Benefits of adding a drug to a single-agent or a 2-agent chemotherapy regimen in advanced non-small-cell lung cancer: a meta-analysis


CRD summary
This reasonably conducted review included 57 randomised controlled trials with 11,160 participants. The authors concluded that adding another drug to single-agent chemotherapy improved tumour response and survival for people with advanced inoperable non-small-cell lung cancer. Adding a third drug had a smaller effect on tumour response and no effect on survival. These conclusions are likely to be reliable.

Authors' objectives
To assess the effect of adding another drug to a single-agent or two-agent chemotherapy regimen for patients with advanced inoperable non-small-cell lung cancer (NSCLC) on response rate, survival and toxicity.

Searching
MEDLINE and EMBASE were searched for studies published between January 1980 and October 2003; the search terms were reported. There were no language restrictions. The authors also searched conference proceedings (published between January 1982 and October 2003) for ASCO, the European Society for Medical Oncology, the European Cancer Conference and the International Association for the Study of Lung Cancer, and handsearched relevant journals. Both full papers and abstracts were eligible.

Study selection
Study designs of evaluations included in the review
Randomised controlled trials (RCTs) performed between 1980 and 2001, with unbiased randomisation, were eligible for inclusion. Studies that allowed crossover between arms were excluded.

Specific interventions included in the review
Studies were eligible if they compared a single-agent versus a double-agent chemotherapy regimen, or compared a double-agent versus a triple-agent regimen. Studies were excluded if they used cisplatin and carboplatin in the same arm or used drugs not considered established cytotoxics. The regimens in the included studies varied widely. Full details were reported in the paper.

Participants included in the review
To be eligible for the review, the studies had to include patients with advanced inoperable NSCLC. Studies were excluded if the participants were candidates for curative surgery or radical radiotherapy, or had received prior chemotherapy.

Outcomes assessed in the review
To be eligible for the review, the studies had to include data on tumour response rate, survival or toxicity. The primary end point for the review was the overall tumour response rate. The secondary end points were overall survival (based on 1-year survival rate), median survival, and toxicity.

How were decisions on the relevance of primary studies made?
The authors did not state how the papers were selected for the review, or how many reviewers performed the selection.

Assessment of study quality
The authors did not report that they specifically assessed validity. Unbiased randomisation was an inclusion criterion, and data on randomisation processes and the use of intention-to-treat analyses were extracted. The authors did not state
how any validity assessment was performed.

**Data extraction**

Two authors extracted the data independently. Data on patient characteristics (e.g. disease stage, histological characteristics and performance status), the primary outcome (tumour response rate) and secondary outcomes (median survival, 1-year survival, and haematologic and non-haematologic survival) were extracted.

**Methods of synthesis**

*How were the studies combined?*

The authors calculated pooled odds ratios (ORs) and 95% confidence intervals (CIs) for objective tumour response, 1-year survival and toxicity using a fixed-effect model. They also calculated pooled median ORs for median survival using a fixed-effect model.

*How were differences between studies investigated?*

The authors defined groups of newer and older drugs and compared these groups separately. They examined statistical heterogeneity by comparing treatment regimens, planned dose reductions and the use of intention-to-treat analyses, and also conducted global tests for heterogeneity and interaction.

**Results of the review**

Fifty-seven RCTs with 11,160 participants were included.

Adding another drug to a single-agent regimen improved tumour response (OR 0.42, 95% CI: 0.37, 0.47), 1-year survival (OR 0.80, 95% CI: 0.70, 0.91) and median survival (OR 0.83, 95% CI: 0.79, 0.89), but was also associated with significantly increased grade 3 and 4 toxicity of all types.

Adding another drug to a double-agent regimen improved tumour response (OR 0.66, 95% CI: 0.58, 0.75), but had no statistically significant effect on 1-year survival (OR 1.01, 95% CI: 0.85, 1.21) or median survival (OR 1.00, 95% CI: 0.94, 1.06). Three-drug regimens were associated with statistically significantly greater grade 3 and 4 haematological toxicity in comparison with two-drug regimens, and also with statistically significantly higher incidences of infection and mucositis.

Heterogeneity statistics for each comparison were reported in the review.

**Authors' conclusions**

The addition of a second drug to a single-agent regimen improved tumour response and survival for people with NSCLC. The addition of a third drug had a smaller effect on tumour response and no effect on survival.

**CRD commentary**

The research question, search strategy and inclusion criteria for this review were clearly defined and the authors took steps to minimise language bias. The authors did not report searching for unpublished trials and this might have increased the possibility of publication bias. The use of methods to minimise bias and error when selecting studies for the review was not reported, and there were insufficient details about any validity assessment undertaken. This makes it more difficult to judge the quality of the studies included in the review, and hence the reliability of its conclusions.

The decision to employ meta-analyses appears appropriate, although the authors did not describe their rationale for using median survival ratios as opposed to other common methods. The comparisons between studies and the use of subgroups for comparisons involving older and newer drugs seem appropriate. This was a reasonably well-conducted review and the authors' conclusions appear appropriate.
Implications of the review for practice and research

Practice: The authors stated that there was no evidence to support the use of three-drug regimens for people with advanced inoperable NSCLC in clinical practice, and that their use should be limited to clinical trials.

Research: The authors stated that further research is needed to explore differences in the effects of third-generation agents.

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