The use of chemotherapy in patients with advanced malignant pleural mesothelioma: a clinical practice guideline
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CRD summary
This review concluded that the stronger evidence supported the use of cisplatin and pemetrexed for the treatment of advanced malignant pleural mesothelioma. The possibility of missing relevant trials, lack of assessment of trial quality, and increases in adverse events, mean that these conclusions should be interpreted with caution.

Authors' objectives
To assess whether palliative chemotherapy improves quality of life, symptom control and survival for patients with advanced malignant pleural mesothelioma, and to identify which chemotherapeutic agents (or combinations of agents) have shown the highest response rates.

Searching
The following databases were searched for English-language studies included up to October 2005: MEDLINE, EMBASE, CANCERLIT and The Cochrane Library. Search terms were reported. Other sources, including the conference proceedings of the American Society of Clinical Oncology from 1997 to 2005, were searched. Reference lists of relevant studies were searched for additional studies.

These searches were updated to September 2012.

Study selection
Randomised controlled trials (RCTs) comparing chemotherapy with best supportive care or another chemotherapy regimen; phase II clinical trials evaluating chemotherapy (single agent or a combination); and phase II clinical trials evaluating chemotherapy, combined with immunotherapy, such as interferon and interleukin; were eligible for inclusion. Eligible participants were patients with malignant pleural mesothelioma or those with both pleural and peritoneal malignant mesothelioma. Trials that primarily assessing immunotherapy, and trials of chemotherapy combined with surgery, radiotherapy or both, were excluded. The outcomes of interest were the treatment response, survival, quality of life, and symptom control.

Most of included trials were non-comparative and phase II; the rest were RCTs. Most trials evaluated non-platinum-based single-agent chemotherapy; the rest evaluated non-platinum-based combination chemotherapy, platinum-based chemotherapy (single agent or a combination), or chemotherapy plus immunotherapy. Two large RCTs compared cisplatin alone with a cisplatin combination; the other RCTs were small or medium sized. There were wide variations in the inclusion and exclusion criteria, within the trials. Many trials recruited patients who had received chemotherapy before the trial. The criteria used to assess treatment response varied across the trials; most used the World Health Organization's criteria (based on the product of two measurements; bidimensional measurement).

Two reviewers performed study selection.

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

Data extraction
The data were extracted on the response rate, time to progression and survival. The authors did not state how many reviewers extracted these data.

Methods of synthesis
Due to the considerable variation in chemotherapy regimens, the results of the RCTs were synthesised in a narrative. Where appropriate, the response rates from the non-comparative phase II trials were pooled, on the basis of four categories: non-platinum single-agent chemotherapy, non-platinum combination therapy, single-agent platinum therapy,
combination platinum therapy, and chemotherapy plus immunotherapy. The pooled response rates, with 95% confidence intervals, were calculated.

**Results of the review**

Eight RCTs and 111 non-comparative phase II trials were included. The RCTs assessed 1,078 patients (range 16 to 458). The non-comparative phase II trials were generally small (3,193 patients; range seven to 105). No trials comparing chemotherapy with best supportive care were found.

One large RCT (448 patients) showed that, compared with cisplatin alone, the combination of pemetrexed and cisplatin was associated with a significantly higher response rate (41% combined versus 17% alone, p<0.001), longer time to progression (5.7 months combined versus 3.9 months alone, p=0.001), and survival (12.1 months combined versus 9.3 months alone; HR 0.77, p=0.02). Combination therapy significantly improved patients’ quality of life on the Lung Cancer Symptom Scale, dyspnoea (p=0.004) and pain (p=0.017) indices. Combination therapy was associated with more events of Grade 3 and 4 toxicity: neutropenia (28% combined versus 2% alone), thrombocytopenia (6% combined versus none alone), vomiting (13% combined versus 4% alone) and febrile neutropenia (2% combined versus none alone).

The other large RCT (250 patients) showed that, compared with cisplatin alone, raltitrexed plus cisplatin was associated with a significant improvement in survival (11.4 months combined versus 8.8 months alone; HR 0.76). The combination regimen also had a higher response rate (23.6%) compared with cisplatin alone (13.6%) and longer progression-free survival (5.3 months combined versus 4.0 months alone; HR=0.78), but these outcomes were not statistically significant.

The remaining RCTs compared different chemotherapy regimens. As they had small-to-medium sized samples, they lacked the power to reach any meaningful conclusions.

The 111 non-comparative phase II trials evaluated various chemotherapy regimens for the treatment of malignant pleural mesothelioma. Compared with non-platinum as single agents (3.6% to 9.0%; 51 trials) or combined (10.4%, 12 trials), a higher pooled response rate was achieved in trials of platinum therapy as a single agent (14.3%, nine trials) or combined (24.9%, 19 trials). The pooled response rate of single-agent carboplatin (10.1%, three trials) was lower than cisplatin (20.0%, five trials). Further results for different groups of chemotherapy were reported.

The updated search found four RCTs, with 1,500 patients (range 187 to 661). These did not alter the original conclusions.

**Authors’ conclusions**

The stronger evidence supported the use of cisplatin and pemetrexed, but raltitrexed and cisplatin could be considered, if pemetrexed was not available.

**CRD commentary**

The review question was supported by appropriate inclusion criteria. Various relevant sources were searched. The search was restricted to reports in English, so relevant trials in other languages may have been missed. Attempts were made to minimise error and bias in study selection, but it was unclear whether data extraction was also duplicated.

A formal quality assessment was not performed, but the authors did discuss some aspects of trial quality, such as sample size. Most of the included trials were small and not powered to detect differences. Given the diversity in the chemotherapy regimens, in the included RCTs, a narrative synthesis was appropriate. The method used to pool the non-comparative phase II trials appears to have been appropriate, as it was based on the different chemotherapy agents. However, the comparison between non-platinum regimens and platinum regimens was based on an indirect comparison, which may not be valid due to considerable variation in patient characteristics between these trials.

The possibility of missing relevant trials and the lack of assessment of trial quality, mean that the authors’ conclusions should be interpreted with caution. Also, the conclusions stated the benefits of cisplatin plus pemetrexed or raltitrexed, but there was an increase in adverse events with these treatments.

**Implications of the review for practice and research**
Practice: The authors recommended cisplatin and pemetrexed for the treatment of advanced malignant pleural mesothelioma. The routine substitution of carboplatin for cisplatin was not recommended. Clinicians should select treatment on the basis of the options available, convenience, goals of therapy and potential adverse effects.

Research: The authors stated that patients with mesothelioma should be encouraged to participate in clinical trials for the treatment of advanced malignant pleural mesothelioma.

Funding
Supported by the Ontario Ministry of Health and Long-Term Care, Canada.

Bibliographic details

Original Paper URL

Indexing Status
Subject indexing assigned by NLM

MeSH
Antineoplastic Combined Chemotherapy Protocols /administration & dosage /adverse effects; Cisplatin /administration & dosage /adverse effects; Clinical Trials, Phase III as Topic; Dose-Response Relationship, Drug; Glutamates /administration & dosage /adverse effects; Guanine /administration & dosage /adverse effects /analogs & derivatives; Maximum Tolerated Dose; Mesothelioma /drug therapy /mortality /pathology; Neoplasm Invasiveness /pathology; Patient Selection; Pleural Neoplasms /drug therapy /mortality /pathology; Practice Guidelines as Topic; Prognosis; Quinazolines /administration & dosage /adverse effects; Randomized Controlled Trials as Topic; Survival Analysis; Thiophenes /administration & dosage /adverse effects; Treatment Outcome

AccessionNumber
12008008038

Date bibliographic record published
09/04/2008

Date abstract record published
05/12/2014

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.