Second-line or subsequent systemic therapy for recurrent or progressive non-small cell lung cancer: a clinical practice guideline

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CRD summary
The review had a number of methodological weaknesses. The authors’ conclusions about survival and quality benefits of docetaxel, pemetrexed and erlotinib were based on single studies per intervention and carried limited weight. The concluded effectiveness in second-line and subsequent therapies was from evidence that related to second-line therapies alone or mixed populations where the distribution of the effect was unknown.

Authors’ objectives
To assess the clinical effectiveness of second-line or subsequent treatments for recurrent or progressive non-small cell lung cancer.

Searching
MEDLINE, EMBASE and The Cochrane Library were searched from 1996 to November 2005; search terms were reported. The conference proceedings of American Society of Clinical Oncology, International Association for the Study of Lung Cancer, European Cancer Conference and European Society for Medical Oncology were searched from 2000 to 2005. The bibliographies of included studies and relevant review articles, and internet sources of national guidelines were searched.

Study selection
Randomised controlled trials (RCTs) or systematic reviews that compared systemic therapies with other systemic therapies or best supportive care, or that compared different doses and/or schedules of systemic therapies, for second-line or subsequent therapy of recurrent or progressive non-small cell lung cancer were eligible for inclusion; only RCTs were identified. Outcome measures were not specified. Trials that included a mix of untreated and previously treated patients, and trials with less than 50 participants per arm were excluded. Studies published in languages other than English were excluded. Most included studies were of single-agent docetaxel or docetaxel-based combination chemotherapies and most data were for second-line therapies. Other therapies assessed included epidermal growth factor receptor inhibitors (EGFRI).

After an initial relevance screen by one reviewer, two reviewers selected articles for inclusion. Any disagreements were resolved by discussion.

Assessment of study quality
The authors did not report that study validity was assessed, although some aspects of study quality were discussed in the report.

Data extraction
Data were extracted on response rates (complete response and partial response), median survival times (months) and 95% confidence intervals (CIs) and one year survival rates and 95% CIs. Any data on quality of life outcomes and the occurrence of grade 3 or 4 toxicity were also extracted.

Six-month survival data used in the meta-analysis were extrapolated from survival curves independently by two reviewers and the average of the two estimates used. No further details were reported on how data were extracted for the review. the number of reviewers involved in data extraction was not reported.

Methods of synthesis
A meta-analysis of mortality data for weekly versus three-weekly administration of second-line or subsequent single-agent docetaxel was planned and conducted using six-month survival data. A post-hoc meta-analysis was conducted to
investigate the impact of weekly versus three-weekly administration on the incidence of grade 3/4 febrile neutropenia. Pooled estimates were presented as relative risks with 95% confidence intervals and were estimated using a random-effects model. Sensitivity analyses were conducted to explore the impact of including data derived from abstracts.

The results of studies not included in the meta-analyses were presented in tables and a narrative synthesis.

**Results of the review**

Twenty four RCTs (n=7,681) were included in the review: 15 fully published and nine available as abstracts only. All trials were described as randomised, multi-centre and industry-supported. Methods of randomisation were not described in detail. None of the trials reported blinding of treatment allocation.

One phase III trial (n=308) showed a significant benefit in overall survival for single-agent docetaxel 75mg/m$^2$ three-weekly compared with best supportive care (median survival time 7.5 months versus 4.6 months, p=0.01). No difference in survival was seen for 100mg/m$^2$ docetaxel; the incidence of febrile neutropenia was significantly higher for 100mg/m2 docetaxel than for 75mg/m$^2$, with grade 3/4 at 22% (including three deaths) versus 2% (no deaths) of patients.

A pooled analysis of four studies (n=540) compared weekly with three-weekly administration of docetaxel and found similar survival between the schedules (relative risk 0.99, 95% CI: 0.84 to 1.16) and no significant difference in the rates of febrile neutropenia.

Two phase III non-inferiority trials showed equivalent survival for single-agent docetaxel and pemetrexed and topotecan.

Three trials compared docetaxel-based combination therapies with single agent docetaxel; none showed a significant difference in any measure of survival. Two further trials compared other single agent therapies, irinotecan and cisplatin with combination therapy and found no significant difference in survival.

One phase III trial (n=731) showed significant benefits in overall survival (hazard ratio 0.70, 95% CI: 0.58 to 0.85, p<0.001) and quality of life for erlotinib compared with placebo. No significant difference in survival was found between gefitinib and docetaxel (one study, n = 141) and between gefitinib and placebo (one study, n=1,692).

**Authors’ conclusions**

Second-line or subsequent therapy with single-agent docetaxel, pemetrexed or erlotinib offered patients a significant survival and quality of life advantage.

**CRD commentary**

The review addressed a clearly stated research question and defined appropriate inclusion criteria, with the exception that no outcome measures were specified. The search strategy was adequate, but the exclusion of publications not in English left a possibility of language bias. Measures to reduce error and/or bias were taken during the study selection process, but no similar measures were reported for most data extraction and no formal assessment of the methodological quality of included studies was reported. The synthesis methods used were generally appropriate (although no assessment of between study heterogeneity was reported), but the authors' conclusions regarding the survival and quality of life benefits offered by docetaxel, pemetrexed and erlotinib are based on very little data (single studies per intervention) and given the other limitations of the review carry limited weight. While the authors’ conclusions generalise to effectiveness for second-line and subsequent therapies, the non-inferiority trial of pemetrexed versus docetaxel included only second-line treatments and the trials of single-agent docetaxel versus best supportive care and erlotinib versus placebo were both in mixed populations that included second-, third- and fourth-line therapies combined (so we did not know whether the observed effect generalised across all three groups or was driven by one group).

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

**Practice:** The authors stated that a practice guideline was developed, based on the evidence reviewed (full details presented in the report).
Single-agent docetaxel 75mg/m² three-weekly was recommended as a second-line therapy for recurrent or progressive non-small cell lung cancer. Pemetrexed 500 mg/m² three-weekly was also an option.

Oral topotecan and combination chemotherapies (docetaxel-based or other) were not recommended as second-line therapies for recurrent or progressive non-small cell lung cancer.

Docetaxel 33-40mg/m² (for six weeks on an eight-week cycle or for three weeks on a four-week cycle) may be considered for patients at high risk of haematological toxicity or with a history of febrile neutropenia.

Erlotinib 150mg/day was recommended as a third-line therapy for recurrent or progressive non-small cell lung cancer. Erlotinib was also an option for second-line therapy, particularly for patients who were not candidates for chemotherapy or who had progression after first-line docetaxel-platinum chemotherapy.

Gefitinib 250mg/day may be considered for second-line and subsequent therapy only for symptomatic patients who were not candidates for chemotherapy and for whom erlotinib was not available.

**Research:** The authors made no recommendations for further research.

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