Efficacy of gemcitabine plus platinum chemotherapy compared with other platinum containing regimens in advanced non-small-cell lung cancer: a meta-analysis of survival outcomes


CRD summary
In a meta-analysis of 13 studies (over 4,000 patients), gemcitabine-containing treatment for advanced non-small-cell lung cancer provided more benefit than non-gemcitabine treatment regimens. The survival benefit was less than one month. Without sufficient detail on the review process, it is difficult to evaluate the reliability of the authors’ conclusions.

Authors' objectives
The aims of the work were to quantify the treatment effect of gemcitabine plus a platinum agent (cisplatin or carboplatin) in the treatment of advanced non-small-cell lung cancer (NSCLC), and to compare the combination with other regimens that are currently in use.

Searching
The authors searched Cancerlit, Current Contents, EMBASE, MEDLINE and PREMEDLINE from 1980 to December 2002, and the annual proceedings of the American Society of Clinical Oncology (1995 to 2002). In addition, ClinicalTrials.gov, Current Controlled Trials and the clinical trial database of Eli Lilly and Company (Indianapolis, USA) were searched for unpublished trials. Review bibliographies were searched manually and principal clinical investigators were contacted for any additional information beyond that published. The search strategy was not presented, and only trials reported in English were eligible for inclusion.

Study selection
Study designs of evaluations included in the review
Published and unpublished randomised controlled trials (RCTs) were eligible for inclusion in the review.

Specific interventions included in the review
Studies that assessed gemcitabine plus cisplatin or carboplatin in the treatment of NSCLC, in comparison with any non-gemcitabine platinum-containing treatment regimen, were eligible for inclusion. The comparators in the included studies were single-, double- or triple-drug regimens of etoposide, vinorelbine, mitomycin, ifosfamide, vinblastine, paclitaxel and docetaxel. The combinations and dosages varied in the included studies.

Participants included in the review
Studies with patients with advanced NSCLC were eligible for inclusion; other than that, no inclusion criteria were specified. The review included participants being treated for histologically or cytologically confirmed NSCLC. In the included studies, the patients were aged from 23 to 84 years and the proportion of males ranged from 45 to 95%. All of the included patients were being given chemotherapy for the first time in 12 months.

Outcomes assessed in the review
The primary outcome of interest was overall survival. Progression-free survival, absolute treatment benefit and median survival were also reported.

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

Assessment of study quality

Database of Abstracts of Reviews of Effects (DARE)
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The authors assessed randomisation, follow-up and the level of data reporting. The authors did not state how the papers were assessed for validity, or how many reviewers performed the validity assessment.

**Data extraction**
The authors did not state how the data were extracted for the review, or how many reviewers performed the data extraction.

Principal investigators were asked to provide summary information; the results published in papers were only used where these data were not forthcoming. The log hazard ratio (HR) and its variance or confidence interval (CI) were recorded. Where these were not reported, they were estimated from published Kaplan-Meier survival curves using standard methodology.

**Methods of synthesis**

How were the studies combined?
Individual HRs were combined using a fixed-effect meta-analysis based on inverse variance weighting. In the presence of statistical heterogeneity, a random-effects model was used. Pooled survival curves for both treatment arms were produced, and survival probabilities were extracted at a common series of time points and pooled. The absolute treatment benefit was calculated as the percentage difference between survival probabilities at a given time since the start of treatment. Median survival times were estimated from survival curves, then combined on a log scale to produce the pooled median survival.

How were differences between studies investigated?
Statistical heterogeneity between studies was investigated using the chi-squared Q test.

**Results of the review**
The review included 13 studies (4,556 participants) for the analysis of overall survival and 11 studies (4,249 participants) for progression-free survival.

Overall survival was significantly better in the gemcitabine group than in the comparator group (HR 0.90, 95% CI: 0.84, 0.96, P<0.001). Median survival was 9.0 months (95% CI: 8.6, 9.3) in the gemcitabine group and 8.2 months (95% CI: 7.9, 8.6) in the comparator group. The corresponding absolute benefit was 3.9% at one year and 2.6% at two years.

Progression-free survival was significantly better in the gemcitabine group than in the comparator group (HR 0.88, 95% CI: 0.82, 0.93, P<0.001). Median progression-free survival was 5.1 months (95% CI: 4.9, 5.3) in the gemcitabine group and 4.4 months (95% CI: 4.2, 4.6) in the comparator group. This corresponds to an absolute benefit of 4.2% at the 1-year follow-up.

For neither outcome was there a difference in the benefit of gemcitabine when compared with either first- and second- or third-generation platinum-based regimens.

The results were essentially unchanged when analyses were restricted to comparisons of gemcitabine with non-gemcitabine doublet regimens, or when carboplatin-based agents were excluded from the comparison arm.

**Authors' conclusions**
The gemcitabine-platinum treatment regimens provided more benefit to patients with advanced NSCLC than non-gemcitabine platinum-based regimens.

**CRD commentary**
The review addressed a clearly defined research question. The search strategy was limited to studies reported in English language reports, which could have introduced bias into the results of the review if trials with less positive results were
published in the non-English language literature. There were insufficient details on the study selection and data extraction processes, so no judgement can be passed as to the extent to which the reviewers attempted to minimise bias and errors. Since no results of a validity assessment were presented, it is not possible to make any comment on the reliability of the presented results.

The role of the pharmaceutical company that makes gemcitabine was not fully clear. Although the review was written without involvement of an Eli Lilly and Company employee, the statement 'the interpretation is in line with the overall findings of the analysis' in relation to the role of Eli Lilly and Company ('Acknowledgements' section of the original article) suggests that the company may have played a role in the interpretation of the results.

The authors' conclusions follow from their results, although it is important to remember the small absolute size of the survival benefit (0.8 months; 24 days).

**Implications of the review for practice and research**
The authors did not state any implications for practice or further research.

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