Chemotherapy in stage IV (metastatic) non-small-cell lung cancer

Authors' objectives
To assess whether chemotherapy improves survival and quality of life in metastatic (stage IV) non-small-cell lung cancer.

Searching
For the original review, MEDLINE and Cancerlit were searched for material published between January 1980 and June 1994. The search terms included 'non-small-cell lung cancer', 'lung neoplasms', 'stage IV', 'metastatic', 'drug therapy', 'supportive care', 'clinical trials', 'research design', 'meta-analysis' and 'guidelines'. Personal files, reference lists and proceedings of meetings were also searched. The search was updated using MEDLINE (to December 2001), Cancerlit (to October 2001), the Cochrane Library (Issue 1, 2002) and proceedings of the American Society of Clinical Oncology (from 1997 to 2001). Material that had been published or submitted for publication was eligible.

Study selection
Study designs of evaluations included in the review
Meta-analyses and randomised controlled trials were eligible if they compared chemotherapy plus supportive care with supportive care alone for people with metastatic (stage IV) non-small-cell lung cancer. Three meta-analyses including many of the same trials were identified in the original search. A total of 11 randomised trials from these meta-analyses were included in the original review. The update included 1 additional meta-analysis and 8 additional randomised trials. The meta-analyses differed in the inclusion criteria used to select the articles for review, the use of group or individual patient data, the number of treatment cycles and the statistical tests used.

Specific interventions included in the review
Supportive care with or without chemotherapy.

The chemotherapy regimens included various combinations of cisplatin, cyclophosphamide, vinblastine, epirubicin, etoposide, lomustine, methotrexate, doxorubicin, vindesine and mitomycin. The studies each used different treatment regimens, details of which are presented in the report and the update (see Other Publications of Related Interest).

The supportive care regimens also differed between the studies. Most offered no additional treatment, but some studies included palliative radiotherapy.

Participants included in the review
People with metastatic (stage IV) non-small-cell lung cancer were eligible. About half of the studies excluded people with brain metastases. Most studies had an age cut-off of 70 or 75 years. The median age ranged between 50 and 65 years. The performance status varied considerably in different studies. Full details are tabulated in the report and the update (see Other Publications of Related Interest).

Outcomes assessed in the review
The primary outcomes were 1-year survival and quality of life. The authors did not describe all the outcomes and measurement instruments in the individual studies.

How were decisions on the relevance of primary studies made?
The studies were selected by three medical oncologists and the Ontario Cancer Treatment Practice Guidelines Initiative project co-ordinator. Apart from the general inclusion criteria, the authors do not report how the papers were selected for the review.

Assessment of study quality
The authors do not report the method used to assess validity, or how the validity assessment was performed.
Data extraction
The authors do not state how the data were extracted for the review, or how many of the reviewers performed the data extraction.

Data were extracted on the following: study characteristics, i.e. design and subgroup analyses; patient characteristics, i.e. age and performance status; treatment regimens; response; overall survival; median survival time; toxicity; and quality of life.

Methods of synthesis
How were the studies combined?
The authors did not pool the meta-analysis studies further because they included many of the same trials. Instead, the authors combined the data from the 11 trials included in the meta-analyses. The trials identified during the update were considered too clinically heterogeneous to pool: 5 trials tested single-agent chemotherapy regimens, 2 involved cisplatin-based combination regimens and 1 involved a carboplatin combination regimen. A narrative synthesis was provided.

The authors do not report methods for weighting the studies or for assessing publication bias.

How were differences between studies investigated?
Heterogeneity was assessed for survival in the original 11 trials (test for heterogeneity, P<0.0001; test for interaction, chi-squared 11.67, P=0.003). Descriptive comparisons were used to assess other differences between the studies. For example, the authors compared the methods used to assess the treatment effects and the types of data used in the original meta-analyses. The trials identified during the update were clinically heterogeneous, i.e. they used different drugs and regimens. No formal method of assessing heterogeneity was reported for the updated data.

Results of the review
The original review identified 3 meta-analyses, which included many of the same trials. In total, 11 randomised trials with 1,190 people were included. The update identified one further meta-analysis and 8 additional randomised trials (n=712).

The authors provided a detailed narrative summary of the findings, including statistics from individual studies. A detailed description of the findings can be obtained by accessing the full text online (see Other Publications of Related Interest).

Based on the 11 trials in the original review, the pooled hazard ratios for 1-year survival (supportive care versus supportive care plus chemotherapy) were:
1.26 (95% confidence interval, CI: 0.98, 1.66) for long-term alkylating agents; 0.87 (95% CI: 0.64, 1.20) for Vinca alkaloids-etoposide; 0.73 (95% CI: 0.63, 0.85) for cisplatin-based regimens; and 0.84 (95% CI: 0.74, 0.95) for all chemotherapy regimens.

The most beneficial strategy appeared to be cisplatin-based regimens, with a median increase in survival of 1.5 months (relative risk reduction for death, 27%). After one year, there was no survival benefit for people receiving any chemotherapy regimen.

Quality of life was not assessed fully in those studies included in the original review. The update suggested that patients receiving chemotherapy have improved quality of life in comparison with those receiving supportive care alone. The overall summary statistics were not provided.

Cost information
The authors estimated the drug acquisition costs (Canadian $) of common chemotherapy regimens as follows:
for vindesine-cisplatin (high-dose), $1,950;
for ifosfamide-cisplatin-etoposide, $850;
for mitomycin-ifosfamide-cisplatin, $750;
for vinorelbine-cisplatin, $590;
for etoposide-cisplatin, $400;
for mitomycin-vinblastine-cisplatin (high-dose platinum), $300;
for mitomycin-vinblastine-cisplatin (low-dose platinum), $250; and
for vinblastine-cisplatin, $50.

Based on one randomised trial, the authors suggested that the addition of radiotherapy to supportive care cost $12,610 per life-year gained.

Authors' conclusions
Cisplatin-based chemotherapy may slightly increase survival for people with metastatic non-small-cell lung cancer and good performance status. Medically suitable patients can be considered for chemotherapy in addition to other supportive care, including palliative radiotherapy. The optimal chemotherapy regimen remains unclear.

CRD commentary
This review, which is regularly updated (see Other Publications of Related Interest), addressed a clear question. The participants, intervention, outcomes and study design were clearly described. The design and results of the individual studies were clearly presented in tabular format. However, there were some omissions in the report.

The search strategy was adequate and clearly described. To enhance quality, additional databases could have been searched and unpublished literature could have been included.

Details of the review process, including systems for assessing relevance and validity, were not reported in depth. The review included randomised trials and meta-analyses, but no validity assessment tool was described. The authors did not provide any indication of how well the trials were designed and conducted to minimise bias.

With regards to the data extraction and analysis, the characteristics of the studies were presented adequately in tabular format. The meta-analysis and narrative summary used to combine the studies were appropriate. However, the review was very broad, including a wide range of different chemotherapy regimens; this made it difficult to pool the data adequately. The authors did not examine statistical heterogeneity in any depth, nor did they perform subgroup analysis to assess whether the studies of individual drugs found heterogeneous effects. This is particularly important for cisplatin regimens as the authors concluded that these have some benefits.

Information from the update was not integrated into the report, it was presented in separate sections instead. This made the updated review more difficult to read and interpret. For clarity, it may be helpful to 'rewrite' the review each time it is updated so that all of the studies are integrated into one analysis.

Overall, the authors' conclusion that cisplatin-based regimens may benefit people with metastatic non-small-cell lung cancer seems appropriate based on the data presented, although a more comprehensive exploration of heterogeneity may be warranted. The survival advantage is unlikely to be clinically meaningful (mean increase in survival, 1.5 months), but there may be improvements in quality of life.

Implications of the review for practice and research
Practice: The authors state that chemotherapy, especially cisplatin-based regimens, can be considered in addition to supportive care for people with stage IV non-small-cell lung cancer. Chemotherapy appears to confer a small survival benefit and improve quality of life. The survival benefit may be minimal, so physicians should discuss the benefits and
potential harms with patients. Chemotherapy with long-term alkylating agents is not recommended and may be detrimental.

Research: The authors did not explicitly recommend further research, although they described several gaps in the existing evidence.

Reviewer's statement: Based on the gaps in knowledge identified by the review, there is a need for further research into the optimal chemotherapy regimen and the cost-effectiveness of different chemotherapy regimens. Further work on quality of life and heterogeneity analyses might also be useful.

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**Other publications of related interest**
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