The safety and efficacy of gefitinib versus platinum-based doublets chemotherapy as the first-line treatment for advanced non-small-cell lung cancer patients in East Asia: a meta-analysis

Chang CH, Chen KY, Young-Xu Y, Kurth T, Orav EJ, Yang PC, Chan KA

CRD summary
The review concluded that one third of chemo-naïve non-small-cell lung cancer patients in East Asia would respond to oral gefitinib monotherapy and 6% would develop severe liver and lung injury. The basic analysis conducted did not take into account confounding variables and there was no assessment of study quality, so the authors' conclusions should be interpreted with caution.

Authors' objectives
To evaluate the risk/benefit profiles of gefitinib compared with platinum-based doublets chemotherapy as a first-line treatment for chemo-naïve patients with advanced non-small-cell lung cancer in East Asia.

Searching
MEDLINE, EMBASE, The Cochrane Library and ClinicalTrials.gov were searched to April 2007; search terms were reported. Reference lists of identified articles and reviews were searched.

Study selection
Randomised and non-randomised phase II or III clinical trials that enrolled Japanese, Taiwanese, Chinese or Korean adults (≥18 years) with non-small-cell lung cancer (stage IIIB/IV or post-operative recurrence) were eligible for inclusion. Patients must not have received previous chemotherapy treatment. One of the trial treatments needed to be gefitinib (250mg/day) or platinum-based (cisplatin, carboplatin) doublet chemotherapy (docetaxel, paclitaxel, vinorelbine, gemcitabine or irinotecan). Studies with other combined disease control rates (complete or partial response or stable disease and both nations of treatments, including single agent chemotherapy or combination therapy of gefitinib) were excluded. Studies also had to clearly present efficacy and safety information. Multi-centred international studies that did not analyse the Asian subpopulation separately were excluded.

The main outcomes of interest were: disease control rates (defined as complete or partial response, or stable disease) and complete and partial response rates, with both based on Response Evaluation Criteria in Solid Tumours (RECIST); elevation of serum transaminase levels; and pulmonary fibrosis or interstitial lung disease (defined according to specified criteria).

Details of included studies were provided only for those eligible for meta-analysis (17 out of 48). Median ages ranged from 59.5 to 75 years. The proportion of female participants ranged from 19% to 88%. Most patients were Japanese. Doublet-chemotherapy regimens varied in dosage and schedule.

Two reviewers independently selected studies for inclusion. Disagreements were resolved by discussion.

Assessment of study quality
Although the authors stated that they assessed study quality, no further details or results were provided.

Data extraction
Two reviewers independently extracted data. Disagreements were resolved by discussion.

Methods of synthesis
It appeared that the authors combined outcomes (reported using RECIST guidelines) using fixed-effect meta-analytic methods. Pooled outcome data was presented with 95% confidence intervals (CI). Where there were few adverse events, Wald CIs were calculated. Platinum-based doublets chemotherapy arms were combined regardless of dose and regimen. Subgroup analyses examined gender, smoking and histology.
Results of the review
Forty-eight trials were included in the review (n=2,974, range 16 to 592 participants): 35 single-arm trials, and 13 comparative trials, of which 17 were eligible for meta-analysis. Follow-up times, where reported, ranged from 7.6 to 23 months. No studies directly compared gefitinib and platinum-based doublets chemotherapy.

Efficacy:
Treatment with gefitinib (six trials, n=189) produced objective response rates with a pooled estimate of 44% (95% CI 29% to 59%); trials of patients with EGFR mutations reported higher response rates (75%, 95% CI 60% to 90%; two trials) than trials of unselected populations (31%, 95% CI 23% to 38%; four trials). Pooled disease control rates were 65% (95% CI 55% to 76%). Median survival ranged from 9.4 to 14.1 months. For subgroups, the response rate was 56% for non-smokers, 55% for women, and 43% for adenocarcinoma/bronchioalveolar carcinoma.

For platinum-based doublets chemotherapy (15 treatment arms, n=1,126) the response rates yielded a pooled estimate of 34% (95% CI 31% to 38%). Pooled disease control rates were 77% (95% CI 70% to 85%). Median survival ranged from 9.5 to 14.4 months.

Safety:
Pooled incidence of elevated serum transaminase levels and interstitial lung disease were higher for patients who received gefitinib (6.3% and 5.8%) than those who received platinum-based doublets chemotherapy (1.1% and 0.2%). There were no substantial differences in hepatic and pulmonary injury between different schedules of platinum-based doublets chemotherapy.

Authors' conclusions
One third of chemo-naive non-small-cell lung cancer patients in East Asia would respond to oral gefitinib monotherapy and 6% would develop severe liver and lung injury.

CRD commentary
The review addressed a clear question and was supported by detailed inclusion criteria. Three databases and a trials website were searched. It was unclear whether there were language restrictions and whether unpublished studies were eligible, so it was possible relevant studies may have been missed. Suitable methods were employed to reduce the risks of reviewer error and bias for selecting studies and extracting data. It appeared that no assessment of study quality was made, so it was difficult to assess the strength of the evidence. Similarly, study details were provided only for the studies that were included in the efficacy meta-analyses. An unconventional meta-analysis was conducted of single-arm trial data. Many of the included populations were clinically heterogeneous, so pooling by meta-analysis may not have been the most appropriate method of synthesis. When the two types of treatment were compared, the analyses conducted were at high risk of being influenced by confounders, which made an informative and reliable result difficult to obtain (p-values were not reported). No assessment of the results of studies that were ineligible for meta-analysis was made and so fewer than half of the trials contributed to the efficacy synthesis. The authors’ conclusions focused mainly on the gefitinib studies and not on the comparison with platinum-based doublets chemotherapy trials that was stated in their aims. The likely impact of confounders on the authors’ simplified synthesis, coupled with the lack of an assessment of study quality, means the authors’ conclusions should be interpreted with caution.

Implications of the review for practice and research
Practice: The authors suggested that patients who received gefitinib should be regularly monitored for abnormal liver function and interstitial lung disease.

Research: The authors stated that further randomised trials were needed to compare the survival benefit of the two types of treatment and to confirm the optimal treatment strategies in subpopulations.

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