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Malignant mesothelioma: New insights into a rare disease

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ABSTRACT

Malignant pleural mesothelioma (MPM) is a rare and aggressive malignancy of the pleura associated with exposure to asbestos. Its incidence is anticipated to increase over the next 10 years in both Europe and the developing nations. In advanced disease, chemotherapy is the cornerstone of treatment, especially platinum-containing regimens. Most efforts are directed toward improving standard first-line therapy or developing effective second-line therapy, which is still not yet standardized 10 years after the first-line standard of care was established.

This review focuses on the systemic management of MPM in patients who are not considered suitable for surgical approaches, and it discusses some questions that remain open such as the benefits of administering a maintenance treatment, whether it is better to give cisplatin or carboplatin as first-line therapy, the role of new drugs as second-line therapy, and the treatment of the elderly population. It also summarizes the results from clinical trials that have evaluated new treatments as first- or second-line therapy, which are based on the understanding of mesothelioma biology, such as antiangiogenic drugs, immunotherapies and growth factors agents.

Introduction

Malignant pleural mesothelioma (MPM) is a rare malignancy that is mainly localized to the pleura. The epithelial histologic subtype is the most common. Asbestos exposure is the dominant etiologic agent, with a latency period of 20–40 years. The global incidence of malignant mesothelioma is poorly reported, but it is likely to continue to increase due to ongoing use of asbestos in the developing world. In Spain, deaths from mesothelioma are expected to continue to increase until at least 2016, as the use of asbestos was banned in 2001.[1]

MPM is more common in men than in women, and 75% of patients are older than 65 years. The median overall survival (OS) of locally advanced or metastatic disease without treatment is 6–9 months. The vast majority of treatments are palliative. Poor prognosis factors of this disease are non-epithelial histologic subtype, a poor performance status (PS), anaemia, high white blood cells and thrombocytosis.[2,3]

In the suspicious diagnosis of MPM, a positive blood test for mesothelin, which is a high specificity test, strongly suggests further diagnostic tests. However, the poor sensitivity of mesothelin limits its use as a screening marker.[4] Given the biologic and phenotypic tumor heterogeneity of MPM, immunohistochemistry helps in the differential diagnosis between MPM and metastatic carcinoma.[5]

Therapeutic options depend mainly on Tumor, Node, Metastasis (TNM) stage,[6] but it should be noted that positron emission tomography/computed tomography (PET/CT) can detect 15% of occult metastases and is a new tool in not advanced MPM.[7] Pleurectomy/decortication (P/D) and extrapleural pneumonectomy (EPP) are the two main cytoreduction surgeries in MPM. Optimal therapy remains controversial, mainly because it is disputed whether surgery increases survival and whether survival benefit is best achieved with EPP or P/D within a multimodal regimen. In the MARS trial, EPP compared with no-EPP within trimodal therapy did not offer any benefits, and possibly harmed patients, but the low accrual and the mortality rate in the surgery arm did not allow final conclusions to be drawn about the role of surgery in MPM.[8]

There are no randomized trials directly comparing EPP with P/D, however in one trial patients who underwent to P/D had a better survival with lower operative mortality, compared to EPP, which may be explained by subject selection.[9,10] The International Association for the Study of Lung Cancer (IASLC) MPM database with 3101 patients showed a better survival with EPP than with P/D in stages I–II MPM.[11] At present, the choice of resection depends on the extent of disease, patient comorbidities, and type of multimodality treatment; and the main goal of surgery should not only be complete resection if possible, but more realistically, the resection of all macroscopic disease as an adjunct to delivery of chemotherapy and radiotherapy.

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This review focuses on systemic management of MPM in patients not considered suitable for surgical approaches.

First-line treatment of patients with MPM

MPM is considered a rare and heterogeneous malignant disease (different prognostic factors and three different histologic subtypes), and it is difficult to evaluate the response rate (RR) to the treatment by classical RECIST criteria (modified RECIST is recommended),[12] and to stage the disease. These facts make it more difficult to perform double-blinded randomized clinical trials, which is the gold-standard of clinical research. Thus, patients with MPM have not yet benefited from the identification and incorporation of novel therapies, such as targeted drugs, into their treatment.

A meta-analysis in unresectable MPM suggested that the RR and survival were greater for combination than for single-agent regimens, and platinum-containing regimens had greater activity than non-platinum-containing combinations, with cisplatin and doxorubicin showed the highest reported RR (28.5%; $p < 0.001$). Also, three-drug chemotherapy combinations did not improve efficacy over two-drug combinations.[13] These results confirm that platinum-based chemotherapy remains the most effective treatment for patients with MPM. In a phase II trial, 63 patients with MPM were treated with high dose methotrexate and showed a RR of 37% and a median OS of 11 months. Based on these results, antifolate drugs were further investigated in this disease.[14]

Two phase III trials with first-line chemotherapy in unresectable MPM have shown that the combination of platinum–antifolate (pemetrexed or raltitrexed) conferred 3 months of survival benefit over cisplatin alone (Table 1). The EMPHACIS trial included 456 patients with MPM who were treated with cisplatin–pemetrexed or cisplatin alone. The combination schedule increased OS to 12.1 months in comparison with 9.3 months in the control arm ($p = 0.02$). Time to progression (TTP) was 5.7 months vs. 3.9 months, respectively ($p = 0.001$), and RR was 41.3% vs. 16.7%, respectively ($p < 0.0001$).[15]

A similar incremental survival benefit was observed in the second phase III trial with 250 patients conducted by the European Organisation for Research and Treatment of Cancer (EORTC) Lung Cancer Group. In this trial, the addition of raltitrexed to cisplatin increased OS to 11.4 months, compared with 8.8 months with cisplatin as single agent ($p = 0.048$). However, TTP (5.3 months vs. 4.0 months, respectively; $p = 0.058$) and RR (23.6% vs. 13.6%, respectively; $p = 0.056$) were not statistically significantly different between the treatment arms.[16] The global health-related quality of life (HR-QoL) scale was comparable at baseline in both treatment arms ($p = 0.848$); at no point was any significant difference apparent for this end point, and both treatments led to an improvement over time in dyspnea, suggesting that chemotherapy does not exert a harmful effect on a patient's QoL.[17]

Although the significance level in the EORTC study is somewhat less than in the EMPHACIS trial, this may also be due to smaller sample size. The main differences between both antifolate drugs are that the use of pemetrexed requires the administration of folic acid and vitamin B12 supplements to reduce the hematological toxicity. The fact that pemetrexed is a multitarget antifolate drug compared with raltitrexed, which only inhibits thymidylate synthase (TS), could explain the differences in the toxicity profiles in these studies.

A complete analysis of the efficacy and cost-effectiveness of first-line chemotherapy in MPM showed that the schedules cisplatin–pemetrexed and cisplatin–raltitrexed were not different in terms of RR, TTP and OS. Both combinations are cost-effective, but the analysis found that the schedule cisplatin–raltitrexed offers marginally higher quality-adjusted life years (QALY) and life years at a substantially lower total cost than cisplatin–pemetrexed.[18] In view of the similar mode of action of both drugs on TS and their observed effects in MPM, it would be interesting to conduct a large, non-inferiority trial in patients with MPM to evaluate the substitution of pemetrexed by raltitrexed. However, this trial would be quite difficult to perform due to the large number of patients needed. In spite of this, it is possible to conclude that platinum–antifolate regimens have become the standard first-line therapy worldwide for patients with advanced or unresectable MPM and good PS.[19,20] However, the results of both phase III trials should not be extrapolated to subgroups that have been insufficiently studied, such as patients with a moderate or poor PS, the elderly (those >75 years of age) and patients with sarcomatous histologic subtype.

Although neither of these trials demonstrated a benefit of platinum-based treatment over best supportive care (BSC), the MS01 study randomized 409 patients to receive active symptom control (ASC) with or without weekly vinorelbine for 12 weeks or mitomycin, vinblastine, and cisplatin (MVP) for four cycles. As a result of the slow accrual, both chemotherapy arms were combined for analysis, but no survival benefit was seen overall when compared with ASC (HR: 0.89; 95% CI: 0.72–1.10; $p = 0.29$), or in terms of QoL. Median OS was 7.6 months in the ASC arm compared with 8.5 months in ASC plus chemotherapy arm. However, exploratory analyses suggested a survival advantage for ASC plus vinorelbine compared with ASC alone, with a 2 months' survival benefit that approached significance (HR: 0.80; 95% CI: 0.63–1.02; $p = 0.08$), although these benefits were not seen for those patients who received MVP (HR: 0.99; 95% CI: 0.78–1.27; $p = 0.95$).[21]

Other combination regimens have been tested. Cisplatin and gemcitabine were incorporated into clinical practice following results from two phase II trials.[22,23] In an institutional review, 81 patients with MPM were treated with platinum plus gemcitabine or platinum plus pemetrexed as first-line treatment. The median OS was 10 months, irrespective of the treatment arm,[24] suggesting that platinum-based doublets might represent a therapeutic ceiling for cytotoxic chemotherapy in patients with MPM. However, given the lack of phase III evidence, the use of gemcitabine as first-line therapy is not supported.

The median age for MPM diagnosis is 65 years and older, but elderly patients with MPM are under-represented in clinical trials. In a retrospective survey of elderly patients ($\geqslant$70 years old), 210 patients were included and 73% received chemotherapy, mainly pemetrexed. The median OS was 11.3 months. However, in spite of the fact that pemetrexed-based chemotherapy is feasible in selected elderly patients, non-epithelial histology, age $\geqslant$ 75 years and the presence of comorbidities were significantly correlated with a shorter survival.[25] Prospective trials including elderly

Table 1
Main efficacy results of two phase III trials in the first-line setting in patients with advanced MPM.

	EMPHACIS Trial[15]		EORTC Trial[16]	
	Cisplatin plus pemetrexed	Cisplatin	Cisplatin plus raltitrexed	Cisplatin
N	226	222	126	124
RR (%)	41.3	16.7	23.6	13.6
p Value	<0.0001		0.56	
OS (months)	12.1	9.3	11.4	8.8
HR	0.77		0.76	
p Value	0.02		0.048	
TTP (months)	5.7	3.9	5.3	4
HR	0.68		0.78	
p Value	0.001		0.058	

HR: hazard ratio; OS: overall survival; RR: response rate; TTP: time to progression.