Impact of third-generation drugs on the activity of first-line chemotherapy in advanced non-small cell lung cancer: a meta-analytical approach


CRD summary
The authors concluded that the third-generation regimens had comparable response rates for chemotherapy-naive patients with advanced non-small cell lung cancer, but produced different rates of disease control. These conclusions appear to reflect the findings, but a lack of reporting of the review methods and no assessment of trial quality make it difficult to confirm their reliability.

Authors' objectives
To assess the impact of different third-generation drugs on the activity of first-line chemotherapy in advanced non-small cell lung cancer (NSCLC), as measured by the response and progressive disease rates.

Searching
MEDLINE was searched for articles from 1980 to 2007 and the search terms were reported. Conference abstracts from the Proceedings of the American Society of Clinical Oncology meetings (1996 to 2007), World Conference on Lung Cancer (2000 to 2007), European Society for Medical Oncology (1998 to 2006) and the European Cancer Conference (1997 to 2007) were also searched. Reference lists of review articles on the treatment of NSCLC were handsearched for additional material. No language restrictions were applied.

Study selection
Phase II or III trials involving patients with pathologically proven advanced NSCLC, with no previous treatment for metastatic disease, and random allocation between a two-drug regimen containing at least one third-generation drug (gemcitabine, vinorelbine, docetaxel, or paclitaxel) and a two-drug combination without the third-generation drug, were eligible for inclusion. Both platinum (cisplatin or carboplatin) and non-platinum combinations were eligible. Trials had to report the response or the progressive-disease rate and the number of patients in each treatment arm. Trials were excluded if they: included irinotecan; compared cisplatin with carboplatin; or used combinations that included biological drugs.

Where reported, the median age ranged from 56 to 72.5 years and the percentage of men ranged from 51 to 93. Most of the patients had NSCLC at stage IIIB or IV. Most of them had not had chemotherapy. Most of the trials assessed response using World Health Organization criteria.

The authors did not state how many reviewers selected the trials.

Assessment of study quality
The authors did not state that they assessed validity.

Data extraction
Data were extracted to calculate odds ratios and 95% confidence intervals. In trials with more than one eligible treatment arm, each third-generation-based regimen was compared with the control.

The authors did not state how many reviewers extracted the data.

Methods of synthesis
In the text the authors stated that a random-effects DerSimonian and Laird model was used to synthesise weighted odds ratios and 95% confidence intervals, but the forest plots showed the results of Mantel-Haenszel fixed-effect meta-analyses. The meta-analysis results appeared to be based on the fixed-effect model. Heterogeneity was assessed using the Cochran Q statistic and a p value of less than 0.1 indicated statistically significant heterogeneity.
Results of the review
Forty-five randomised controlled trials (RCTs) were included in the meta-analysis (n=11,867 patients). Twenty-five were phase III and 20 were phase II trials. Trials excluded patients for various reasons including no treatment or ineligible (12 RCTs), discontinued treatment early (two RCTs), and missing data or insufficient follow-up (two RCTs). Eight trials did not report the reasons for exclusion.

Response rates: No differences were observed in the response rates between regimens containing gemcitabine (32 RCTs, n=8,136), vinorelbine (32 RCTs, n=7,333), docetaxel (16 RCTs, n=4,935), or paclitaxel (24 RCTs, n=6,826) and regimens that did not contain these drugs. No significant between-trial heterogeneity was observed.

Progressive disease: There was a significantly lower risk of disease progression for patients receiving gemcitabine compared with those receiving regimens that did not contain gemcitabine (OR 0.86, 95% CI 0.77 to 0.95; 23 RCTs, n=6,681). There was a significantly increased risk of disease progression for patients receiving paclitaxel compared with those receiving regimens not containing paclitaxel (OR 1.22, 95% CI 1.09 to 1.37; 16 RCTs, n=5,536). There were no significant associations between disease progression and the use of docetaxel (12 RCTs, n=4,642) and vinorelbine regimens (23 RCTs, n=6,048). No significant between-trial heterogeneity was observed.

Authors' conclusions
The third-generation drug regimens had comparable response rates for chemotherapy-naive patients with advanced NSCLC, but they produced different rates of disease control. Gemcitabine-based regimens provided better disease control and paclitaxel-containing regimens significantly increased the risk of immediate progression.

CRD commentary
This review addressed a defined research question, which was supported by clear inclusion criteria. The authors searched one database and several conference abstracts without language restrictions, which reduced the chances of language bias. There were some attempts to find unpublished material, which reduced the risk of publication bias. The authors did not assess validity and so the quality of the trials could not be used to inform the synthesis. The methods used to select trials and extract data were not described, and so it is not clear whether efforts were made to reduce reviewer bias and error. The method of synthesis appears to have been appropriate.

The authors' conclusions appear to reflect the results, but a lack of reporting of the review methods and no assessment of trial quality make it difficult to determine their reliability.

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

Research: The authors stated that researchers should take the findings of this review into account when designing future trials.

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