Second-line treatments in non-small cell lung cancer: a systematic review of literature and metaanalysis of randomized clinical trials

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CRD summary
The authors concluded that second-line treatments seemed to improve outcomes in advanced non-small cell lung cancer compared with best supportive care, and that docetaxel chemotherapy every three weeks probably remained the 'gold standard', since insufficient evidence was available about alternative treatments. The review was mostly well conducted, but differences between trials make it difficult to be certain of their reliability.

Authors' objectives
To evaluate the efficacy of second-line treatment for patients with advanced non-small cell lung cancer: to compare second-line treatment with best supportive care, and to compare docetaxel chemotherapy every three weeks with alternative treatments.

Searching
MEDLINE, EMBASE, CINAHL, the Cochrane Library, CRISP (Computer Retrieval of Information on Scientific Projects) and the National Cancer Institute Database of Clinical Trials were searched from 2000 to July 2008. Search terms were reported. No language restrictions were applied. In addition, reference lists of reviews and retrieved studies were screened. Studies reported as congress proceedings were eligible.

Study selection
Randomised controlled phase III trials (RCTs) in patients with progression of non-small cell lung cancer, following first-line chemotherapy for advanced disease, were eligible for inclusion if they compared second-line treatment (chemotherapy or an epidermal growth factor receptor) plus best supportive care with best supportive care alone, or compared docetaxel chemotherapy every three weeks with any other alternative treatment. Trials had to report adequate information about the randomisation process and one-year survival data.

The primary review outcome was one-year survival for anti-neoplastic treatment versus best supportive care. Secondary outcomes were response rate and time to progression for anti-neoplastic treatment versus best supportive care and one-year survival, response rate and time to progression for docetaxel every three weeks versus any other alternative treatment.

The included trials compared: chemotherapy using docetaxel or epidermal growth factor receptor (gefitinib or erlotinib) plus best supportive care with best supportive care alone; or compared docetaxel chemotherapy three times weekly with pemetrexed docetaxel, oral topotecan, paclitaxel poliglumex, vinflunine, gefitinib, docetaxel-gemcitabine or a different dose of docetaxel.

Two reviewers independently selected studies. Disagreements were discussed with a third reviewer

Assessment of study quality
Two reviewers independently assessed study design and methods of randomisation. Trials published in full in peer-reviewed journals were scored using the Nicolucci score; quality scores were based on the percentage of items fulfilled. Disagreements were resolved by consensus with a third reviewer.

Data extraction
Two reviewers independently extracted data. Disagreements were resolved by consensus with a third reviewer.

Methods of synthesis
Where possible, differences in trial methods and clinical characteristics were examined. Pooled odds ratios (OR) and 95% confidence intervals (CI) were calculated using a random-effects model. Heterogeneity was assessed using I².
regression was used to examine the effects of several factors on outcomes including age, sex, Eastern Cooperative Oncology Group (ECOG) performance status, and response rate to first-line treatment. Trials reported as full-text reports in peer-reviewed journals were also analysed separately. For docetaxel versus alternative treatments, analyses were repeated excluding trials that used docetaxel 100mg/m². Publication bias was assessed using a funnel plot and Egger’s test.

**Results of the review**
A total of fourteen RCTs were included. Nicolucci scores of the nine fully published studies ranged from 54 to 89% (median 70%).

**Any anti-neoplastic treatment versus best supportive care** (three RCTs, n=2,627 patients): Significant heterogeneity was found for one-year survival (I²=60%). Any anti-neoplastic treatment was associated with a statistically significant improvement in one-year survival (OR 0.736, 95% CI 0.559 to 0.970). Meta-regression showed a significant influence on results of age, sex and response rate to first-line chemotherapy. There was significant heterogeneity in one-year survival between the two studies evaluating epidermal growth factor receptor inhibitors (I²=75%). There was no significant heterogeneity for response rate (I²=0%). Any anti-neoplastic treatment was associated with a statistically significant improvement in response rate (OR 0.166, 95% CI 0.09 to 0.303) and time to progression (OR 0.714, 95% CI 0.535 to 0.953).

**Docetaxel therapy three times weekly versus other treatments** (11 RCTs, n=5,952 patients): There was modest heterogeneity for one-year survival (I²=27%) and response rate (I²=43%). There was no statistically significant difference between docetaxel three times weekly and alternative treatments in one year survival (11 RCTs), response rate (10 RCTs) or time to progression (2 RCTs).

The funnel plot showed no clear evidence of publication bias.

Results of other subgroup analyses were also reported.

**Authors’ conclusions**
Second-line treatments seemed to improve outcomes in advanced non-small cell lung cancer compared with best supportive care, and docetaxel every three weeks probably remained the ‘gold standard’, since there was insufficient evidence available to support the greater efficacy of alternative treatments.

**CRD commentary**
The review question was clearly stated and inclusion criteria were appropriately defined. Several relevant sources were searched, no language restrictions were applied and trials reported as abstracts were included. Publication bias was assessed and no evidence was found. Appropriate methods were used to minimise reviewer error and bias during the review process.

Only RCTs were included in the review and validity was assessed using a referenced method. However, criteria used for the assessment were not presented in the review and only aggregate scores were reported; this made it difficult to judge the quality of the evidence. Data were pooled using meta-analysis. Heterogeneity was assessed and various potential sources of heterogeneity were examined. However, there were clinical differences between trials and moderate to large heterogeneity was found, which suggested that pooling data may not have been appropriate.

Much of the review was well conducted, but differences between trials make it difficult to be certain of their reliability.

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

**Practice:** The authors stated that until further research is undertaken, docetaxel treatment every three weeks should be considered the ‘gold standard’ treatment for second-line metastatic non-small cell lung cancer.

**Research:** The authors stated that further studies of second-line treatment of advanced non-small cell lung cancer patients are required to determine the clinical and biological characteristics that predict treatment response, and to
identify a criterion that can be used to identify patients for chemotherapy or epidermal growth factor receptor treatment. Studies are also required to assess the effects of second-line treatments on symptom control or quality of life. Further evaluation of epidermal growth factor receptor inhibitors is also required.

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