Cisplatin- versus carboplatin-based chemotherapy in first-line treatment of advanced non-small-cell lung cancer: an individual patient data meta-analysis


CRD summary
This individual patient data meta-analysis showed that cisplatin should remain the platinum agent in chemotherapy for non-small cell lung cancer, especially in patients with early disease or advanced disease but good prognosis. This was a well-conducted piece of research and the conclusions appear reliable.

Authors' objectives
To compare the efficacy of cisplatin and carboplatin in first-line chemotherapy treatment of advanced non-small cell lung cancer (NSCLC).

Searching
MEDLINE and CANCERLIT were searched; search terms were reported, but not dates. Meeting abstracts, US National Cancer Institute Physicians Data Query Clinical Protocol and reference lists of trials, reviews and oncology books were searched. Individual trialists or research groups were contacted. Only published or unpublished studies in English were included.

Study selection
Randomised controlled trials (RCTs) for the treatment of NSCLC that compared cisplatin-based or carboplatin-based first-line chemotherapy without additional agents were eligible. The primary endpoint was overall survival. Secondary endpoints were overall response rate (total of partial and complete response) and toxicity, graded according to National Cancer Institute Common Toxicity Criteria.

Included trials evaluated etoposide, mitomycin with vindesine or vinblastine, cisplatin or carboplatin with paclitaxel, docetaxel, gemcitabine, or cisplatin and carboplatin in combination with tirapazamine. Doses varied between trials. The median number of cycles was four (range 0 to 22). The median patient age was 60 years, 76% were male, 86% of patients had performance stages zero to one, 68% who received cisplatin treatment and 69% who received carboplatin treatment had stage IV disease.

The authors did not state how studies were selected for the review.

Assessment of study quality
Raw data were checked to ensure the accuracy of the database and the quality of randomisation and follow-up. Queries were resolved by the study co-ordinator of the trial.

Data extraction
Raw data for all patients (including any who had been excluded from the original trial analyses) were requested from the principal investigators. Details of the variables requested were reported in the paper.

Methods of synthesis
Overall survival was calculated as the duration from randomisation until death from any cause. Patients still alive were censored at their last known follow-up assessment. All analyses were intention to treat (ITT). An individual patient data meta-analysis was performed using a general variance-based method. Summary hazard ratios (HR), odds ratios (OR) and 95% confidence intervals (CI) were presented. Statistical heterogeneity was assessed with a $\chi^2$ test and the $I^2$ statistic. In the presence of statistically significant heterogeneity, a random-effects survival analysis was performed using a Cox proportional hazards model with a frailty term. Median follow-up times were estimated using the reverse Kaplan-Meier method. Subgroup analyses were age (<65 versus ≥65 years), disease stage (IIIb versus IV), performance stage (0-1 versus 2), histology (squamous versus non-squamous) and regimen type (second versus third generation chemotherapy). Subgroups were assessed by including interaction terms in regression models (taking $p<0.10$ as
Results of the review

Nine RCTs (n=2,968) were included. Median follow-up time was 1,021 days.

**Survival**: The median survival was 9.1 months for cisplatin and 8.4 months for carboplatin treated patients. There was no evidence of a difference between the two treatments (HR 1.07, 95% CI 0.99 to 1.15). Moderate heterogeneity (I² 52%) was found, but the random-effects model showed a similar conclusion. Subgroup analyses showed that the effects of treatment differed according to histology (p=0.098) and chemotherapy regimen (p=0.093). There was a significantly increased risk of death for patients with non-squamous disease who received carboplatin treatment (HR 1.12, 95% CI 1.01 to 1.23) and for patients who received third generation carboplatin treatment (HR 1.11, 95% CI 1.01 to 1.21).

**Response rate**: Response rates were 30% for cisplatin and 24% for carboplatin treated patients, which showed a significant benefit for cisplatin (OR 1.37, 95% CI 1.16 to 1.61, p<0.001). There was no heterogeneity (I² 0%). Subgroup analyses showed that the effects of treatment differed according to histology (p=0.046). Significant benefits of carboplatin were seen only in patients with non-squamous disease (OR 1.58, 95% CI 1.27 to 1.97).

**Toxicity**: Patients treated with carboplatin were significantly more likely to experience thrombocytopenia (OR 2.27, 95% CI 1.71 to 3.01, p=0.001), but less likely to suffer nausea and vomiting (OR 0.42, 95% CI 0.33 to 0.53, p<0.001) or renal toxicity (OR 0.37, 95% CI 0.15 to 0.88, p=0.018). There was no difference between treatments in the occurrence of leucopenia, neutropenia, anaemia and neurotoxicity.

Authors’ conclusions

Based on the results of this and previously published meta-analyses, cisplatin should remain the the reference platinum agent for treating NSCLC, especially in patients with earlier disease or advanced disease with good prognosis.

CRD commentary

This individual patient data meta-analysis was performed by a collaborative group and had a clearly defined question and inclusion criteria. The search strategy was limited by inclusion only of trials published in English. This increased the risk of publication bias, but hopefully any missed trials were found when contacting people who performed the trials. Raw data were checked and data for all patients were included on an intention-to-treat basis. The statistical analysis methods were appropriate and the results were clearly reported in the text, tables and figures. Sensitivity analyses were performed to look at the impact of between trial heterogeneity. Subgroup analyses were prespecified and kept to a minimum number.

This was a well-conducted and clearly reported meta-analysis. The authors compared their findings with other research in this area. These conclusions appear to be reliable.

Implications of the review for practice and research

**Practice**: The authors stated that cisplatin should remain the platinum agent of choice for patients with early stage NSCLC or advanced disease but good prognosis.

**Research**: The authors did not state any implications for research.

Funding

Not stated.

Bibliographic details

PubMedID
17551145

DOI
10.1093/jnci/djk196

Original Paper URL
http://jnci.oxfordjournals.org/cgi/content/full/99/11/847

Indexing Status
Subject indexing assigned by NLM

MeSH
Antineoplastic Agents /therapeutic use; Carboplatin /therapeutic use; Carcinoma, Non-Small-Cell Lung /drug therapy; Cisplatin /therapeutic use; Humans; Lung Neoplasms /drug therapy; Randomized Controlled Trials as Topic; Survival Rate; Treatment Outcome

AccessionNumber
12007005734

Date bibliographic record published
07/02/2008

Date abstract record published
09/12/2009

Record Status
This is a critical abstract of a systematic review that meets the criteria for inclusion on DARE. Each critical abstract contains a brief summary of the review methods, results and conclusions followed by a detailed critical assessment on the reliability of the review and the conclusions drawn.