Activity of chemotherapy and immunotherapy on malignant mesothelioma: a systematic review of the literature with meta-analysis


Authors' objectives
To assess the effectiveness of different chemotherapy and immunotherapy regimens for patients with malignant mesothelioma.

Searching
MEDLINE, HealthSTAR and the National Cancer Institute's databases were searched for articles published in English, French or Dutch between 1965 and June 2001; no search terms were reported. In addition, references found in papers, books, reviews or known to the authors were assessed for inclusion. Studies that had been reported in abstract form only were excluded.

Study selection
Study designs of evaluations included in the review
Randomised or single-arm phase II or phase III trials with a minimum of 14 participants were eligible for inclusion. Where less than 14 participants were included in a phase II trial, the study was included if at least one objective response was observed when targeting a response rate of 20%.

Specific interventions included in the review
Studies that assessed single or combination cytotoxic and/or immunomodulatory agents, administered by systemic or local routes, were eligible for inclusion. The included trials were separated into four groups according to the treatment regimens assessed. Group 1 (n=20), assessed cisplatin but not doxorubicin. Group 2 (n=8) examined the effectiveness of doxorubicin without cisplatin. Group 3 (n=6) assessed a combination including both cisplatin and doxorubicin. Group 4 (n=56) assessed regimens without cisplatin or doxorubicin, and which included ifosfamide and cyclophosphamide, vinca-alkaloids (vincristine, vinblastine, vindesine and vinorelbine), etoposide, gemcitabine, amsacrine, methotrexate, trimetrexate, edatrexate, diaziquone, CB 3717, aciclovir, 5-fluorouracil, paclitaxel, docetaxel, irinotecan, topotecan, mitomycin C and 5-azacytidine.

Participants included in the review
Participants with malignant mesothelioma were eligible for inclusion.

Outcomes assessed in the review
The inclusion criteria for outcome assessment measures were not reported. The actual outcome that was assessed in the review was the response rate.

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
The validity of the primary studies was assessed using an adaptation of the methodological evaluation scale of the European Lung Cancer Working Party (see Other Publications of Related Interest). The scale allows each trial to score a maximum of 100 points. A copy of the scale was presented in an appendix. A team of eight reviewers independently assessed the quality of the included studies. Any disagreements were resolved by consensus, with at least six members of the team present at consensus resolution.

Data extraction
The authors did not state how the data were extracted for the review, or how many reviewers performed the data extraction. Data on the number of participants, intervention, the quality assessment score, the response rate and 95% confidence intervals (CIs) were tabulated.

The authors stated a priori that it would be assumed that an intervention was potentially clinically useful if the objective response rate was at least 20% in a trial. A study would be considered negative if the upper limit of the 95% CI was less than or equal to 20%. Studies were considered positive if the lower limit of the 95% CI was greater than 20%, and as not conclusive but potentially positive if the upper limit of the 95% CI was greater than 20% but the lower limit was less than 20%. Response rates and 95% CIs were calculated for each intervention.

Methods of synthesis
How were the studies combined?
The authors categorised trials, according to the reported response rates, as either negative, true positive or potentially positive. The results of the potentially positive and true-positive trials were combined and named 'positive trials'. The response rates for each treatment group were then combined in a meta-analysis.

How were differences between studies investigated?
Differences between the studies were investigated using chi-squared tests. The authors also assessed the influence of study quality, methods of tumour response assessment, type of regimen (monotherapy versus combination) and year of publication.

Results of the review
Eighty-five studies (overall n=2,317) were included: 3 randomised phase II studies and 82 single-arm phase II studies. The analysis was based on 88 trial arms.

Among the 88 eligible trial arms, the authors reported that 35 were negative, 5 true positive and 48 potentially positive in terms of the anti-tumoural response. No significant differences in methodological scores were found between the positive and negative trials in terms of global quality score, or internal or external validity scores. Furthermore, no significant difference was observed between the four groups according to the type of therapeutic regimen. However, there was a significant quality difference between the single and combination agent therapies: median values were 52.2 and 63.3% (P=0.01), respectively, for the global score, 36.7 and 56.7% (P=0.01) for internal validity and 66.7 and 72.5% (P=0.01) for external validity.

A significant difference was observed between the four types of regimen, as defined by the presence or not of cisplatin and/or doxorubicin (P<0.001). Group 3 (cisplatin with doxorubicin) had a better overall response rate than group 1 with cisplatin alone (28.5% versus 23.2%; P=0.22) and group 2 with doxorubicin alone (28.5% versus 11.3%; P<0.001). Group 1 had a significantly better response rate than group 4 which had neither cisplatin nor doxorubicin (23.5% versus 11.6%; P<0.001). Group 1 had a significantly better response rate than group 2 (23.2% versus 11.3%; P<0.001). No significant differences were observed between the response rates of groups 2 and 4 (11.3% versus 11.6%; P=0.97).

The results between cisplatin- and carboplatin-containing regimens significantly favoured treatment with cisplatin, with response rates of 24% versus 11.6% respectively (P=0.004). The comparison between doxorubicin and 4-epirubicin showed a significant difference in favour of doxorubicin (18.4% versus 9.1%; P=0.02), but when studies containing cisplatin were withdrawn from the comparison, the difference was no longer significant (11.3% versus 9.1%; P=0.70). Comparisons of combination therapy with monotherapy regimens showed significantly better response rates with combination-agent regimens relative to single-agent regimens (22.6% versus 11.6%; P<0.001). Comparisons of the methods used to detect tumour response indicated that there was a significant difference according to the method of response assessment, with studies using computed tomography having better scores than studies using other methods. These studies were also significantly more recent.

Authors' conclusions
The results of the review suggested that the most active chemotherapeutic agent, in terms of anti-tumoural response rate, was the combination of cisplatin and doxorubicin and the best single agent was cisplatin, with objective response
rates of about 28 and 23%, respectively.

**CRD commentary**
The review question was broad, but well defined in terms of the intervention, participants and study designs. A number of sources were searched for relevant studies and efforts were made to minimise language bias. However, as only trials published in full were included, the review may be subject to publication bias. The methods used to assess the studies for inclusion and to extract the data were not reported. It is therefore not known whether any efforts were made to minimise errors and bias in the review process. The quality of the studies was assessed. The studies were combined appropriately in a meta-analysis, with differences between the studies being discussed. Overall, although some methodological aspects of the review process were not reported, the authors' conclusions appear valid.

**Implications of the review for practice and research**

Practice: The authors did not state any implications for practice.

Research: The authors stated that, given the low response rates and high mortality rates associated with malignant mesothelioma, there is a need for trials with new drugs and innovative regimens. On the basis of the results obtained in the review, they further suggested that the combination therapy of cisplatin and doxorubicin should be used as the reference arm.

**Bibliographic details**

**PubMedID**
12399121

**Other publications of related interest**

**Indexing Status**
Subject indexing assigned by NLM

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**Record Status**
This is a critical abstract of a systematic review that meets the criteria for inclusion on DARE. Each critical abstract
contains a brief summary of the review methods, results and conclusions followed by a detailed critical assessment on the reliability of the review and the conclusions drawn.