Efficacy and side effects of cisplatin- and carboplatin-based doublet chemotherapeutic regimens versus non-platinum-based doublet chemotherapeutic regimens as first line treatment of metastatic non-small cell lung carcinoma: a systematic review of randomized controlled trials

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CRD summary
This review concluded that cisplatin-based, but not carboplatin-based, doublet regimens were associated with slightly better survival and had different side effects compared with non-platinum based doublet regimens in the first-line treatment of non-small cell lung cancer. These conclusions did not acknowledge that there were no significant differences for most outcomes assessed and should be interpreted with some caution.

Authors' objectives
To compare the effects of platinum based doublet regimens with non-platinum based regimens for the first-line treatment of non-small cell lung carcinoma.

Searching
PubMed, BIOSIS Previews and CINAHL were searched from 1996 to February 2007. Search terms were reported. The authors did not state that any language restrictions were applied, but one study was excluded as it was published in Chinese. The review was restricted to published studies; studies available only as abstracts were excluded.

Study selection
Randomised controlled trials (RCTs) (phase II or III) that compared non-platinum-based doublet regimens with platinum-based (carboplatin or cisplatin) doublet regimens, as first-line treatment for histologically proven non-small cell lung carcinoma, in chemotherapy naive adults (age >18 years), were eligible for inclusion. Patients were required to have a 0 to 2 Eastern Cooperative Oncology Group (ECOG) performance status and not to have undergone radiotherapy during chemotherapy. Trials had to include at least one year of follow-up.

The primary outcome was survival at one year. Secondary outcomes included survival at two years, complete response, partial response, stable disease, progressive disease, and grade 3 or 4 side effects (anaemia, neutropenia, thrombocytopenia, leukopenia, febrile neutropenia, nausea, vomiting, nephrotoxicity, neurotoxicity, diarrhoea, and toxic death).

In included trials, platinum-based therapies assessed included carboplatin on day one (5 to 7 area under the curve - AUC), and cisplatin (75 to 100 mg/m²) on day one to 15 (and additionally on day 22 in one trial). Non-platinum based therapies included epirubicin (100mg/m² on day one), etoposide (50mg daily on days one to 14), gemcitabine (1000 to 1250mg/m² on days one and eight), irinotecan (60mg/m² on days one, eight, 22 and 29), paclitaxel (175mg/m² on day one) and vinorelbine (25mg/m² on day one and eight in some trials). Second agents included paclitaxel, vinorelbine, gemcitabine, and docetaxel. The proportion of included patients with stage IIIIB disease ranged from 14 to 46%; the proportion with ECOG of 2 status ranged from 0 to 47% (where reported). The proportion of patients surviving at one year ranged from 27 to 58%.

Two reviewers independently assessed studies for inclusion.

Assessment of study quality
To reviewers independently assessed trial quality using the Jadad scale including the following items: randomisation, blinding of outcome assessors and withdrawals. Trials were assigned a score out of 5 based on the items fulfilled.

Data extraction
Two reviewers independently extracted data using a standardised form. For dichotomous outcomes, data were extracted to calculate relative risks (RR) together with 95% confidence intervals (CIs) and standard errors (SE). Data were
extracted on an intention-to-treat basis. Authors were contacted for further information, where necessary.

**Methods of synthesis**
Summary relative risks were estimated using fixed-effect models in the absence of heterogeneity, or random-effects models where heterogeneity was present. Heterogeneity was assessed statistically using the $I^2$ statistic and visually using forest plots. Publication bias was assessed using a funnel plot and the Egger test. Results were pooled for all trials combined and stratified according to whether the intervention was cisplatin-based or carboplatin based.

Sensitivity analysis was conducted by repeating the analysis using odds ratios (OR) and by restricting the analysis to trials with a Jadad score of 3 or more.

**Results of the review**
Seventeen trials reporting 18 comparisons were included in the review (approximately 4900 patients, exact number unclear). Thirteen studies scored 3 or more on the Jadad scale for quality.

**Platinum-based versus non-platinum-based doublet regimens**: The use of platinum-based therapy was associated with greater survival at one year compared with non-platinum-based therapy (RR 1.08, 95% CI 1.01 to 1.16; 17 comparisons) and increased the number of patients showing a partial response (RR 1.11, 95% CI 1.02 to 1.21; 17 comparisons). There was no evidence of heterogeneity ($I^2$=25% and 0% respectively). There was no difference in survival at two years (seven comparisons), complete response (13 comparisons), stable disease (15 comparisons), or progressive disease (15 comparisons). Platinum-based therapy was also associated with increased risk of side effects, with a higher risk of anaemia (RR 2.02, 95% CI 1.37 to 2.98), neutropenia (RR 1.25, 95% CI 1.01 to 1.54; 16 comparisons), thrombocytopenia (RR 1.82, 95% CI 1.06 to 3.10; 17 comparisons), nausea and vomiting (RR 2.16, 95% CI 1.18 to 3.94), and neurotoxicity (RR 1.99, 95% CI 1.07 to 3.71). There was no difference between treatment groups for other adverse events. There was evidence of heterogeneity for these outcomes.

**Cisplatin-based versus non-platinum-based doublet regimens**: Restriction of the analysis to 11 comparisons of cisplatin-based therapy showed similar results to those for platinum-based therapy overall, for efficacy and adverse events, except that there was also a significant improvement in complete response (RR 2.29, 95% CI 1.08 to 4.88).

**Carboplatin-based versus non-platinum-based doublet regimens**: Seven comparisons of carboplatin-based doublet regimens showed no significant difference compared with non-platinum-based therapy for any of the outcomes assessed. Carboplatin was associated with a greater risk of thrombocytopenia and anaemia compared with non-platinum based therapy, but there was no difference in the risk of nausea and/or vomiting.

Sensitivity analysis did not alter the results.

Funnel plots suggested no evidence of publication bias.

**Authors’ conclusions**
Cisplatin-based, but not carboplatin-based, doublet regimens were associated with slightly better survival compared with non-platinum based doublet regimens for the first-line treatment of non-small cell lung cancer. Side effects of cisplatin and carboplatin based regimens differ from each other and from non-platinum-based doublets.

**CRD commentary**
The review addressed a clear objective and inclusion criteria were defined. The literature search involved three relevant databases, but no additional attempts were made to locate studies, such as screening reference lists or contacting authors. It appeared that language restrictions were applied and unpublished studies were excluded. Relevant studies may have been missed and language and publication bias was a possibility. Publication bias was assessed in the review and no evidence was found. Appropriate steps were taken to minimise bias and errors at all stages of the review.

Trial quality was assessed using some relevant criteria, but the results were only presented as the number of trials scoring above 3 points on the summary scale, with no details on the individual items fulfilled. This meant that it was difficult to interpret the quality of the included trials. Relevant trial details were clearly summarised in tables, helping to
assess the generalisability of the review findings. Appropriate methods were used to pool data, but comparisons between cisplatin and carboplatin regimens were based on indirect evidence, which has limitations (as acknowledged by the authors).

The authors’ conclusions were supported by the results of the review, but they did not acknowledge that no significant differences were found between treatment regimens for most of the outcomes assessed, including survival at two years. Therefore, the authors’ conclusions should be interpreted with some caution.

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

**Practice:** The authors stated that clinicians should carefully choose an appropriate treatment regimen, based on individual patient toxicities and preferences.

**Research:** The authors stated that further evidence could be gained by meta-analysis of individual patient data.

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