Chemotherapy in non-small cell lung cancer: a meta-analysis using updated data on individual patients from 52 randomised clinical trials
Non-small Cell Lung Cancer Collaborative Group

Authors' objectives
To evaluate the effect of cytotoxic chemotherapy on survival in patients with non-small cell lung cancer (NSCLC).

Searching
MEDLINE and CANCER-CD were searched for bibliographies, although the search dates are unclear. Abstracts from meetings, bibliographies of books, reviews and specialist journals were all handsearched. Trial registers (National Cancer Institute, UK Coordinating Committee for Cancer Research, Union Internationale Contre le Cancer) were consulted, whilst experts in the field, pharmaceutical companies and all included trialists were contacted for additional material.

Study selection
Study designs of evaluations included in the review
Randomised controlled trials (RCTs).

Trials were included if they randomised patients between one of the four primary treatments (surgery, surgery plus radiotherapy, radical radiotherapy, supportive care) and the same treatment plus an established form of cytotoxic chemotherapy. Recruitment had to begin after January 1, 1965 and be completed by December 31, 1991.

Excluded trials were those allowing patients to have received chemotherapy before randomisation; trials of neo-adjuvant chemotherapy; trials of radical radiotherapy using orthovoltage radiotherapy or a total radiation dose of <30 Gy; those in which drugs were used with the primary aim of sensitisation to radiation; and those allocating treatment by quasi-random methods such as patient's date of birth.

Specific interventions included in the review
Chemotherapy. The analysis distinguished between cisplatin-based drugs, long-term alkylating agents, vinca alkaloid or etoposide, and ‘other’ drugs. Drugs included in the analysis were: busulphan, cisplatin, cyclophosphamide, doxorubicin, epirubicin, etoposide, fluorouracil, lomustine, methotrexate, mitomycin C, nitrogen mustard, prednisolone, procarbazine, tegafur, UFT (uracil and tegafur), vinblastine, vincristine and vindesine.

Participants included in the review
Patients with NSCLC were included.

Outcomes assessed in the review
Survival was assessed.

How were decisions on the relevance of primary studies made?
The authors do not state how the papers were selected for the review, or how many of the authors performed the selection.

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

Data extraction
Individual patient data were obtained directly from trialists. All data were checked for internal consistency, and against the trial protocol and published reports. Each trial was analysed individually and sent to the trialists for verification.
Methods of synthesis
How were the studies combined?
The data were combined to calculate the individual and overall pooled hazard ratios (HRs) using the fixed-effect model. The analysis was undertaken on an intention to treat basis. The absolute survival differences were also calculated. Subgroup analysis was undertaken to look for differences due to stage, age, sex, histological cell type and performance status.

How were differences between studies investigated?
Tests for heterogeneity were undertaken over all trials, and for both between- and within-chemotherapy categories.

Results of the review
Fifty-two RCTs involving 9,387 patients were included.

Combined surgery and chemotherapy versus surgery (14 trials, 4,357 patients).
There was significant heterogeneity between trials (p=0.02) and between categories of chemotherapy (p=0.004), so results are reported for the predefined chemotherapy categories rather than overall. For cisplatin-based regimens, the HR was 0.87 (95% confidence interval, CI: 0.74, 1.02, p=0.08). For other regimens, the HR was 0.89 (95% CI: 0.72, 1.11, p=0.30). For the older long-term alkylating agents, the HR for surgery plus chemotherapy versus surgery was 1.15 (95% CI: 1.04, 1.27, p=0.005).

Combined surgery, radiotherapy and chemotherapy versus combined surgery and radiotherapy (7 trials, 807 patients).
The overall HR was 0.98 (p=0.76). The test for heterogeneity was not significant (p=0.73). For the 6 cisplatin-based trials, the HR was 0.94 (95% CI: 0.79, 1.11, p=0.46).

Radical radiotherapy plus chemotherapy versus radical radiotherapy (22 trials, 3,033 patients).
The overall HR was 0.90 (p=0.006). The heterogeneity between trials and chemotherapy categories was not significant (p=0.56 and p=0.59 respectively). Eleven of the trials used cisplatin-based drugs, and the HR for these trials was 0.87 (95% CI: 0.79, 0.96, p=0.005). The HRs for all other chemotherapy categories were not significantly different from 1.

Supportive care combined with chemotherapy versus supportive care (11 trials, 1,190 patients).
There was significant heterogeneity both between trials (p<0.0001) and between chemotherapy categories (p=0.003). For the 8 cisplatin-based trials the HR was 0.73 (95% CI: 0.63, 0.85, p<0.0001). The results for the trials using long-term alkylating agents suggested a detrimental effect of chemotherapy, but since there were only 2 trials the result is not significant. HR was 1.26 (95% CI: 0.96, 1.66, p=0.095).

The subgroup analyses were undertaken for cisplatin-based regimens only. No evidence of any differences was found.

Authors' conclusions
For all comparisons, results for modern cisplatin-based regimens favoured chemotherapy and were conventionally significant in the locally advanced and supportive care settings. In all but the radical radiotherapy setting, older trials using long-term alkylating agents tended to show a detrimental effect of chemotherapy. Modern chemotherapy regimens may have a role in treating all stages of NSCLC, although further research is needed to confirm any potential benefit. Further clinical trials are needed to assess short-term chemotherapy and to compare different chemotherapies.

CRD commentary
This is a thorough review.
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