Review Article

Chemotherapy treatment in malignant pleural mesothelioma: a difficult history

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Abstract: Malignant pleural mesothelioma (MPM) is a rare neoplasm that typically arises from mesothelial surfaces of the pleural cavity. Despite treatment improvements, it carries a dismal prognosis. The majority of patients either have unresectable disease or are not candidates for surgery due to medical comorbidities or old age. For such patients, chemotherapy (CT) represents the gold-standard treatment. To date, combination CT with cisplatin plus pemetrexed represents the most widely used regimen in first-line setting for patients with unresectable MPM. Other first-line options are currently available, including the use of raltitrexed instead of pemetrexed combined with platinum. In this review, we discuss the role of CT in MPM mainly focusing on the results of the trials conducted in first-line setting.

Keywords: Chemotherapy (CT); malignant pleural mesothelioma (MPM); pemetrexed; platinum

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Introduction

Malignant pleural mesothelioma (MPM) is a rare neoplasm linked to asbestos exposure that typically arises from mesothelial surfaces of the pleural cavity. It is characterized by a poor prognosis, with a medium life-expectancy between 12 and 18 months after diagnosis (1). However, carefully selected patients with localized disease who receive multimodal treatment have relatively prolonged survival.

Males are 3.8 times more affected than females and have a worse survival rate (2,3). Moreover, two prognostic scoring systems published from EORTC and CALGB include pleural primary site, high serum level of LDH, poor ECOG performance status, high serum levels of platelets, non-epithelial histology and advanced age as independent predictors of poor outcome (4,5).

Notably, the global incidence and mortality of MPM is rising, primarily in developing countries, in which the incidence peak is predicted within 2025 (6). Thus, health and economic burden correlated to this disease is expected to increase.

The pathogenesis of MPM is multifactorial, though up to 80% of MPM cases is correlated to asbestos exposure due to occupational, para-occupational or environmental factors. However, the other 20% of patients does not report any exposure, suggesting that genetic predisposition could play a crucial role in MPM pathogenesis (6).

Symptoms are generally present only once extensive intrathoracic disease has developed, with dyspnea, pleural effusion and chest pain occurring in 60–70% of cases (6,7). Clinical suspicion may arise in the setting of respiratory symptoms associated with pleural thickening or effusion on chest imaging and a history of asbestos exposure. However, a pleural biopsy or at least a cytological examination is necessary to confirm the diagnosis (8).

Unfortunately, the outcome of MPM has not been substantially improved over the last decades and its treatment remains a critical challenge.

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Several new drugs and potential molecular prognostic factors are under investigation in order to tailor treatment approaches and to improve the outcome of these patients.

Clinical management

Every patient should be initially evaluated by an expert multidisciplinary team and the following multidisciplinary treatment plan should be based upon the assessment of the extent of the disease, the patient's general conditions (age, performance status, cardiopulmonary function, comorbidities) and their preferences for aggressive potentially curative or only palliative treatment (3).

To date, therapeutic options are represented by surgery, radiotherapy (RT) and chemotherapy (CT), differently combined in a multimodal approach.

Approximately, only 20% of patients are suitable for radical surgery, intended as macroscopic complete resection (R0 or R1), and more than 85% of them die within 5 years. The remaining 80% of patients will not be candidate for combined approach including definitive surgery; in these cases, CT remains the standard treatment option (9).

Patients with resectable disease

The role of definitive surgery for MPM is controversial. No prospective randomized clinical trial has yet established whether this approach leads to an improvement in survival. Moreover, both invasive extrapleural pneumonectomy (EPP) and, to a lesser extent, pleurectomy/decortication (P/D) are associated with substantial morbidity and mortality, though a better outcome has been observed when surgery was performed in centers with adequate expertise (10).

Additionally, the optimal procedure to be performed (EPP or P/D) is uncertain and there are no data from randomized trials comparing these two different approaches.

Local and distant recurrence rates after surgery are still high, leading to the development of new treatment strategies to evaluate adjuvant therapy in order to improve local control and particularly OS.

Several non-randomized studies have evaluated a trimodality treatment consisting of induction CT with active agents such as cisplatin and pemetrexed, followed by surgery and subsequent RT, with median OS ranging from 14 to 25.5 months (6). Krug *et al.* performed a multicenter phase II trial evaluating neoadjuvant cisplatin plus pemetrexed followed by EPP and adjuvant RT; the results of this trial showed a median survival of 17 months. However, the impact of a high selection of patients in these trials should not be underestimated (11).

Accordingly, the Mesothelioma and Radical Surgery (MARS) trial randomized 50 patients to EPP or no EPP in the setting of trimodal treatment (12). The authors demonstrated no survival or quality of life benefit deriving from EPP; on the contrary, patients in the no-EPP group had a better outcome compared to EPP-group (HR adjusted for prognostic variables 2.75). Additionally, Stahel *et al.* reported no differences in loco-regional relapse-free survival (RFS) between patients receiving hemithoracic RT after neoadjuvant CT and EPP compared with those receiving only observation (13). Nevertheless, carefully selected patients may benefit from multimodality approach.

Patients with unresectable disease: the mainstay role of CT

For patients who have unresectable disease and for those in which surgery is not feasible due to medical comorbidities or old age, CT and symptomatic treatment, including the management of pleural effusion, represent the gold-standard.

First-line single-agent CT

Since the 1980s, several phase II studies have evaluated the role of single-agent CT with anthracyclines, taxanes, platinum compounds, alkylating agents, and topoisomerase inhibitors in mesothelioma patients; however, these trials showed low response rates ranging from 0% to 13% (3,14-16). Tsao *et al.* reported single-agent response rates from 7% to 20% in patients treated with platinum analogues, antimetabolites (e.g., pemetrexed, raltitrexed, methotrexate), doxorubicin, vinorelbine, and gemcitabine (17).

Furthermore, a randomized trial performed by Muers *et al.* has evaluated the impact of first-line CT on survival compared with active symptoms control alone (18). In this study, which has been the only one where CT has been directly compared with no active anti-cancer treatment, 409 patients with MPM were randomly assigned to symptomatic treatment, symptomatic treatment plus CT including cisplatin, vinblastine and mitomycin or to symptomatic treatment plus single-agent vinorelbine. The authors demonstrated a trend toward improved outcome only in the vinorelbine group compared with symptom control alone (HR 0.8, P=0.08; mOS 9.5 months) (*Table 1*).

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Table 1 First-line randomized chemotherapy trials in MPM

Authors	Vogelzang *et al*. (9)	van Meerbeeck *et al*. (19)	Muers *et al*. (18)
Phase	3	3	2
Primary endpoint	OS	OS	OS
Regimen	Cisplatin + pemetrexed; cisplatin	Cisplatin + raltitrexed; cisplatin	VNR + ASC; MVP + ASC; ASC
Results			
OS	12.1 mo; 9.3 mo; P=0.012	11.4 mo; 8.8 mo; P=0.048	8.5 mo; 7.6 mo; P=0.29*/9.5 mo; 7.6 mo; P=0.08**
PFS	5.7 mo; 3.9 mo; P=0.001	5.5 mo; 4.0 mo; P=0.058	5.6 mo; 5.1 mo; P=0.39*
ORR	41%; 17%	24%; 14%	

*, combined analysis of chemotherapy + ACS *vs.* ACS alone; **, exploratory analysis of VNR + ACS *vs.* ACS alone. OS, overall survival; PFS, progression-free survival; ORR, overall response rate; mo, months; MVP, mitomycin C, vinblastine and cisplatin; VNR, vinorelbine; ACS, active symptoms control; P, P value.

First-line combination CT

To date, the combination CT with cisplatin plus pemetrexed represents the most widely used regimen for patients with unresectable MPM. The role of this regimen was initially assessed in a phase I trial where 11 patients were enrolled and were given pemetrexed combined with cisplatin, at increasing doses of both drugs.

The results of the trial showed that the combination was tolerable as well as active with five (45%) out of 11 patients experiencing a partial response (20). Subsequently, cisplatin plus pemetrexed was approved by FDA on the basis of the phase III EMPHACIS trial published by Vogelzang *et al.*, that randomized 456 patients to cisplatin plus pemetrexed or cisplatin alone (9). The results showed a statistically significant prolongation of median OS (12.1 *vs.* 9.3 months, HR, 0.77), progression-free survival (PFS, 5.7 *vs.* 3.9 months) and overall response rate (ORR, 41% *vs.* 17%) in the combination arm (*Table 1*). Notably, patients who received folic acid plus vitamin B12 during CT showed the most striking differences in outcome, less toxicities and a greater number of administered cycles compared with patients not receiving supplementation.

In the EMPHACIS trial quality of life was also assessed through the LCSS-Meso questionnaire which had been previously validated in mesothelioma patients. The overall symptom score favored the combination arm after 6 cycles. Moreover, a statistically significant improvement in pain, cough and dyspnea was noted after 4 cycles in the pemetrexed plus cisplatin arm. Likewise, an improvement in global quality of life and fatigue was also observed in the combination arm (21).

The International Expanded Access Program (EAP) allowed more than 3,000 MPM patients to receive single-agent pemetrexed or pemetrexed in combination with cisplatin or carboplatin in 13 different countries. In the pemetrexed plus cisplatin arm a response rate of 26.3% was observed compared with 21.7% in the pemetrexed plus carboplatin arm. The 1-year survival rates were 63.1% versus 64.0%, respectively; median TTP was also similar (7 *vs.* 6.9 months) (22).

Additionally, a randomized EORTC phase III trial compared cisplatin 80 mg/mq plus the antimetabolite raltitrexed 3 mg/mq every 21 days to cisplatin alone (19). This first-line combination showed an improvement of both OS (mOS 11.4 *vs.* 8.8 months, P=0.04; 1 year-OS 46% *vs.* 40%, P=0.06) and PFS (5.3 *vs.* 4 months), with a magnitude of clinical benefit similar to that reached in the previous pemetrexed study (*Table 1*). A quality of life analysis was also performed in this trial showing no differences or deterioration of overall health status/QoL scale with the addition of raltitrexed to cisplatin.

However, currently there are no data to support a preference of pemetrexed *vs.* raltitrexed. A recent network metanalysis of these two randomized trials provided an indirect comparison between cisplatin-pemetrexed and cisplatin-raltitrexed. The authors found no significant difference in OS, ORR and safety between the two regimens, suggesting a comparable efficacy.

Thus, the clinical choice between the two antifolates should also be guided by pharmacoeconomic aspects, different toxicity profiles and personal clinical experience.

Both the EMPHACIS trial and the EORTC trials not only highlighted the role of thymidylate synthase inhibitors,

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in addition to platinum, in the treatment of MPM but they also showed that the combination regimens are superior to single-agent CT, and therefore, indirectly, also to palliative care only (18).

In clinical practice, carboplatin has often been substituted for cisplatin to decrease toxicity, particularly in fragile patients. Three non-randomized phase II trials evaluated the role of carboplatin plus pemetrexed in MPM patients, and reported median OS ranging from 12.7 to 14 months (23-25). In the study by Ceresoli *et al.*, 102 patients were treated with carboplatin 5AUC plus pemetrexed 500 mg/mq every 21 days, with folic acid and vitamin B12 supplementation. Objective responses were observed in 19% of cases, with a median PFS and OS of 6.5 months and 12.7 months, respectively (24). Furthermore, a secondary combined analysis of two of these trials found that this combination was well tolerated and had a similar level of activity in elderly patients (≥70 years), compared with younger ones (26). These results are similar to those with the cisplatin-based combination. Additionally, Santoro *et al.* reported similar survival outcome between patients treated with cisplatin plus pemetrexed and those receiving carboplatin plus pemetrexed (mPFS 7 *vs.* 6.9 months; 1 year-OS 64% *vs.* 63.1%) (22). To date, carboplatin-pemetrexed regimen may be a reasonable alternative if cisplatin toxicity represents a concern.

The combination of cisplatin plus gemcitabine was also evaluated in some phase II trials suggesting that it may be an alternative in patients not candidates to pemetrexed, despite heterogeneity between studies with response rates and survival ranging from 12–48% and 9.5–12 months, respectively (3,27-31). Furthermore, the use of carboplatin with gemcitabine has been investigated showing good tolerance and a response rate of 26% (32).

In a multicenter randomized phase II trial performed by Kindler *et al.* (33), 106 chemonaive patients were treated with cisplatin plus gemcitabine with or without bevacizumab; no OS benefit (15 months in both arms) was observed with the addition of bevacizumab, though a potential benefit may have potentially been obscured by the use of second-line pemetrexed.

Cisplatin has also been tested in combination with other older chemotherapeutic agents, such as anthracyclines, mitomycin, methotrexate and vinblastine (15,34-37). However, these phase II trials do not suggest any possible advantage of these regimens, either in terms of activity or of toxicity, compared with the combination of cisplatin with pemetrexed or gemcitabine.

More recently, the large multicenter phase III MAPS trial randomized 448 naive patients to receive cisplatin-pemetrexed alone or cisplatin-pemetrexed plus bevacizumab (38). The addition of bevacizumab to CT improved both median PFS (9.2 *vs.* 7.3 months, HR, 0.61, 95% CI: 0.50–0.75) and median OS (18.8 *vs.* 16.1 months, HR, 0.77, 95% CI: 0.62–0.95) compared with CT alone, though with an increased toxicity (grade 3 hypertension, proteinuria, thrombotic events). Despite its role remains controversial, this regimen is now an option for first-line therapy in carefully selected patients with unresectable mesothelioma. No data from large studies regarding the addition of bevacizumab to a carboplatin-based regimen are available as yet.

Another issue is the appropriate timing of first-line CT start, particularly in asymptomatic or symptomatically stable patients. The randomized MED trial showed a trend towards a longer time-to-symptom-progression in patients receiving immediate CT (mitomycin-vinblastine-cisplatin/carboplatin) compared with patients randomized to initial best supportive care (BSC) and subsequent addition of CT (39). These data support the early start of CT also in patients with stable symptoms, suggesting a superiority of immediate treatment. strategy. However, the small sample size of the trial does not allow to draw any definitive conclusions and, in everyday clinical practice, a watchful waiting strategy in carefully selected and asymptomatic patients can be considered as an option.

Additionally, to date, there are no standard assays for biomarkers that are currently recommended to predict response to first-line CT. In a multivariate regression analysis of prognostic factors derived from EMPHACIS trial, predictive variables that seem to be related to longer OS were represented by therapy group, vitamin supplementation, Karnofsky performance status, stage of disease, histologic subtype and white blood cell count (40). A retrospective study of 60 patients with MPM receiving pemetrexed correlated low thymidylate synthase levels with improved outcome (41). A prospective trial evaluating the role of thymidylate synthase as a predictive biomarker for pemetrexed-based therapy is ongoing (42).

Second-line treatment with single-agent CT

Most MPM patients progressing after first-line treatment can receive further courses of CT. Few data are available to guide the clinical decision making in the selection of second-line therapy.

If disease progression occurs after a prolonged break

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from a platinum-pemetrexed-based regimen, patients can be rechallenged with the antifolate. As a matter of fact, Jassem *et al.* conducted a phase III trial to compare pemetrexed to BSC in 243 previously treated pemetrexed-naive patients showing a statistically improvement in median PFS, time to progression (TTP) and time to treatment failure (TTF) in the pemetrexed arm. However, no statistically significant differences were detected in terms of overall survival (43).

To date, single agent-based CT is an accepted practice, based upon phase II studies demonstrating improved response rates with gemcitabine, vinorelbine or anthracyclines (44-47). The combination of cisplatin-gemcitabine (48), irinotecan-cisplatin-mitomycin (49), and oxaliplatin-raltitrexed (50,51), have also been evaluated as second-line approaches. Additionally, in the phase II trial by Giaccone *et al.*, the platinum-complex ZD0473 showed no benefit as second-line strategy (52).

However, few prospective studies have been published regarding pemetrexed-pretreated MPM patients; as a result, it is still unknown which are the best agents to be used in the second-line setting.

Currently, trials assessing the role of maintenance therapy with pemetrexed are ongoing (53).

Conclusions

The management of MPM currently represents a critical challenge.

Cumulative evidence suggests that CT does have a role in the palliative treatment of advanced mesothelioma yielding an objective response in 40–50% of patients, an improvement of symptoms in most patients and a modest survival benefit over BSC. Most guidelines therefore recommend its use with the combination of platinum compounds plus pemetrexed, with or without bevacizumab, representing the standard first-line CT for MPM patients. Despite the systemic treatment, the prognosis of these patients remains poor, with median OS of approximately 12 months (3).

Many therapeutic strategies have been studied or are under development in order to improve the outcome of MPM patients, focusing on the underlying biology and molecular pathways of the disease.

However, the molecular heterogeneity and the low incidence of mesothelioma hinder the development of tailored effective treatments. Thus, patients' participation in clinical trials should also be encouraged whenever possible.

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Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

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