Preoperative chemotherapy for non-small cell lung cancer: a systematic review and meta-analysis of individual participant data
NSCLC Meta-analysis Collaborative Group

CRD summary
This review found that preoperative chemotherapy significantly improved survival for patients with resectable non-small cell lung cancer. It was a large, collaborative review of individual patient data, and its findings are very likely to be reliable.

Authors' objectives
To establish the effect of preoperative chemotherapy for patients with resectable non-small cell lung cancer.

Searching
MEDLINE, EMBASE, trial registers, conference proceedings, review articles and reference lists of publications were searched for articles from 1965 to May 2013, without language restrictions. Some search terms were reported. Collaborators were asked to identify any further trials.

Study selection
Randomised controlled trials of chemotherapy with subsequent surgery, compared with surgery alone, in patients with resectable non-small cell lung cancer, were eligible. Patients had to have received no previous chemotherapy, be suitable for surgery, and have no previous malignancy. Trials that planned to use postoperative radiotherapy for both groups, or postoperative chemotherapy only for the preoperative group, were included. The primary outcome was overall survival; secondary outcomes included recurrence-free survival, time to locoregional and distant recurrence, disease-specific survival, complete and overall resection rates, and postoperative mortality.

The included trials were conducted between 1985 and 2007. About 40% of patients were younger than 60 years, 80% were male, 50% had cancer of squamous histology, and over 90% were at clinical stages IB to IIIA. Various mostly platinum-based chemotherapy drugs were used. Eight trials included postoperative radiotherapy for both groups; five gave postoperative chemotherapy for responders in the chemotherapy group only.

The authors did not state how many reviewers performed the study selection.

Assessment of study quality
The individual patient data were checked for quality, including checks for validity, consistency, missing data, treatment allocation, imbalance in initial characteristics, and complete follow-up data.

The authors did not state how many reviewers were involved in this process.

Data extraction
Individual patient data were sought for all trials through contact with the original trial team. Inconsistencies in the data were verified with these team members.

The authors did not state how many reviewers were involved in this process.

Methods of synthesis
Hazard ratios with their 95% confidence intervals were extracted for each outcome, in each trial, using the log-rank method by calculating the observed and expected numbers of events. Hazard ratios were pooled using fixed-effect and random-effects meta-analyses. I² and Cochran’s Q were used to assess heterogeneity. The results were presented as Kaplan-Meier survival curves. Individual-level subgroup analyses were performed for a range of pre-specified clinical factors. For dichotomous outcomes, the Peto odds ratio was calculated for each trial, and pooled using a fixed-effect meta-analysis.
Results of the review

Nineteen trials were eligible, and individual patient data were collected from 15 of them (2,385 patients, range 10 to 519; 92% of all eligible randomised patients). The risk of bias was judged to be low. Median follow-up ranged from 2.2 to 12.9 years.

Preoperative chemotherapy improved overall survival rates (HR 0.86, 95% CI 0.75 to 0.98; I²=25%). There was no evidence of a difference in survival across a range of patient characteristics including age, performance status, clinical stage, gender, histology, use of postoperative chemotherapy, and type of chemotherapy. There was some evidence that trials that stopped early had different treatment effects.

Preoperative chemotherapy improved recurrence-free survival (HR 0.85, 95% CI 0.76 to 0.94; 14 trials) and time to distant recurrence (HR 0.69, 95% CI 0.58 to 0.82; 13 trials). The benefit for locoregional recurrence was not statistically significant (HR 0.88 95% CI 0.73 to 1.07; 13 trials).

There was no statistically significant evidence of a difference between treatments for 30-day mortality (OR 1.48, 95% CI 0.85 to 2.58; nine trials), six-month mortality (OR 0.88, 95% CI 0.67 to 1.14; 15 trials), and complete resection (OR 0.88, 95% CI 0.68 to 1.14; 11 trials).

Authors’ conclusions

Preoperative chemotherapy significantly improved overall survival, time to distant recurrence, and recurrence-free survival in patients with resectable non-small cell lung cancer, and was a valid treatment for these patients.

CRD commentary

This was a well-conducted, collaborative, review of individual patient data. It addressed a relevant research question, with appropriate inclusion criteria. A suitable search was conducted, without language restrictions, and it identified both published and unpublished trials. While some processes of the review were not reported in detail, its large collaborative nature suggests that appropriate action was taken to avoid error and bias. The data were checked to assess trial quality, and were judged to be at a low risk of bias. Individual patient data were pooled, using appropriate meta-analyses.

This was a large, carefully conducted review and its results, and the authors’ conclusions, are very likely to be reliable.

Implications of the review for practice and research

Practice: The authors suggested that clinicians might consider preoperative chemotherapy for patients who had a poor prognosis, who were less able to tolerate postoperative therapy, or who were in areas where waiting lists were long. Postoperative therapy might be preferred where immediate treatment was desired, for patients with early-stage disease, or to establish if subsequent chemotherapy was appropriate.

Research: The authors suggested that trials were needed to determine which drugs to use, the duration of chemotherapy, and the role of genetic biomarkers.

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