Lung adjuvant cisplatin evaluation: a pooled analysis by the LACE Collaborative Group


CRD summary
This meta-analysis of individual patient data concluded that postoperative cisplatin-based chemotherapy significantly improved survival compared with no chemotherapy in patients with non-small-cell lung cancer. This was a well-conducted meta-analysis and the authors’ conclusions were likely to be reliable.

Authors’ objectives
To evaluate the effect of postoperative cisplatin-based chemotherapy on survival in patients with non-small-cell lung cancer (NSCLC) using individual patient data and to identify treatment options associated with a higher benefit and patient groups who particularly benefit from treatment.

Searching
Trials were identified using the search strategy described in the protocol of the 1995 NSCLC meta-analysis, which involved searches of MEDLINE, Cancerlit, Cochrane Central Register of Controlled Trials and proceedings of ASCO (1995-2003). Also searched were trials registers, proceedings of several oncology conferences, bibliographies of trial reports and review articles. Experts were contacted.

Study selection
Randomised controlled trials including more than 300 patients were eligible if they compared post-operative cisplatin-based chemotherapy versus no chemotherapy or cisplatin-based chemotherapy plus postoperative radiotherapy versus radiotherapy alone in patients with completely resected NSCLC. Only trials conducted after the 1995 NSCLC meta-analysis were included. The primary endpoint was overall survival. Secondary endpoints included disease-free survival (DFS), lung cancer-related deaths, non lung cancer-related deaths, treatment delivery and toxicity. Most included trials enrolled patients with Stage I, II or III (or IIIA) disease and evaluated three or four cycles of cisplatin chemotherapy. Radiotherapy after chemotherapy was optional in most trials. The authors did not state how trials were selected for the review.

Assessment of study quality
All individual patient data (IPD) were verified in collaboration with the individual trial investigators and statisticians. Each trial was analysed individually and analyses were verified by the principal investigators.

Data extraction
Data collected for each patient included baseline patient and tumour characteristics, planned and received treatment, toxicity and outcomes. Events included in DFS were recurrence at any site and death from any cause in the absence of recurrence.

Methods of synthesis
Studies were combined by IPD meta-analysis. Median follow-up was computed using the reverse Kaplan-Meier method. Treatment groups were compared using the intention-to-treat principle. Log-rank observed minus expected (O-E) numbers of deaths and their variances were used to calculate individual hazard ratios (HRs) and a pooled HR using a fixed-effect model. X² and I² tests were used to assess heterogeneity. Interactions between treatments and covariates (associated drugs, cisplatin dose, radiotherapy, patient age, sex and performance status, disease stage and histology, and type of surgery) were studied in an analysis stratified by trial and adjusted on the covariate, with a different treatment effect for each covariate value.

Results of the review
Five RCTs (n = 4,584) were included. Median follow-up was 5.2 years (range per trial 4.7 to 5.9 years). Chemotherapy significantly reduced risk of death by 11 per cent compared with no chemotherapy (HR 0.89, 95% CI: 0.82, 0.96) without significant heterogeneity. There was also a significant benefit of chemotherapy for DFS (HR 0.84, 95% CI: 0.78, 0.91) without significant heterogeneity. The benefit of chemotherapy for overall survival varied with disease stage.
was statistically significant for stages II and III but not for stages IA and IB. Chemotherapy effect was more marked in patients with better performance status, but was not affected by the other chemotherapy drugs used. There was no significant interaction between chemotherapy effect and age, sex, histology, type of surgery, planned radiotherapy or planned total cisplatin dose.

**Authors’ conclusions**
Post-operative cisplatin-based chemotherapy significantly improved survival in patients with NSCLC.

**CRD commentary**
The inclusion criteria for the review were clear and the authors made a thorough search for relevant trials, including unpublished trials. It was unclear whether any language restrictions were imposed, so the risk of language bias was uncertain. Data were checked and analyses verified in collaboration with trial investigators. Data were pooled using standard methods for IPD meta-analysis. Statistical heterogeneity was assessed and shown not to be significant. Analyses were performed to investigate the relationship between various pre-specified factors and the effect of chemotherapy. Methods to minimise errors and bias appeared generally rigorous, although some methods (such as how decisions on trial eligibility were made) were not reported. This was a well-conducted meta-analysis. The authors’ conclusions were in line with the evidence presented and evidence from other sources, and were likely to be reliable.

**Implications of the review for practice and research**
Practice: The authors stated that the analysis supported the use of cisplatin-based chemotherapy in routine clinical practice.

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

**Funding**
Institut Gustave-Roussy, Programme Hospitalier de Recherche Clinique, Ligue Nationale Contre le Cancer, Sanofi-Aventis (unrestricted grants) and Pierre Fabre Oncology (unrestricted grants)

**Bibliographic details**

**PubMedID**
18506026

**DOI**
10.1200/JCO.2007.13.9030

**Additional Data URL**
NSCLC meta-analysis protocol available on [http://www.ctu.mrc.ac.uk](http://www.ctu.mrc.ac.uk)

**Other publications of related interest**

**Indexing Status**
Subject indexing assigned by NLM

**MeSH**
Adult; Aged; Antineoplastic Agents /therapeutic use; Antineoplastic Combined Chemotherapy Protocols /therapeutic use; Carcinoma, Non-Small-Cell Lung /drug therapy /mortality; Chemotherapy, Adjuvant; Cisplatin /therapeutic use; Disease-Free Survival; Female; Humans; Kaplan-Meier Estimate; Lung Neoplasms /drug therapy /mortality; Male;
Middle Aged; Randomized Controlled Trials as Topic

**AccessionNumber**
12008105000

**Date bibliographic record published**
01/12/2008

**Date abstract record published**
13/05/2009

**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.