Combination of chemotherapy without platinum compounds in the treatment of advanced non-small cell lung cancer: a systematic review of phase III trials

Barlesi F, Pujol J L

CRD summary
This review concluded that there was insufficient evidence to draw firm conclusions about the equivalence of or differences between non-platinum and platinum-based doublet regimens for patients with non-small-cell lung cancer. Considering the limitations of the review, the authors' conservative conclusions seem appropriate.

Authors' objectives
To compare non-platinum with platinum-based doublet regimens for patients with non-small-cell lung cancer (NSCLC).

Searching
PubMed was searched from 1994 to the end of 2004 for studies published in the English language; the search terms were reported. The reference lists of retrieved papers were screened. Searches of available abstracts from the last meetings of the American Society of Clinical Oncology, International Association for the Study of Lung Cancer and the European Society for Medical Oncology, were also conducted. Attempts were made to contact authors of unpublished studies for updated information. The authors stated that three potentially relevant studies were excluded since they were only published in Chinese.

Study selection
Study designs of evaluations included in the review
Phase III randomised controlled trials (RCTs) were eligible for inclusion. The studies had to report clear methods of randomisation and have a median follow-up of at least 2 years.

Specific interventions included in the review
Studies that compared a platinum-based regimen containing cisplatin or carboplatin plus a third-generation anti-cancer agent with a regimen containing at least one third-generation anti-cancer drug were eligible for inclusion. The included studies used various platinum-free regimens, such as gemcitabine-vinorelbine and gemcitabine-taxane doublets (details of all regimens were reported).

Participants included in the review
Studies of previously untreated patients with histologically or cytologically proven advanced NSCLC were eligible for inclusion. No details of the participants in the included studies were given.

Outcomes assessed in the review
Inclusion criteria for the outcomes were not specified. The review assessed partial and complete response, overall survival at 1 year, toxic deaths, and grades 3-4 haematological toxicity and non-haematological toxicity.

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

Assessment of study quality
The studies were assessed for the following: definition of hypothesis in statistical section; description of patient characteristics with respect to prognostic factors; definition of treatment protocol and survival; methods used to assess response and toxicity and the number of evaluable patients; length of follow-up and loss to follow-up; method of
randomisation; and use of an intention-to-treat analysis. Two reviewers independently assessed some validity criteria.

**Data extraction**

Two reviewers independently extracted the data. The percentage response rate and median survival time were extracted from each study.

**Methods of synthesis**

*How were the studies combined?*

The studies were grouped by type of non-platinum-based regimen and combined in narrative.

*How were differences between studies investigated?*

Some study details were tabulated and some differences between the studies were mentioned in the text.

**Results of the review**

Fourteen RCTs were included (total number of patients not reported). Although details of 14 studies were provided in the tables (n=5,931), other studies seem to have been discussed in the text.

The results of the quality assessment were not reported and study quality was not considered during the review. However, the authors did state that all but one of the studies were powered to assess superiority of the non-platinum-based regimen.

Gemcitabine-vinorelbine doublets versus vinorelbine alone (2 phase III studies, n unreported).

One study suggested that the combination improved outcomes compared with vinorelbine alone. The other RCT found no difference between treatments.

Gemcitabine-vinorelbine doublets versus cisplatin-containing regimens (4 RCTs, n=1,687).

Two RCTs showed no difference in survival between treatments. The third study showed a trend toward shorter survival with the gemcitabine-vinorelbine regimen, while preliminary results from the fourth RCT showed significantly improved 1-year survival with the gemcitabine-vinorelbine regimen. All 4 RCTs reported a higher incidence of toxicity with the cisplatin-based regimen.

Gemcitabine-paclitaxel doublet (3 RCTs, n=1,463).

Two RCTs showed no difference in survival between the gemcitabine-taxane doublet and carboplatin-paclitaxel or carboplatin-gemcitabine. The third RCT showed shorter overall survival with the gemcitabine-taxane doublet in comparison with paclitaxel-cisplatin or gemcitabine-cisplatin. One RCT reported no difference in toxicity between the gemcitabine-taxane doublet and carboplatin-paclitaxel or carboplatin-gemcitabine. Another RCT reported increased myelosuppression with carboplatin-gemcitabine.

Gemcitabine-docetaxel doublets (4 RCTs, n=1,897).

All 4 studies showed no difference in survival between treatments. Three studies reported less myelosuppression with docetaxel-gemcitabine; one of these studies reported increased oedema and fluid retention with docetaxel-gemcitabine. Preliminary results from the fourth RCT showed no difference in toxicity between treatments.

Other treatment combinations (3 RCTs, n=884).

None of the studies showed any difference in survival between gemcitabine-epirubicin versus cisplatin-gemcitabine (1 study), gemcitabine-ifosfamide versus platinum-based regimens (1 study), or paclitaxel-vinorelbine versus paclitaxel-carboplatin (1 study). All 3 studies showed increased haematological toxicity with the non-platinum-containing regimen.
Authors’ conclusions
There was insufficient evidence to draw firm conclusions about the equivalence of or differences between treatments in clinical outcomes.

CRD commentary
The review addressed a clear question that was defined in terms of the participants, intervention and study design. There were no inclusion criteria for the outcomes. Only a single database was searched, although this was supplemented by other relevant sources. Attempts were made to locate unpublished studies, thus limiting the possibility of publication bias. The restriction to English language studies might have introduced language bias. The authors identified three potentially relevant studies published in Chinese that were excluded; however, two of these were phase II studies and should not, therefore, have been deemed to meet the inclusion criteria. Methods were used to minimise errors and bias in the assessment of some aspects of validity and extraction of data, but it was unclear whether similar steps were taken during the study selection process. Validity was assessed using established criteria but the results of the assessment were not reported, hence the quality of the included studies was unknown and the impact of quality on the results of the review was not investigated. There would seem to be some discrepancy between the text and tables regarding the primary studies included. The tables presented details of 14 studies, while additional studies for which no details were provided seem to have been discussed in the text. Therefore, it is difficult to verify the results reported in the text of the review. The narrative synthesis of the studies was appropriate, but potential reasons for differences in results between the studies were not discussed. Considering the limitations of the review, the authors' conservative conclusions seem appropriate.

Implications of the review for practice and research
Practice: The authors did not state any implications for practice.

Research: The authors stated that future studies comparing new doublet regimens with classical platinum-based regimens could assess quality of life, treatment costs, time without symptoms and toxicity. Future studies could also assess platinum-free regimens in patients with contraindications for cisplatin.

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