Duration of chemotherapy for advanced non-small-cell lung cancer: a systematic review and meta-analysis of randomized trials

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CRD summary
This well-conducted review concluded that extension of chemotherapy, particularly with a third-generation regimen, substantially improved progression-free survival and had a lesser, but still statistically significant, impact on overall survival in patients with non-small-cell lung cancer. Future trials should assess the extension of treatment with more effective and/or better-tolerated treatments. These conclusions are likely to be reliable.

Authors' objectives
To determine if there are benefits to extending chemotherapy beyond a standard number of cycles in patients receiving first line chemotherapy for advanced non-small-cell lung cancer (NSCLC).

Searching
MEDLINE, EMBASE, Cochrane Central Register of Controlled Trials (CENTRAL) and Cochrane Lung Cancer Group registry were searched from inception to July 2006. Some search terms were reported. Proceedings of American Society of Clinical Oncology and World Conference on Lung Cancer were searched from 1994 to 2008. References of identified studies were checked. Five registers of ongoing trials were searched.

Study selection
Randomised controlled trials (RCTs) in chemotherapy-naive patients with histologically or cytologically proven stage IIIB or IV NSCLC that assessed unconfounded comparisons of additional cycles of chemotherapy were included. The primary outcome was overall survival. Secondary outcomes included progression-free survival, health-related quality of life and toxicity. Eligible trials assessed the comparisons: fixed number of cycles versus continuation of the same chemotherapy until disease progression; fixed number of cycles versus a larger number of cycles of the same chemotherapy; and fixed number of cycles versus the same treatment plus additional cycles of alternative chemotherapy. Trials only in patients with stage IIIB cancer who received neoadjuvant therapy before radical radiotherapy were excluded from the review.

In included studies the number of cycles in the standard duration groups ranged from two to eight; the number of additional cycles ranged from six to continuation until progression or prohibitive toxicity. Most trials extended chemotherapy with a third generation agent (gemcitabine, vinorelbine, paclitaxel docetaxel or pemetrexed). Where reported, the percentage of men ranged from 62% to 91% and median age ranged from 57 to 66 years.

Three reviewers independently assessed the studies for inclusion in the review; disagreements were resolved through consensus.

Assessment of study quality
Studies were assessed for validity using criteria of: randomisation and concealment of allocation; blinding patients, clinicians and outcome assessors; treatment of withdrawals and dropouts; use of intention-to-treat analysis; and baseline comparability. A global quality score of A, B1, B2 or C was produced by summing scores from each criterion.

It appeared that three reviewers independently assessed the studies with disagreements resolved through consensus.

Data extraction
Three reviewers independently extracted data using standardised data extraction forms. Where possible, authors were contacted for updated results (particularly of trials published as abstracts only). Log hazard ratios (HR) and their variances were estimated from summary statistics or Kaplan-Meier curves or were calculated when only median survival times were reported.
Methods of synthesis
Hazard ratios were pooled in a fixed-effect model using a generic inverse variance method. Statistical heterogeneity between studies was assessed using $\chi^2$ and $I^2$ statistics. A secondary analysis using a random-effects model was undertaken where significant heterogeneity was detected. Subgroup analyses were carried out to examine the impact of: additional chemotherapy cycles that included a platinum agent or a third-generation chemotherapy agent; different trial designs; and publication status. Interaction tests were used to compare differences between estimates for different subgroups. Sensitivity analyses that excluded trials with a high risk of bias were conducted.

Results of the review
Thirteen RCTs (3,027 patients) were included in the review; median sample size was 220 (range 23 to 663). One RCT was judged to be at low risk of bias, 10 trials were judged to have low to moderate risk and two had high risk of bias.

Overall survival was statistically significantly increased, albeit by a clinically modest amount, by extending the duration of chemotherapy (HR 0.92, 95% CI 0.85 to 0.99). There was no evidence of statistically significant heterogeneity. Subgroup and sensitivity analyses showed no significant differences in treatment effect apart from a greater effect in trials published only as abstracts ($p=0.01$).

Progression-free survival was clinically and statistically significantly increased by extending the duration of chemotherapy (HR 0.75, 95% CI 0.69 to 0.81). Subgroup analyses showed significant differences in treatment effects, notably greater effects in trials that used a third generation agent to extend treatment ($p=0.003$), trials that used a non-platinum agent ($p=0.03$) and trials that used an alternative agent to extend treatment ($p=0.01$).

Five of seven RCTs did not demonstrate major differences in quality of life between treatment groups; two RCTs showed a trend towards better quality of life in patients in the standard chemotherapy groups. Where available, comparative data showed that extended duration chemotherapy was generally associated with higher rates of adverse events.

Authors' conclusions
Extending chemotherapy, particularly with a third-generation regimen, substantially improved progression-free survival and had a lesser, though still statistically significant, impact on overall survival. Future trials should assess the extension of treatment with more effective and/or better-tolerated treatments.

CRD commentary
The review question and the inclusion criteria were clear. The authors searched relevant databases and other sources and made efforts to identify unpublished trials. This reduced the chances that relevant studies were omitted and that publication bias was present in the review. The authors used methods designed to reduce reviewer bias and error in study selection and data extraction; they appeared to also use such methods during validity assessment, which was based on relevant criteria and used to inform the synthesis. The use of meta-analysis was reasonable and assessment and exploration of heterogeneity between studies was thorough.

The authors' conclusions accurately reflected the results of the review and appear likely to be reliable.

Implications of the review for practice and research
Practice: The authors stated that it may be reasonable to extend chemotherapy beyond a standard number of cycles in patients who have stable or responding disease after four to six cycles and who are tolerating treatment well. However, the additional toxicity and possible impairment of quality of life argue against routine extension of third-generation chemotherapy for all advanced NSCLC patients.

Research: The authors stated that future trials should assess extension of chemotherapy in patients with stage IIIB or IV NSCLC with more effective and/or better-tolerated treatments.

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