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Review article

A systematic review and meta-analysis of second-line therapies for treatment of mesothelioma

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ABSTRACT

Introduction: Advanced malignant pleural mesothelioma (MPM) is generally treated with platinum/pemetrexed-based first-line therapy. Once the disease progresses, evidence for the efficacy of palliative treatments is lacking, and platinum re-challenge or single-agent chemotherapy are commonly used. To assess the effects of cytostatic or targeted therapy for treating MPM, we performed a systematic review and meta-analysis.

Material and methods: PubMed, the Cochrane Library, and Embase databases were searched to identify published articles on second-line treatments for recurrent or advanced mesothelioma. Inclusion criteria were publication in the English language, describing clinical trials with 20 or more patients, and evaluability for efficacy and for receiving second-line systemic therapies. Data were pooled using number of events/number of evaluable patients, median overall survival (OS) and progression-free survival (PFS), according to a fixed or random effect model. Pooled median OS was the primary endpoint.

Results: A total of 49 eligible studies (n = 3938 patients; range, 12–400) were identified. Median progression-free survival (PFS) was 3.4 months (95%CI 2.87–3.93). Median pooled OS was 7.86 (95%CI 7.01–8.72). The pooled overall response rate (ORR) was 8.63% (95%CI 6–11.26), and the pooled disease control rate (DCR) was 54.8% (95%CI 48.9–60.6). Median pooled OS with platinum- and pemetrexed-based chemotherapy were 7.93 and 7.78 months, respectively.

Conclusions: There remains uncertainty about the ideal second-line agent for MPM. Based on this meta-analysis, palliative chemotherapy or other experimental agents can be considered for patients with MPM who desire further treatment after their disease has progressed, during or after first-line therapy.

1. Introduction

Malignant pleural mesothelioma is a rare neoplasm that arises from the mesothelial surfaces of the pleural cavity. It generally has poor prognosis, with a median survival of four to 13 months for untreated patients, and six to 18 months for treated patients, regardless of the therapeutic approach [1]. Primary debulking surgery is reserved for those with resectable disease, limited to one emithorax. Otherwise, for all other patients, palliative chemotherapy, with platinum-based chemotherapy (including pemetrexed) is typically prescribed and increases overall survival (OS) by roughly three months, compared to single-agent cisplatin, in cases where disease is either unresectable, or where patients are not otherwise candidates for potentially curative surgery [2]. Recently, the addition of bevacizumab to this standard doublet has increased OS by 2.7 months, compared to cisplatin/pemetrexed only [3].

Once the disease recurs, the are no approved standard drugs or regimens for second-line therapy. Rechallenging using the same upfront therapy, platinum-based therapy including gemcitabine or other single-agent chemotherapies (gemcitabine, vinca alkaloids, or anthracyclines), or enrollment in clinical trials are possible treatment options. The most extensive data pertaining to second-line settings is derived from pemetrexed, which can increase progression-free survival (PFS), but not OS, compared to best supportive care only [4]. On the other hand, interesting new data have become available regarding targeted therapies and immunotherapy.

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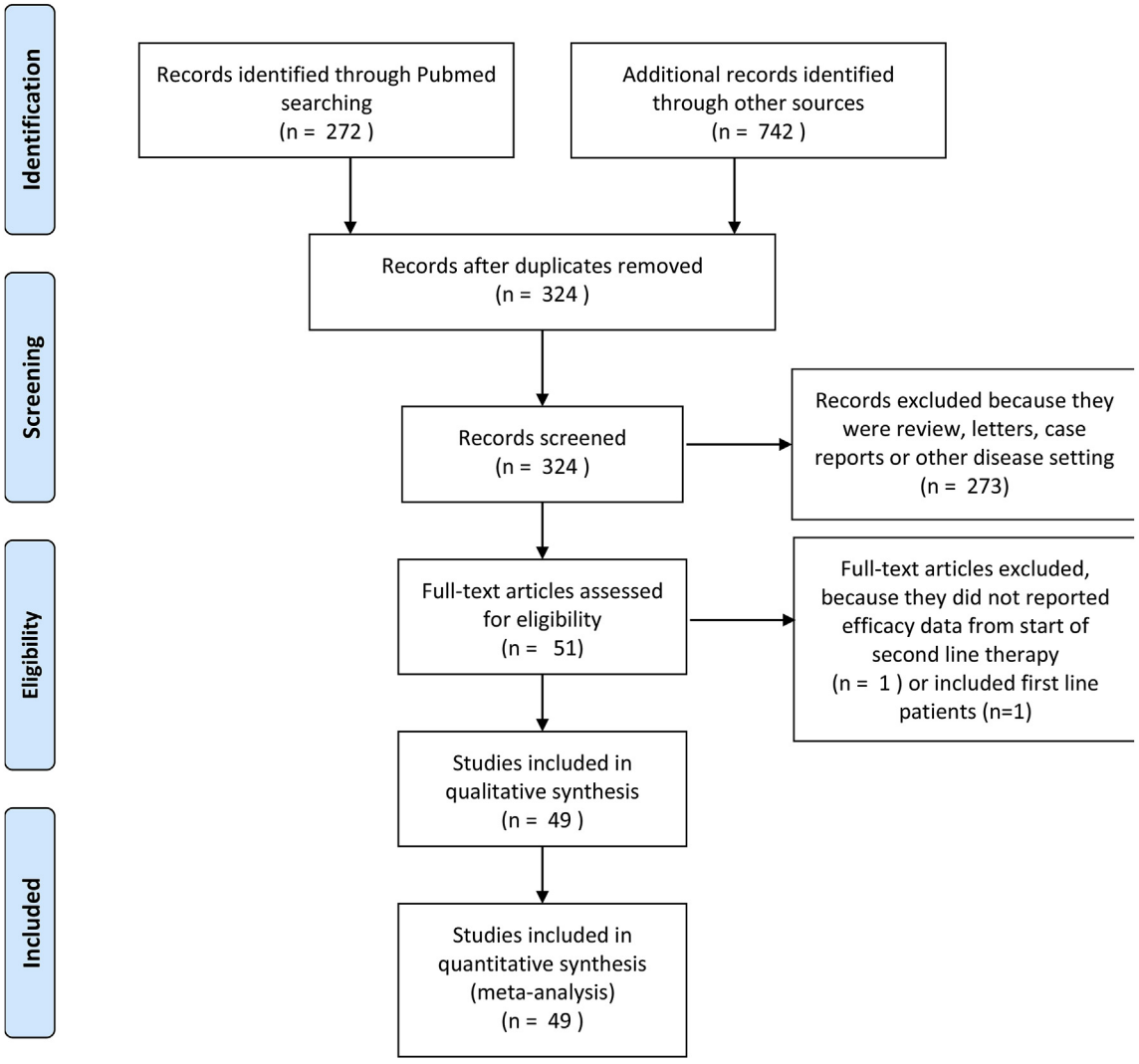

Fig. 1. Flow diagram of included studies.

Due to the limited availability of relevant data from randomised trials, summarising the available evidence of second-line therapies for malignant pleural mesothelioma can increase insight into whether chemotherapy and targeted therapies are potentially suitable for pre-treated individuals with advanced disease. We have designed this meta-analysis with the aim to aggregate the largest number of existing studies employing salvage therapies. We also performed sub-group analyses wherever possible to investigate whether the overall results were consistent across sub-sets of treatments and participants, due to the possible heterogeneity of the included studies in terms of intervention and participant groups.

2. Material and methods

2.1. Search strategy and inclusion criteria

PubMed, the Cochrane Library, and Embase databases were searched to identify published articles on second-line treatment for recurrent or advanced mesothelioma. The search used the terms 'mesothelioma' and ('second-line' OR ('recurrent' or 'relapsed' or 'progressed'))). Inclusion criteria were publication in the English language, describing clinical trials with 20 or more patients evaluable for efficacy and whit data available for efficacy of second-line systemic therapies. Publications in other languages or those that were available only in abstract form were excluded. Case reports or small case series were also excluded, as were pre-clinical studies or reviews, and studies adopting locoregional treatments alone, or that were associated with systemic agents, were also excluded. A manual review of the references of retrieved articles was performed to locate additional relevant publications.

2.2. Data extraction and statistical analysis

Data describing the demographics of the patient population treated, as well as the efficacy of all treatments, were extracted from the included studies by one author (FP), and then reviewed by a second author (AG) to ensure accuracy. Discrepancies were discussed with a third author for consensus. The demographic characteristics of patients treated consisted of country, median age, and previous platinum-based chemotherapy for advanced disease. Response rate (RR), defined as the sum of complete (CR) and partial (PR) responses, disease control rate (DCR), defined as the sum of RR and stable disease (SD), median progression-free survival (PFS) or time-to-progression (TTP), as well as median OS, with their 95% confidence intervals (95% CI), were