Third-generation chemotherapy agents in the treatment of advanced non-small cell lung cancer: a meta-analysis
Baggstrom M Q, Stinchcombe T E, Fried D B, Poole C, Hensing T A, Socinski M A

CRD summary
This review investigated the efficacy of third generation (3G) chemotherapy agents on response and survival in stage IIIIB/IV non-small cell lung cancer. The authors found that 3G monotherapy improved one-year survival in comparison with best standard care, but a number of reporting and methodological limitations meant that these conclusions may not be reliable.

Authors' objectives
To determine the efficacy of third generation (3G) chemotherapy agents on response and survival in stage IIIIB/IV non-small cell lung cancer.

Searching
MEDLINE was searched from January 1980 to March 2004. Search terms were reported. Bibliographies of retrieved randomised clinical trials, meta-analyses and narrative reviews were searched. Pharmaceutical companies contacted to identify additional clinical trials.

Study selection
Randomised controlled trials (RCTs) of patients diagnosed with advanced stage non-small cell lung cancer that had not received treatment previously were eligible for inclusion. The included patients had a median age of 58 to 74 years. Most were male (61 to 93%). The percentage of patients with stage IIIIB disease varied from 0 to 61% and those with stage IV from 39% to 100% in the included studies. Treatment combinations eligible for inclusion were: 3G monotherapy versus best supportive care; 3G monotherapy versus second generation (2G) platinum-based regimen; and 3G platinum-based versus 2G platinum-based regimen (3G agents were defined as paclitaxel, docetaxel, gemcitabine, vinorelbine and irinotecan; 2G regimens were defined as platinum alone or platinum in combination with older agents including etoposide, vindesine, ifosfamide and mitomycin). The outcomes of interest were response to treatment and one-year survival rate. A variety of drugs and therapy classes were investigated in the included studies. All of the trials that compared 3G agents combined with platinum therapy with 2G regimens were published in 1994 or after.

Study selection was by consensus among reviewers. The authors did not state how many reviewers performed the study selection.

Assessment of study quality
The authors did not state that they assessed validity.

Data extraction
Data were extracted for response (overall, complete, partial, stable disease and progression) and one-year survival rate.

The authors did not state how data were extracted.

Methods of synthesis
Risk differences and corresponding 95% confidence intervals (CIs) were pooled as inverse variance weighted averages of estimates from each study. Studies were only pooled when there was little evidence of heterogeneity (p>0.1) or publication bias. Number needed to treat was calculated and survival at one year was based on intention to treat analysis and response rates based on assessable patients. Publication bias was investigated with funnel plots and Begg's Test. Statistical heterogeneity was assessed (test not described).

Results of the review
Nineteen randomised trials were included in the review (n=5,895).

3G agents were associated with improvement in one-year survival compared with best supportive care (risk difference 7%, 95% CI: 2% to 12%; five trials, n=1,029). Number needed to treat was 14. Response was greater with 2G platinum-based therapy compared with 3G monotherapy (risk difference was -6%, 95% CI: -11% to 0%; four trials, n=871).

3G combination regimens including platinum-based compounds had a higher response rate than 2G platinum based regimens (risk difference was 12%, 95% CI: 10% to 15%; 12 trials, n=3,995). The number needed to treat was eight. There was no evidence of statistically significant heterogeneity or publication bias for these outcomes. There was a high degree of statistical heterogeneity for one-year survival when 3G combination regimens including platinum-based compounds were compared with 2G platinum-based regimens (p=0.1).

No difference in one-year survival was found between 3G monotherapy and 2G platinum-based combined regimens.

**Authors' conclusions**
3G monotherapy improved one-year survival in comparison with best standard care.

**CRD commentary**
The inclusion criteria were clear regarding participants, study design and intervention. Criteria for outcomes were not clearly stated, which could have led to subjective decisions in study selection. No information was provided about the languages eligible for inclusion, so potential language bias could not be assessed. Only published studies were included. Publication bias was not found, but could not be ruled out due to the limited number of included trials in each group. The review process was not well described, so any steps taken to reduce the possibility of reviewer bias and error were unknown. The authors did not report any assessment of the methodological quality of the included studies, so it was unknown whether the results of these studies and, therefore, their synthesis is reliable. As there were a number of reporting and methodological limitations, the authors' conclusions may not 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 estimation of the response rate with previous regimens from a meta-analysis may assist in the development of future trials. Further trials were needed to evaluate differences in rates and severity of treatment-related toxicity or quality of life between treatment with 3G agents compared with previous therapies.

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