Optimal duration of first-line chemotherapy for advanced non-small cell lung cancer: a systematic review with meta-analysis

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CRD summary
This review aimed to identify the optimal duration of first-line chemotherapy for advanced non-small cell lung cancer. The authors concluded that four cycles of treatment with third-generation doublets appeared to be the optimal first-line treatment. This was a generally well-conducted review that appeared to reflect the limited evidence available, so the authors' conclusions are likely to be reliable.

Authors' objectives
To identify the optimal duration of first-line chemotherapy for advanced non-small cell lung cancer.

Searching
MEDLINE, EMBASE, LILACS and Cochrane Central Register of Controlled Trials were searched from January 1973 to December 2007 for published studies in any language. Search terms were reported. In addition, reference lists of relevant reviews were manually searched.

Study selection
Randomised controlled trials (RCTs) with a parallel design including patients with histologically diagnosed non-small cell lung cancer and with evidence of cancer progression or advanced disease not amenable to curable treatment, were eligible for inclusion. Included trials had to compare first-line treatment duration of either: a defined number of cycles with a higher number of cycles of the same chemotherapy; or a defined number of cycles of chemotherapy with continuing treatment. Trials including biological agents were excluded.

Included trials were conducted in USA, Europe and Asia and were published between 1989 and 2007. The majority of trials assessed platinum combinations. Some trials included second-line treatment. The majority of treatments were administered every three weeks with three or four cycles in shorter treatment arms, and six cycles, or continuing treatment until disease progression, in the longer treatment arms. Included trials reported progression-free survival and overall survival as the primary outcomes. Other endpoints included response rates and toxicities.

Two reviewers independently screened papers for inclusion, with decisions reached through consensus.

Assessment of study quality
Two reviewers assessed study validity, including items on: randomisation, allocation concealment, blinding, intention-to-treat analysis, source of funding, and use of placebo. The authors did not state how discrepancies were resolved.

Data extraction
Two reviewers independently extracted hazard ratios, odds ratios or risk differences, with their 95% confidence intervals (CIs). Where this information was not available, estimates were calculated using the reported number of events and the corresponding p value for the log-rank statistics, or extracting data from survival curves. Adjustments were made to trials not reporting intention-to-treat data, to reflect the number of patients undergoing randomisation.

Authors were contacted for missing information, and disagreements were resolved by referral to a third reviewer.

Methods of synthesis
A fixed effect model was used to pool hazard ratios, odds ratios and risk differences. Heterogeneity was assessed using the $\chi^2$ and $I^2$ tests and, where heterogeneity was reasonably explained, results were combined. Sensitivity analyses were conducted by generation of treatment combination and by excluding studies assessing non-platinum-based treatments.

Publication bias was assessed using funnel plots.
Results of the review
Seven RCTs (n=1,559) were included in the review. Sample sizes ranged from 74 to 314 participants. The authors reported that none of the trials were placebo-controlled or double-blind. Randomisation was adequate for three trials and allocation was adequate for one trial.

There were no significant differences in overall survival between treatment arms with shorter treatment (hazard ratio 0.97, 95% CI: 0.84, 1.11, seven RCTs). Sensitivity analyses did not significantly alter the results. Two RCTs showed a significant increase in progression-free survival using treatment of longer durations (hazard ratio 0.75; 95% CI: 0.65, 0.85, p<0.0001, six RCTs). There were no significant differences in response rates between treatment groups (four RCTs) or non-haematological toxicity. However, there was a significant increase in haematological toxicity in patients receiving treatment of longer duration (odds ratio 1.31; 95% CI: 1.01, 1.69, p=0.04, five RCTs). Subgroup analyses were also reported.

There was evidence of significant statistical heterogeneity for haematological toxicity (p=0.16, I²=40%) but no evidence of publication bias.

Authors' conclusions
Progression free survival in patients with advanced non-small cell lung cancer is significantly improved with more than four cycles of first-line chemotherapy with third-generation regimens but there is a higher incidence of adverse events. Overall survival is not significantly affected. The evidence does not support continuous chemotherapy until progression in patients with lung cancer.

CRD commentary
The review question was clear and was supported by appropriate criteria for patients, intervention and study design. An adequate search of the literature was undertaken in any language, reducing the potential for language bias. Only published studies were searched, which may have introduced publication bias but funnel plot analyses did not indicate this. Validity was assessed but the quality of the included trials was fairly limited. Attempts were made to reduce reviewer error and bias at each stage of the review. Appropriate methods were used to synthesise the data and investigate statistical heterogeneity. This was a generally well-conducted review that appeared to reflect the limited evidence available, so the authors' conclusions are likely to be reliable.

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

Research: The authors stated that the evaluation of new therapies is warranted.

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