

A narrative review of current treatment strategies and emerging therapies in malignant pleural mesothelioma

Élise Di Lena^{1,2#}, Ali Aboalsaud^{1#}, Christian Sirois³, David Mulder³, Jonathan Spicer³, Lorenzo Ferri³, Jonathan Cools-Lartigue³

¹Department of Surgery, Division of General Surgery, McGill University Health Center, Montreal, Quebec, Canada; ²Department of Surgery, Division of Experimental Surgery, Goodman Cancer Research Center, McGill University, Montreal, Quebec, Canada; ³Department of Surgery, Division of Thoracic and Upper Gastrointestinal Surgery, Montreal General Hospital, Montreal, Quebec, Canada

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[#]These authors contributed equally to this work.

Correspondence to: Jonathan Cools-Lartigue. Division of Thoracic and Upper Gastrointestinal Surgery, Montreal General Hospital, 1650 Cedar Av., Montreal, Quebec, H3G 1A4, Canada. Email: jonathan.cools-lartigue@mcgill.ca.

Abstract: Malignant pleural mesothelioma is a rare but extremely lethal disease for which there is no single curative therapy. Given this, a significant lack of consensus exists regarding optimal treatment strategies. Patients typically present late in the course of their disease, which has led many to advocate for palliative approaches to therapy, while others believe that macroscopic resection of disease in conjunction with multimodal therapy is preferable in highly selected individuals. Surgical strategies have recently evolved from the maximally invasive extrapleural pneumonectomy (EPP) to the more conservative extended pleurectomy and decortication. The addition of chemotherapy and radiotherapy to surgical interventions have allowed to extend progression-free survival, but this is still measured in months rather than years. Moreover, there is a lack of high-quality evidence to support all interventions, leading to variations in guidelines regarding trimodal therapy and a paucity of data demonstrating superiority of a single approach to care. Given this, new and promising treatment options are emerging which may allow to better control and treat malignant pleural mesothelioma. These include immunotherapy, virotherapy, T-cell therapies, and vaccines, among others. This paper therefore aims to give a comprehensive overview of current available treatments with a focus on surgical and trimodal therapies, as well as emerging treatment options for malignant pleural mesothelioma.

Keywords: Malignant pleural mesothelioma (MPM); mesothelin; trimodal therapy

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Introduction

Malignant mesothelioma is a disease which can occur in the pleura, the peritoneum, the pericardium, or the tunica vaginalis, though 90% of cases are malignant pleural mesothelioma (MPM) (1). Occupational asbestos exposure accounts for 85–90% of cases in men, and paraoccupational exposure accounts for the majority of cases in women, with a dose-dependent risk of MPM (1); other etiologies include radiation therapy, chronic pleural inflammation, chemical

carcinogens, and possibly contamination of the polio vaccine prior to 1963 by simian virus-40 (2), as well as likely genetic factors (3,4). The typical presentation of MPM includes males between 50 and 70 years of age presenting with either dyspnea secondary to an effusion or non-pleuritic chest wall pain from local invasion (3), with an insidious onset and chest X-ray findings consistent with a pleural effusion in 80% to 95% of patients (2). The highest prevalence of cases is seen in the United Kingdom and the incidence is

expected to peak in high-income countries roughly 40 years after asbestos regulations were implemented due to the long latency period (2), though they continue to rise and to be underreported in low- and middle-income countries (1). In the United States, it is thought that roughly 40% of the workforce was exposed between 1940 and 1979 (3). Despite this, MPM remains a rare and lethal disease, with only 2% to 10% of exposed individuals developing MPM and an expected survival of 6 months if left untreated (3). However, thanks to new diagnostic technologies including next-generation sequencing, the landscape of MPM is quickly changing, with new potential therapeutic targets being discovered constantly (5). This paper therefore aims to give a comprehensive overview of current available treatments as well as emerging therapies for MPM. We present the following article in accordance with the Narrative Review Checklist (available at <http://dx.doi.org/10.21037/ccts-20-112>).

Methods

PubMed was searched using the keywords “malignant pleural mesothelioma” and “mesothelioma” from 2000 to April 2020. High-quality randomized-control trials, cohort and cross-sectional studies, and systematic and narrative reviews written in English or in French were evaluated for inclusion. North American and European society guidelines were also included and referenced. Manuscripts focusing on non-pleural malignant mesothelioma as well as case-reports were excluded.

Current treatments

Surgery

As early as 1922, and before MPM was found to be distinct from lung cancer, radical surgical intervention for diffuse MPM was advocated by Eiselsberg, who recommended pleurectomy for these cases, and radical pleuropneumectomy or extrapleural pneumonectomy (EPP) (resection of pleura, lung, lymph nodes, ipsilateral pericardium and diaphragm) became one of the treatment options in the 1950s (6,7). However, palliative treatments remained standard of care and few advocated for radical intervention given abysmal outcomes until Butchart *et al.* documented long-term cure in 2 of a 29 patient cohort, though in-hospital mortality rates were 31% and total complication rates were 44.8% (6).

Over time, as patient selection and perioperative care have

improved, so have the surgical outcomes (8% perioperative mortality today compared to 33% in the 1970s for EPP) (8), though survival is still measured in months rather than years and there has not been any significant improvement in survival over 4 decades (9,10). Contrary to other oncologic resections, the aim of surgery for MPM is to perform maximal cytoreduction and to obtain a macroscopically complete (R1) resection and to use other local and systemic therapies as adjuncts, given the high morbidity and technical difficulty of aiming for an R0 resection (7,9,11-14). However, the role for surgical resection in MPM has been and remains controversial, with many societies advising against extensive surgical intervention outside of clinical trials (15,16), while others are in favor of macroscopically complete surgical resection in patients with early-stage disease (11,17-20). Even among thoracic surgeons, there exist wide discrepancies in practice and beliefs regarding the curative potential of surgery for MPM (21). This variability in recommendations and practice is explained by various studies with conflicting outcomes, disease and treatment heterogeneity, and the lack of high-quality randomized control trials (RCTs) (22). Review of data from the Surveillance, Epidemiology, and End Results (SEER) database demonstrated that cytoreductive surgery is associated with improved survival, leading to the authors' suggestion that surgically-centered therapy be the mainstay of treatment (10). Indeed, surgical intervention may confer a 9-month survival benefit, but its associated morbidity and mortality are high (23). Even in elderly patients, if properly selected, surgery may confer a survival benefit, though few are candidates for this option (24).

Among believers in surgery for MPM, there remains a lack of consensus regarding the optimal surgical intervention (25), and no society has taken a position in this regard (9,26,27). There are strong advocates for EPP who believe that it offers the most oncologically complete resection, especially in earlier-stage cancers (please refer to *Tables 1,2* for current staging) (7,13,29). Another argument in favor of EPP is that resection of the lung allows for high-dose adjuvant radiation therapy (14). Retrospective data has shown some survival benefit from EPP in highly-selected patients, especially with neoadjuvant or adjuvant chemoradiotherapy (30), with a possible benefit in progression-free survival (PFS) (31). However, EPP is associated with significant morbidity (25%) and mortality (4–15%) (15). In fact, the 2011 Mesothelioma and Radical Surgery (MARS) trial comparing EPP to no EPP recommended against EPP given the high morbidity and

Table 1 Eight International Association for the Study of Lung Cancer (IASLC) TNM classification of malignant pleural mesothelioma (MPM) (28)

Classification	Description
Primary tumor (T)	
Tx	Not assessable
T0	No evidence of primary tumor
T1	Tumor involving ipsilateral parietal pleura (incl. mediastinal/diaphragmatic pleura) with or without involvement of visceral pleura
T2	Tumor involving all ipsilateral parietal pleural surfaces (parietal, mediastinal, diaphragmatic, visceral) with one or more of the following features: <ul style="list-style-type: none"> • Confluent visceral pleural tumor • Involvement of diaphragm • Invasion of lung parenchyma
T3	Tumor involving all ipsilateral parietal pleural surfaces (parietal, mediastinal, diaphragmatic, visceral) with one or more of the following features: <ul style="list-style-type: none"> • Invasion of endothoracic fascia • Extension into mediastinal fat • Solitary, resectable focus invading soft tissues of chest wall • Non-transmural pericardial involvement
T4	Tumor involving all ipsilateral parietal pleural surfaces (parietal, mediastinal, diaphragmatic, visceral) with one or more of the following features: <ul style="list-style-type: none"> • Diffuse/multifocal invasion of soft tissues of chest wall • Rib involvement • Invasion of peritoneum • Invasion of any mediastinal organ • Direct extension to contralateral pleura • Invasion of spine or brachial plexus • Transmural invasion of pericardium or myocardial invasion
Regional lymph nodes (N)	
Nx	Not assessable
N0	No regional lymph node metastases
N1	Metastases into any ipsilateral lymph nodes (bronchopulmonary, hilar, mediastinal, including internal mammary, peridiaphragmatic, pericardial fat pad, intercostal), except supraclavicular lymph nodes
N2	Metastases to any contralateral lymph nodes or supraclavicular lymph nodes
Metastases (M)	
Mx	Not assessable
M0	No evidence of distant metastases
M1	Evidence of distant metastases

Table 2 Eight International Association for the Study of Lung Cancer (IASLC) TNM staging of malignant pleural mesothelioma (MPM) (28)

Stage	T	N	M
I			
IA	1	0	0
IB	2,3	0	0
II	1,2	1	0
III			
IIIA	3	1	0
IIIB	1-3	2	0
IV	4	0-2	0
	Any	Any	1

30-day mortality of the procedure, though this trial was a feasibility study and was underpowered (32). Considering this, other experts advocate for the less morbid pleurectomy and decortication (PD) (also referred to as extended PD), during which the visceral and parietal pleurae are resected, and occasionally the pericardium and diaphragm, but not the lung (7,13). Some studies have found comparable survival outcomes with significantly less morbidity and mortality associated with this procedure (8,31,33,34). Furthermore, certain systematic reviews have found a survival benefit in favor of PD, likely secondary to the decreased peri-operative mortality (35,36), and PD may also offer improved quality of life (34,37), leading many to favor PD today in the treatment of MPM. However, other retrospective studies, systematic reviews and propensity matched comparisons have noted no difference in morbidity and mortality between the two procedures (38-40). The data is therefore extremely heterogeneous (12). Overall, most experts agree that patients should be evaluated as part of a multi-modal team and proper RCTs must be conducted to further determine the best surgical intervention in MPM (12,22,26,41-43). The MARS-2 trial is currently underway, looking at whether PD with neoadjuvant chemotherapy offers a survival benefit compared to chemotherapy alone, and preliminary results should be made available in September 2020 (26,44,45).

Trimodal therapy

Few RCTs have been conducted comparing multimodality therapy to use of chemotherapy or surgical resection

alone, and the recommendations for chemotherapy as part of trimodal therapy have mostly been extrapolated from these few trials, feasibility trials, and trials evaluating effects of chemotherapy in unresectable disease. Several societies recommend the use of trimodal therapy (surgery, chemotherapy, radiation therapy) (11,20,46,47), though the British Thoracic Society and the European Respiratory Society suggest that multimodal therapy only be used in the context of a clinical trial (15,48); however the appropriate timing of therapy remains unknown, with no clear evidence for the sequence in which to provide various treatments (48). Furthermore, even with trimodal therapy, long-term survival is poor, with 10% of patients surviving at 5 years (49).

General recommendations for chemotherapy are a platinum-based therapy [cisplatin, typically, or carboplatin in older or more frail patients (50,51)] in addition to pemetrexed (folate antimetabolite) with B12 and folic acid supplementation (11,15,20,46-48). The recommendations for the addition of pemetrexed emerged from RCTs which demonstrated improved survival (by 2.8 months) compared to cisplatin alone, with B12 and folic acid reducing toxicity (52,53). In patients with a poor functional status or in elderly patients, carboplatin offers adequate survival benefits and is recommended in combination with pemetrexed (54). Bevacizumab (vascular endothelial growth factor (VEGF) inhibitor) may also be added to standard chemotherapy in patients with a good performance status (11,15,20). This recommendation is derived from a large phase III trial, MAPS, comparing pemetrexed/cisplatin alone to this combination with bevacizumab (55). This study demonstrated improved overall survival (by 2.7 months) with the addition of the VEGF inhibitor; however, this study was only performed in unresectable MPM (55). No second-line chemotherapy is generally specifically recommended, and it is advised that patients be enrolled in a clinical trial or offered palliative care (11,15,46,48). The American Society of Clinical Oncology (ASCO) and the National Comprehensive Cancer Network (NCCN) suggest possible use of vinorelbine as second-line therapy in patients who cannot be enrolled in a trial (11,20), with NCCN also suggesting immunotherapy and rechallenge with chemotherapy as second-line (20). Second-line pemetrexed has shown some effect on tumor response and delayed disease progression when compared to best supportive care in a phase III trial (56). The recommendation for vinorelbine stems from an RCT demonstrating a trend in improved survival (non-statistically significant) in patients treated with vinorelbine compared

to active symptom control (57). Other treatments being investigated include PD with intraoperative intracavitary hyperthermic chemotherapy, though no society recommends this treatment outside of clinical trials; more evidence is required before this treatment option can be recommended (58-66).

Most studies evaluating trimodal therapy have either been retrospective reviews or feasibility studies with no control or randomization, and have used historical data as a comparator (67-73). In 2007, a multicenter trial was published evaluating the feasibility of neoadjuvant chemotherapy (3 cycles of cisplatin/gemcitabine) followed by EPP in all patients and the recommendation of adjuvant radiation (74). Operability was 74%, with resectability of 61%, with an intention-to-treat median overall survival of 19.8 months compared to 23 months in those who underwent EPP (74). A similar study was published the same year by an Italian group with similar results (75). In 2009, a multicenter phase II trial was published evaluating neoadjuvant cisplatin/pemetrexed in the context of trimodal therapy (76). Patients with stage I–III MPM received 4 cycles of cisplatin/pemetrexed and then those without disease progression underwent EPP followed by adjuvant hemithoracic radiation (76). Patients who completed all therapies had a median survival of 29.1 months with a 2-year survival of 61.2%, and the primary endpoint of pathological complete response was achieved in 5% of patients; however, by intention-to-treat analysis, the median survival was only 16.8 months with a 2-year survival of 37.2% (76). This study led to the authors' conclusion that, in highly selected patients, trimodal therapy may be beneficial (76). A similar multicenter phase II study was published in 2010 by the European Organisation for Research and Treatment of Cancer (EORTC) with the primary end-point defined as "success of treatment" (77). Seventy-four percent of patients underwent EPP and 65% completed adjuvant radiotherapy, but only 42% of patients met the definition of success, leading the authors to conclude that, "although feasible, trimodality therapy in patients with mesothelioma was not completed within the strictly defined timelines of this protocol and adjustments are necessary" (77). Overall, though feasible in certain patients, trimodal therapy involving neoadjuvant chemotherapy, EPP, and adjuvant radiotherapy proves to be challenging for patients, with low completion rates, and poor results in patients with N2 disease (contralateral lymph node metastases, see *Table 1*) or biphasic/sarcomatoid histology (70,74).

As surgical practice has shifted from EPP to PD, few

studies evaluating trimodal therapy with PD have been published. In 2012, a study was published attempting to compare EPP to PD in the trimodal setting (8). This was a non-randomized, prospective trial comparing neoadjuvant chemotherapy (3 cycles of either cisplatin/gemcitabine or cisplatin/pemetrexed) followed by EPP and adjuvant radiotherapy to PD with hyperthermic pleural lavage with povidone-iodine and adjuvant chemotherapy (4–6 cycles of either cisplatin/gemcitabine or cisplatin/pemetrexed) and prophylactic radiotherapy (8). Sixty-eight percent of patients completed all treatment in the EPP group, with 2 patients surviving more than 50 months (median survival 12.8 months) (8). A majority of patients (96.3%) completed all treatment in the PD group, with a median survival of 23 months in the PD group compared to 12.8 months in the EPP group, leading the authors to conclude that PD was more feasible and had better outcomes than EPP in the context of trimodal therapy (8).

Specifically regarding the addition of adjuvant or neoadjuvant radiation therapy, the data is similarly mixed, uncontrolled and nonrandomized. Classically, hemithoracic radiation involved irradiating the entire pleural cavity, including ipsilateral nodal beds, with photon/electron radiation using anteroposterior/posteroanterior fields and blocks shielding vital organs, in the context of EPP where lung-associated complications are not a concern (78). However, it remained difficult to spare other vital organs (esophagus, heart, bowel, etc.) from radiation exposure as well as challenging to target the posterior diaphragmatic sulcus (79). Intensity-modulated radiation therapy (IMRT) was initially developed for use in head-and-neck and prostate cancers, using three-dimensional computerized planning to allow radiation doses to conform more closely with target areas (80,81). In 2007, a prospective study evaluating local control with adjuvant IMRT following EPP (with or without chemotherapy) demonstrated improved median and 3-year survival, with only 5% of irradiated patients having a local recurrence within the irradiated field (79). In 2013, a retrospective study also demonstrated safety and improved local recurrence rates with adjuvant IMRT following EPP (82), and feasibility was further demonstrated by another phase II trial (83). In 2014, a European group attempted a multicenter, international RCT (SAKK 17/04) to evaluate the effect of the addition of adjuvant IMRT compared to neoadjuvant cisplatin/pemetrexed and EPP alone (84). Unfortunately, accrual was slow and the primary endpoint of 1-year relapse-free survival could not be reached, leading the authors to

advocate against the use of routine hemithoracic adjuvant radiotherapy (84). The 2014 SMART trial aimed to evaluate neoadjuvant IMRT in T1–3N0 MPM followed by EPP with adjuvant chemotherapy (cisplatin and an anti-folate) offered to those with ypN2 disease [ipsilateral or subcarinal nodal involvement, using the 7th edition of the International Association for the Study of Lung Cancer (IASLC) TNM classification] (5,85). The 3-year survival was 84% in the epithelial subtype, compared to 13% in the biphasic subtype; however, there was no comparison to adjuvant radiotherapy (85). Another study, published the same year, evaluated adjuvant radiotherapy following PD, with most patients (95%) receiving either adjuvant, neoadjuvant, or sandwich chemotherapy (86). This study demonstrated a median overall survival of 33 months and PFS of 29 months (86). Given the need for close monitoring and adequate selection of patients, this approach is not generally widely recommended outside of highly specialized centers (78). In 2016, a group from Memorial Sloan Kettering Cancer Center (MSKCC) published results of the IMPRINT phase II trial, demonstrating feasibility and acceptable complication rates associated with adjuvant IMRT following neoadjuvant chemotherapy and PD (87); the following year, the same group retrospectively compared PD trimodal therapy with conventional radiotherapy to hemithoracic IMRT, finding improved overall survival in those who had received IMRT (20.2 months compared to 12.3 months) (88). Overall, completion of adjuvant IMRT remains low at roughly two-thirds, regardless of whether patients receive EPP or PD (89).

At least in the United States, where both ASCO and NCCN guidelines recommend multimodality treatment, this seems to be underutilized, with up to 29% of patients with stage I–III epithelioid MPM not receiving curative-intent therapy, especially in low-volume settings (90). A review of the National Cancer Database further demonstrated that only 20% of patients receive cancer-directed surgery, 2.6% of whom receive trimodal therapy (91), which may be a result of the lack of compelling data and demonstrate a need for further well-conducted RCTs (44). Systematic reviews have shown the failure of enrolment in RCTs, the need for further phase II trials including a control group, and the need to systematically publish intention-to-treat analyses (92,93). The upcoming MARS-2 results in September 2020 (see section ‘Surgery’) may help clarify the benefit of multimodality treatment (45). Additionally, the MSKCC group should be publishing results of their phase II toxicity study comparing adjuvant versus neoadjuvant platinum/pemetrexed in

combination with PD and adjuvant IMRT in July 2021; this may help clarify the optimal order of chemotherapy in trimodal therapy (94).

Emerging therapies and future prospects

Current treatment of malignant mesothelioma includes surgery, chemotherapy, and radiation therapy. However, prognosis remains poor despite multimodality treatment with overall survival being 9 to 17 months after diagnosis (75,95,96). In light of this, a number of new emerging and experimental treatments are becoming available for patients not responding to conventional treatment, including immunotherapy, T-cell therapies, anti-tumor vaccines, and virotherapy.

Immunotherapy

The immune system plays an important role in MPM with interactions between the tumor and the immune system being driven mostly by local immunoregulatory mechanisms, and there is evidence of systemic response to tumor-directed immunotherapies (97,98). Patients with MPM have shown improved survival when tumors were highly infiltrated by cytotoxic CD8+ T cells (tumor-infiltrating lymphocytes), whereas programmed death-ligand 1 (PDL1) expression is associated with reduced survival (median OS 5 months in patients who are PDL1-positive *vs.* 14.5 months PDL1-negative patients; $P < 0.0001$) (99–101). Off-label usage of anti-PD1 antibodies pembrolizumab and nivolumab as single agents, or nivolumab with the cytotoxic T lymphocyte antigen 4 (CTLA-4) antibody ipilimumab have shown promising activity (102,103).

Popat *et al.* presented preliminary results of a phase III trial in which 144 patients with advanced pre-treated MPM were randomised to either pembrolizumab or standard chemotherapy. Pembrolizumab improved the objective response rate (22%) relative to gemcitabine or vinorelbine (6%). However, PFS (2.5 *vs.* 3.4 months) as well as overall survival (10.7 *vs.* 11.7 months) were similar in both groups (102). In another trial, Alley *et al.* treated 25 patients with PDL1-positive MPM with pembrolizumab. Five (20%) patients had a partial response and 13 (52%) had stable disease (104).

Other immunotherapies have been assessed. For example, a multicenter randomised, non-comparative, open-label, phase 2 trial (MAPS2) conducted in 21 hospitals in France aiming to assess nivolumab alone or in combination with

ipilimumab achieved 12-week disease control in 24 (44%) out of 54 patients who received nivolumab, and in 27 (50%) out of 54 receiving nivolumab plus ipilimumab. Objective responses were 10 (19%) with nivolumab and 15 (28%) with nivolumab plus ipilimumab (103). Another single-arm, phase II trial (INITIATE) assessed the combination of ipilimumab and nivolumab for the treatment of recurrent MPM. In the study, 34 patients were evaluated for response at 12 weeks. Ten patients (29%) had a partial response and 13 patients (38%) had stable disease. However, adverse events were reported in 33 patients (94%) with 12 patients (34%) reporting grade 3 toxicity (105). These findings show promising activity of both single and double agent blockade in MPM.

Another CTLA-4 inhibitor, tremelimumab, was studied in a randomized phase II trial (DETERMINE) in 571 patients but did not provide survival benefit compared to placebo (median 7.7 *vs.* 7.3 months, respectively) (106). When combined with the anti-PDL1 antibody durvalumab in a phase II study, there was suggestion of activity as 11 (28%) out of 40 patients had an immune-related objective response (all partial responses) with a median response duration of 16.1 months, and 25 patients (63%) had disease control with median PFS of 5.7 months and median overall survival of 16.6 month (107). However, randomized data are required.

Older immunotherapeutic approaches using interferons or interleukin-2, either alone or in combination with chemotherapy, have not offered substantive advantage (108-110).

T-cell therapies

Mesothelin (MSLN) is a recently characterised cell-surface glycoprotein and biomarker which is expressed on normal mesothelial cells (111), but also on malignant mesothelioma and other solid tumors' cell surface (5). It has been found to shed from malignant mesothelioma cells and certain other solid tumors (112), and serum levels of MSLN may be elevated in as many as 80–84% of patients with MPM (113,114). Adoptive T-cell therapy represents a promising new strategy in MPM. A phase I trial investigating chimeric antigen receptor (CAR) T-cell therapy targeting MSLN in MPM patients recently reported encouraging results. In the study, 18 patients were treated with a single dose of CD28-costimulated MSLN CAR-T cells with the I-caspase-9 safety gene administered intrapleurally with or without cyclophosphamide preconditioning. Fourteen patients

received subsequent anti-PD-1 therapy, off-protocol. Of those 14 patients, 2 had complete metabolic response on PET, 5 had partial responses, and 4 had stable disease. Regarding safety, no CAR-T cell-related toxicities higher than grade 1 were observed (115). This shows promise for future developments especially when combining CAR-T cell therapy with anti-PD-1 therapy giving previous pre-clinical data showing that CAR-T cells become functionally exhausted in the presence of a large tumor burden and, in some patients, CAR-T cells expand following PD1 blockade (116).

Vaccines

Another way to prime acquired anti-tumoral activity of the immune system is vaccination, which has led to significant research on vaccine therapy in MPM. One promising candidate is the Wilms tumor-1 (WT1) protein in MPM which is highly expressed compared to normal (117), making it an ideal target for a tumor-selective cancer vaccine. A double-blind, controlled, two center phase II trial randomized 41 pre-treated MPM patients to either galinpepimut-S, a WT1 analogue peptide vaccine, with Granulocyte-macrophage colony-stimulating factor (GM-CSF) and Montanide, which are immunologic adjuvants, or GM-CSF and Montanide alone. The vaccine arm had improved PFS at 1 year (45%) compared to the control arm (33%) with median PFS of 10.1 *vs.* 7.4 months. Median overall survival was 22.8 months in the vaccine group versus 18.3 months in the control group. However, this study was not powered for comparison between the treatment arms (118). This shows promise for new treatment modalities given the limited treatment options for MPM.

Another therapeutic target is dendritic cell (DC) therapy which is a cell-based vaccination used to instigate an anti-tumor immune response. DCs present tumor-associated antigens (TAAs) to the T-cells in lymph nodes, inducing proliferation and activation of tumor-specific CD4+ and CD8+ T-cells. DC function is impaired in cancer patients (119,120). In DC therapy, DCs are matured and activated *ex vivo* to enhance their immunogenic function and circumvent tumor immunosuppression, and they are then loaded with TAAs. Phase I trials demonstrated promising clinical response with long-lasting radiological response (121,122). Recently, a multicenter, randomized phase II/III trial was initiated with the aim of assessing DCs loaded with allogenic tumor cell lysate (MesoPher) in MPM patients after chemotherapy (DENIM trial) to evaluate whether this will improve survival

and prove effective as a maintenance therapy (123).

Virotherapy

Oncolytic virotherapy has recently emerged as a promising experimental modality. Virus vectors are used to infect tumor cells, leading to cell lysis while releasing tumor-associated and viral antigens and thus triggering an anti-tumor immune response (124,125). In most viral platforms, the preferred route of administration is intratumoral (IT) which makes MPM an ideal model for the study of oncolytic virotherapy given the accessibility of the pleural cavity and the pattern of growth (126,127). Adenovirus has been the most studied oncolytic virus preclinical and clinical trials. It has shown good results in animal studies with tumor regression and improved survival (128). Human trials using adenoviral vectors have shown good safety profiles, but low response rates (129-131).

Herpes simplex virus type 1 (HSV-1) is another virus that has been studied in preclinical trials, but no human trials have been published. An ongoing phase I/IIa trial is seeking to evaluate the safety and biological effects of single and multiple administrations of HSV1716, an oncolytic virus which is a mutant HSV-1, in the treatment of MPM (132).

Other investigational therapies

Other systemic treatment modalities have been studied, but none so far are indicated outside the setting of a clinical trial. For example, nintedanib [a vascular endothelial growth factor receptor (VEGFR), platelet-derived growth factor receptor (PDGFR), and fibroblast growth factor receptor (FGFR) tyrosine-kinase inhibitor] has shown promising benefits in PFS in a phase II trial when added to conventional chemotherapy (133), but those benefit were not reproducible once a phase III trial was conducted (134). Similarly, Vorinostat, an oral histone deacetylase inhibitor, showed promise in an early trial (135), but when a phase III trial involving 661 patients was conducted, there was no significant benefit compared to placebo (136).

Conclusions

MPM is a rare tumor predominantly caused by asbestos exposure with a very prolonged latency period. It remains lethal with poor outcomes despite aggressive therapy as patients typically present with advanced disease. Given this,

surgical intervention remains controversial, and is typically reserved for patients with earlier-stage disease who are candidates for multimodal therapy. Surgical approach is also contentious, though recently surgical culture has shifted from the historically preferred but highly morbid EPP to the more conservative extended PD, while aiming for an R1 resection. Additional chemoradiotherapy is also the mainstay of treatment, though there is a lack of evidence regarding the optimal timing of such interventions. Overall, patient selection remains critical, especially given the lack of consensus.

Other treatment options are beginning to emerge and continue to evolve as our understanding of the disease improves. In the last few years, the genetics, immunobiology, biomarkers, and tumor microenvironment have been studied, and the knowledge derived has thus opened the door to many emerging therapies. Currently, there are multiple clinical trials interrogating various treatment modalities as well as combination therapies. However, evidence supporting the use of these new therapeutic modalities remains scarce mainly due to the lack of randomized trials.

Given the rarity of the disease and the lack of success with a one-size-fits-all approach in MPM patients, scientific collaborations are warranted to conduct well designed studies that will attempt to slow disease progression, decrease morbidity of current therapies, and improve patient survival.

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Footnote

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