

Searching
PubMed and Cochrane Central Register of Controlled Trials (CENTRAL) were searched from inception to May 2009 for full-text studies in any language. Search terms were reported. The reference lists of original articles and reviews were checked for further studies.

Study selection
Eligible randomised controlled trials (RCTs) that compared the efficacy and toxicity of gefitinib versus docetaxel for histologically or cytologically confirmed stage IIIB or IV non-small cell lung cancer, previously treated with at least one course of chemotherapy. All the included studies were multi-centred. Participants were Korean, Japanese or of mixed ethnicity. Where reported, the median age was 57 to 63 years; 30 to 43% were female; 20 to 46% had never smoked; 13 to 48% had locally advanced disease; 55 to 78% had adenocarcinoma; and 63 to 96% had grade 0-1 performance status. No studies selected participants by epidermal growth factor receptor status.

Interventions were gefinitib 250mg daily or docetaxel 60 to 75mg/m² three weekly. In most studies treatment continued until disease progression, intolerable toxicity or discontinuation for other reasons. Outcomes reported in the review were overall and progression-free survival, response (Response Evaluation Criteria in Solid Tumours), quality of life (improvement rates using the Functional Assessment of Cancer Therapy-Lung or Trial Outcome Index), symptom improvement rates (Functional Assessment of Cancer Therapy-Lung subscale) and grade 3 or 4 toxicity.

The authors did not state how many reviewers performed the selection.

Assessment of study quality
Two reviewers independently evaluated trial quality with the Jadad scale of randomisation, double blinding, withdrawals and drop-outs. Studies were awarded a score up to a maximum of 5.

Data extraction
Hazard ratios were extracted or calculated for survival outcomes, risk ratios (RRs) for response rates, quality of life and symptom improvement and odds ratios (ORs) for toxicity outcomes, all with 95% confidence intervals (CIs). Intention-to-treat data were used for survival and response rates and data on evaluable populations were used for other outcomes.

Two reviewers independently extracted the data; disagreements were resolved by discussion with a third reviewer.

Methods of synthesis
The studies were combined to calculate pooled hazard ratios, odds ratios and risk ratios, each with 95% confidence intervals. Numbers-needed-to-treat (NNT) were calculated for response rates. Heterogeneity was assessed using X². A fixed-effect model was used unless there was significant statistical heterogeneity (p<0.1), in which case a random-effects model was used. Publication bias was assessed with a funnel plot, Begg's test and Egger's test.
Results of the review
Four RCTs were included in the review (2,257 patients, range 141 to 1,466). One trial was phase II and three were phase III. One RCT scored 3 on the Jadad scale and three RCTs scored 2.

There was no statistically significant difference in overall or progression-free survival between the gefitinib and docetaxel groups (four RCTs). Gefitinib was associated with a significantly higher response rate (RR 1.58, 95% CI 1.02 to 2.45, NNT 23; four RCTs) and quality of life (Functional Assessment of Cancer Therapy-Lung RR 1.55, 95% CI 1.27 to 1.88; 1,598 patients and Trial Outcome Index RR 1.86, 95% CI 1.43 to 2.42; 1,458 patients). There was no significant difference between the groups in symptom improvement. Gefitinib was associated with significantly less grade 3 or 4 neutropenia (OR 0.02, 95% CI 0.01 to 0.03; 2,053 patients) and fatigue (OR 0.47, 95% CI 0.32 to 0.70; 2,223 patients) but more rashes (OR 2.87, 95% CI 1.24 to 6.63; 2,223 patients). Rates of nausea, vomiting and diarrhoea were comparable.

There was significant heterogeneity for response rate (p=0.06) but not for other outcomes. No publication bias was detected.

Authors’ conclusions
Gefitinib and docetaxel were associated with similar rates of overall and progression-free survival when used for previously treated advanced non-small cell lung cancer. Gefitinib was associated with increased response rates, quality of life and tolerability.

CRD commentary
The objectives and inclusion criteria of the review were clear and relevant sources were searched without language restrictions. Only two databases were used, so some studies may have been missed. The exclusion of unpublished studies increased the risk of publication bias, but there were too few studies to assess this reliably. Steps were taken to minimise risks of reviewer bias and error as more than one reviewer extracted the data and assessed quality; it was unclear whether this applied to trial selection. Appropriate statistical techniques were used to pool the studies and assess heterogeneity. Where significant heterogeneity was detected the authors did not explore likely causes (such as differences between the studies).

The authors noted that overall survival rates were at risk of confounding due to participants who crossed to the other treatment arm post trial. Trial quality scores were fairly low and information was lacking on some important trial characteristics (such as allocation concealment, drop-out rates and duration of follow-up).

The authors’ conclusions require cautious interpretation due to the small number of studies, suboptimal trial quality and unexplained statistical heterogeneity.

Implications of the review for practice and research
Practice: The authors stated that gefitinib was an important and valid treatment option for previously treated advanced non-small cell lung cancer.

Research: The authors stated a strong need for an RCT to compare gefitinib versus docetaxel as second-line treatment for individuals with non-small cell lung cancer selected by epidermal growth factor receptor status.

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Bibliographic details

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Record Status
This is a critical abstract of a systematic review that meets the criteria for inclusion on DARE. Each critical abstract contains a brief summary of the review methods, results and conclusions followed by a detailed critical assessment on the reliability of the review and the conclusions drawn.