Gefitinib compared with systemic chemotherapy as first-line treatment for chemotherapy-naive patients with advanced non-small cell lung cancer: a meta-analysis of randomised controlled trials

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CRD summary
The authors concluded that gefitinib prolonged progression-free survival, compared with systemic chemotherapy, in molecularly or histologically defined patients with non-small cell lung cancer, and that it improved survival for those with lung adenocarcinoma. Limited evidence and the possibility of error and bias, mean that the reliability of the authors' conclusions is uncertain.

Authors' objectives
To compare the efficacy of gefitinib, versus systemic chemotherapy, as the first chemotherapy for patients with advanced non-small cell lung cancer (NSCLC).

Searching
MEDLINE, EMBASE, Cochrane Central Register of Controlled Trials (CENTRAL), and Science Citation Index were searched to January 2011, for articles published in English. Search terms were reported. Reference lists of included articles were handsearched to locate further studies.

Study selection
Phase III randomised controlled trials (RCTs) evaluating gefitinib therapy versus conventional therapy, in patients with NSCLC, who had not previously had chemotherapy, were eligible for inclusion. Eligible trials had to report progression-free survival or overall survival. Progression-free survival was measured from enrolment, randomisation, or treatment start, to disease progression, relapse, or death. Overall survival was measured from the same starting points to death from any cause.

In the included trials, the mean patient age ranged from 57 to 64 years; the percentage of female patients ranged from 23.3 to 79.5. Most of the trial populations were Asian. Therapy ranged from three to nine cycles. Gefitinib monotherapy was used in just over half the trials; in the others, the intervention was either gefitinib combined with systemic chemotherapy (paclitaxel carboplatin or gemcitabine cisplatin) or gefitinib administered after chemotherapy (paclitaxel carboplatin). Conventional systemic chemotherapy (paclitaxel carboplatin, cisplatin docetaxel, or gemcitabine cisplatin) was the control in all trials.

Two reviewers independently selected studies for inclusion.

Assessment of study quality
Two reviewers independently assessed the quality of the trials, by assigning yes, no, or unclear for the following criteria: allocation concealment; drop-out description; masking of randomisation, intervention, and outcome assessment; intention-to-treat analyses; and final analysis reporting.

Data extraction
Data were extracted to calculate hazard ratios, with 95% confidence intervals. The log ranks of the hazard ratios and their standard errors were calculated; if these were unavailable, they were estimated using methods proposed by Parmar, et al. (reference provided in the review).

Two reviewers independently extracted the data.

Methods of synthesis
The effect estimates were pooled using a random-effects inverse-variance method. Statistical heterogeneity was assessed using $X^2$ and $I^2$. When $I^2$ was 25% it was low; when it was 50%, it was moderate; and when it was 75%, it was high. Subgroup analyses were performed, according to mutation status of the epidermal growth factor receptor (EGFR),
lung adenocarcinoma status, and reception of gefitinib combined with chemotherapy.

**Results of the review**

Seven RCTs were included in the review (4,656 patients). Follow-up ranged from 81 days to two years. Five trials reported final analyses, one reported an interim analysis, and one was only reported as an abstract. Two trials reported blinding and all trials reported intention-to-treat analyses. Drop-outs were reported in the five published trials.

Compared with chemotherapy, progression-free survival was significantly prolonged with gefitinib, within the subgroup of patients with lung adenocarcinoma (HR 0.71, 95% CI 0.60 to 0.83; three trials; $I^2=57\%$) and among patients with the EGFR mutation, who received gefitinib monotherapy (HR 0.43, 95% CI 0.32 to 0.58; four trials; $I^2=58\%$). Progression-free survival was significantly less for patients without the EGFR mutation, who received gefitinib monotherapy, versus those treated with chemotherapy (HR 2.16, 95% CI 1.17 to 3.99; two trials; $I^2=73\%$).

A borderline statistically significant increase in overall survival was reported for patients with lung adenocarcinoma who received gefitinib, versus those who received chemotherapy (HR 0.89, 95% CI 0.81 to 0.99; four trials; $I^2=0$).

Other results were reported, none was statistically significant.

**Authors' conclusions**

Initial treatment with gefitinib prolonged progression-free survival, compared with systemic chemotherapy, in molecularly (EGFR mutation) or histologically (adenocarcinoma) defined patients with NSCLC, and it improved survival in the subgroup of patients with lung adenocarcinoma.

**CRD commentary**

The review question was clear and was supported by replicable inclusion criteria. Relevant databases were searched, but the restriction to trials reported in English means that language bias was possible. Efforts were made to minimise error and bias at all stages of the review. The quality assessment criteria seem to have been suitable, but the results were not fully reported, making it difficult to assess the possibility of bias in the trials. Trial details were presented, and most trials focused on Asian populations.

The methods of synthesis seem to have been appropriate, but the limited quality reporting means that this cannot be certain. This is further supported by the inclusion, in the meta-analysis, of the results from an unpublished abstract, for which a quality assessment could not be performed. The authors acknowledged that the evidence was limited by methodological and clinical diversity among the trials.

Limited evidence and the possibility of error and bias, mean that the reliability of the authors' conclusions is uncertain.

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

**Practice:** The authors stated that gefitinib could be the standard first treatment for histologically or molecularly defined populations. The potential for harm associated with gefitinib therapy, versus chemotherapy, in patients without the EGFR mutation, suggested that patients should be selected by their EGFR mutation status.

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

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