Review Article: Oncology-Other

An update in malignant peritoneal mesothelioma diagnosis and treatment—a narrative review

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Contributions: (I) Conception and design: JH Terhune; (II) Administrative support: JH Terhune; (III) Provision of study materials or patients: JH Terhune; (IV) Collection and assembly of data: JH Terhune; (V) Data analysis and interpretation: JH Terhune; (VI) Manuscript writing: All authors; (VII) Final approval of manuscript: All authors.

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Background and Objective: Malignant peritoneal mesothelioma (MPM) poses a multitude of treatment challenges due to its insidious presentation, frequently advanced disease at the time of presentation, resistance to treatments and high rate of recurrence. Since MPM's discovery in the 1700s and the recognition of the association between mesothelioma and asbestos in the mid-20th century, the treatment and detection landscape have changed and improved for all cancer types. Despite tremendous medical advancements elsewhere, patients with MPM continue to have relatively poor prognoses. The objective of this review is to summarize current practices and present recent advances in therapy.

Methods: An initial query of PubMed articles was performed in 2021 using terms including mesothelioma, malignant mesothelioma, and peritoneal mesothelioma; additional queries were performed in 2022 and 2023 using the same search terms. Subsequently, a search of the Clinicaltrials.gov database was performed as well to assess for ongoing to trials. Articles written in English from 1840–2023 were included in the study.

Key Content and Findings: Pre-operative assessment of the disease burden has improved with advancement in imaging techniques that allow better characterization of intra- and extra-peritoneal disease. For surgical candidates, cytoreductive surgery and heated intraperitoneal chemotherapy continue to remain mainstays of therapy. For non-surgical candidates, Pemetrexed-based regimens have been widely incorporated as a primary chemotherapeutic option for the treatment of mesothelioma given its improvement in overall survival. With advances in medical therapy, improvements in outcomes have been seen with chemotherapy in conjunction with immunotherapy, chimeric antigen receptor (CAR)-T, photodynamic, or oncolytic virus therapy.

Conclusions: MPM is a rare and fatal disease, primarily treated surgically, with high rates of recurrence resulting in overall poor outcomes. However, with advances in detection and characterization of disease, and improvements in targeted therapy, outcomes can improve.

Keywords: Malignant peritoneal mesothelioma (MPM); novel therapies; mesothelioma; carcinomatosis

Received: 01 December 2022; Accepted: 25 May 2023; Published online: 21 July 2023.

doi: 10.21037/asj-22-37

View this article at: https://dx.doi.org/10.21037/asj-22-37

Introduction

Background

Mesothelioma is a disease of the mesothelial lining of the pleura, pericardium, peritoneum and the tunica vaginalis. Malignant peritoneal mesothelioma (MPM) is a rare disease with fewer than 500 cases diagnosed in the United States each year, making it more challenging to study than other

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Table 1 The search strategy summary

Items	Specification
Date of search	5/11/2021 to 1/13/2023
Databases and other sources searched	PubMed, ClinicalTrials.gov
Search terms used	"Mesothelioma", "Malignant peritoneal mesothelioma", "staging", "Cytoreductive surgery and hyperthermic intraperitoneal chemotherapy", "Targeted therapy", "BAP1 mutations", "Immunotherapy", "Photodynamic therapy", "Mesothelin", "CAR-T cell", "Oncolytic virus", "Monoclonal antibodies"
Timeframe	1840–2023
Inclusion and exclusion criteria	Only studies in the English language were included; no strict inclusion and exclusion criteria were used. All papers were reviewed and excluded if not pertinent
Selection process	Data selection was conducted independently by JJN and MDM, and reviewed by JHT. Literature selection was agreed upon by all three authors

more common cancers (1,2). It can be associated with a preceding asbestos exposure and typically presents with disease years after the initial exposure. Mesothelioma confined to the peritoneal cavity, or MPM, is an exceedingly rare disease; its symptoms are often non-specific and as a result, diagnosis is often obtained at a late stage. Treatment consists of a combination of surgical debulking and systemic therapy, yet recurrence remains common, and death from the disease is nearly universal. New modalities of therapy are continuously being developed in order to improve prognosis.

Rationale and knowledge gap

The rarity of MPM makes clinical trial enrollment challenging and limits basic science research into the disease. This means that clinical data often come from single-institution studies or are extrapolated from pleural mesothelioma trials, which reduces the generalizability of the results. Over the last several years, new therapeutic avenues, including molecular targeted treatments and immunotherapy, have revolutionized the management and outcomes of many cancer types. Some of these new strategies are currently being explored in mesothelioma, including MPM. While other reviews have broadly highlighted history, diagnosis, and treatment of MPM, we felt that a review of the available literature with a focus on recent advances in mesothelioma biology, experimental treatments, and ongoing clinical trials was timely.

Objective

The purpose of the study is to review the available MPM literature in order to summarize current practices and present recent advances in basic research and new therapies. We present this article in accordance with the Narrative Review reporting checklist (available at https://asj.amegroups.com/article/view/10.21037/asj-22-37/rc).

Methods

Relevant studies on MPM were identified through a PubMed search using various combinations of search terms reported in *Table 1*, connected by the Boolean operator AND. Additional publications of interest were identified from reference lists of landmark papers in the field. Information on ongoing clinical trials on mesothelioma were identified searching the ClinicalTrial.gov website. Only studies in the English language were included. Data were extracted and reviewed by all authors of this review to determine adherence to the topic and relevance.

Presentation and diagnosis

MPM is a rare disease with only 300 to 400 cases diagnosed in the United States each year (1,2). There are approximately 3,000 people are diagnosed with malignant mesothelioma each year; the majority of cases are pleural in origin, with only 10–25% of cases arising primarily from the peritoneal layer (1-3). The diagnosis of peritoneal mesothelioma is often delayed due to the non-specific and vague symptoms, which are attributable to the diffuse spread of many small tumors throughout the abdominal cavity. When symptoms are present, they can be variable and most commonly include increased abdominal girth/distension (up to 80%) and/

or abdominal pain in the majority of patients (up to 58%) (3-6). Additional signs and symptoms include weight loss, shortness of breath, abdominal mass, fever, night sweats, change in bowel habits, new onset hernia, or an incidental imaging or intra-operative finding (5-7). In two recent analyses, 36–92% were diagnosed while undergoing surgery for separate pathology emphasizing that many patients can be asymptomatic (8,9).

Peritoneal mesothelioma tumors are frequently first identified by cross-sectional imaging and then confirmed with a percutaneous needle biopsy. When biopsies are performed percutaneously, they should occur along the midline so that the tract can be excised later to prevent tumor seeding (10). Paracentesis can also provide a diagnosis; however, the ascites fluid infrequently yields a sufficient amount of tumor cells and thus it is primarily used for symptom relief from abdominal distention (10). Once a biopsy is performed, the tissue is stained using immunohistochemistry markers specific for a diagnosis of MPM such as calretinin, cytokeratin 5/6, Wilms tumor 1 (WT1), and podoplanin, while other tumor markers including CEA, B 72.3, MOC-31, and Ber-EP4, frequently stain negative (10-12) BRCA1 associated protein (BAP1) is inactivated in approximately half of pleural mesotheliomas and has recently been shown to be among the most common germline and somatic mutations in peritoneal mesothelioma (13-15). BAP1 expression can reliably help to differentiate mesothelioma from other malignancies that may be on the differential (16). Prognostically, the loss of BAP1 protein nuclear expression has been shown to be associated with longer overall survival compared to those with intact BAP1 expression and thus BAP1 germline mutation testing should be considered in patients with peritoneal mesothelioma (15,17).

Peritoneal mesothelioma has several subtypes whose biological behavior varies widely, and it is thought to exist along a spectrum of disease from indolent to rapidly progressive. Benign multicystic and well-differentiated papillary mesotheliomas (WDPM) are at the indolent end of the spectrum and considered relatively benign. Several series advocate for observation unless a patient is symptomatic and/or there is progression of disease, in which case cytoreductive surgery (CRS) with or without hyperthermic intraperitoneal chemotherapy (HIPEC) may be considered (8,9).

Malignant mesothelioma itself has three subtypes with varying degrees of aggressiveness: epithelioid, sarcomatoid, and biphasic. Epithelioid mesothelioma accounts for 75–90% of reported cases of peritoneal mesothelioma and is associated with the best overall prognosis of the malignant subtypes (4,18-20). Sarcomatoid mesothelioma is extremely rare and has a very poor prognosis, while the mixed or biphasic subtype contains both epithelioid and sarcomatoid elements and accounts for up to 25% of cases (20).

Tumor markers in peritoneal mesothelioma play a limited role in diagnosis of the disease, but may help in assessing response to therapy and/or surveillance similar to many other solid malignancies: soluble/serum mesothelin-related protein (SMRP) and CA-125 are two such candidates (4,5,21) In one study, CA-125 was found to be elevated in >50% of patients prior to treatment and served as an accurate surrogate for complete cytoreduction and disease recurrence after an initial treatment response (21).

Prognosis and outcomes

Peritoneal mesothelioma has clinicopathologic features that have been shown to have prognostic significance. Improved survival has been demonstrated to correlate with younger age (<60 years old), completeness of cytoreduction (CCR), low grade histology, use of intraperitoneal cisplatin as compared to mitomycin C during HIPEC, and epithelioid histology (22,23). On the other hand, features that have been identified which portend a worse prognosis include: high peritoneal cancer index (PCI) score, thrombocytosis (platelets ≥367), high Ki-67 level (>25%), presence of lymph node metastasis, incomplete cytoreduction, and sarcomatoid or biphasic histology (23-27).

Overall survival for MPM varies widely; without treatment survival is typically less than a year (5,28-31) while selected patients who undergo CRS and HIPEC have overall survival ranging from 29 to 98 months (22,30,32-36). The widely disparate outcomes for surgical versus non-surgical patients demonstrate that careful selection for surgical management is paramount. Two prognostic features worthy of careful consideration to surgeons are the subtype of mesothelioma and the ability to have a complete cytoreduction. A retrospective analysis demonstrated that overall survival was 51.5 months for patients with epithelioid or well-differentiated papillary/cystic mesothelioma versus 10.5 months for patients with sarcomatoid and biphasic histology; registry study data has further supported this finding (19,36). Regarding the CCR in peritoneal mesothelioma, Magge *et al.* demonstrated a median overall survival of 56.7 months in patients who had a CCR 0/1 versus 7.4 months for those with a CCR 2/3 resection, emphasizing

the importance of careful pre-operative evaluation and patient selection (19). Furthermore, at experienced, high-volume centers, post-operative complications and mortality following CRS are reduced compared to other high risk procedures (e.g., trisegmental hepatectomy, esophagectomy, etc.) emphasizing the importance of institutional experience and CRS outcomes (37).

Staging

The ability to accurately assess the extent of disease pre-operatively and the ability to completely cytoreduce is of utmost importance in mesothelioma as suggested by the disparate outcomes between patients who have a complete versus an incomplete cytoreduction. Similar to other malignancies which may cause carcinomatosis, MPM is staged using the peritoneal cancer index (PCI). Briefly, the PCI divides the abdomen into nine regions and four small bowel sections. Each region is scored on a scale from 0 to 3 based on the burden of disease and scores are summed with totals ranging from 0–39 (38). The threshold at which the PCI score becomes a negative prognostic factor for CCR varies depending on the disease and histology. For example, in gastric cancer, a PCI >12 is a negative predictive factor, whereas in peritoneal mesothelioma a higher PCI cut-off of 20 has been shown to be associated with poor survival (25,39). PCI is determined pre-operatively using cross-sectional imaging and then again intra-operatively, either at the time of a diagnostic (or staging) laparoscopy or during CRS/HIPEC.

Recently, the concept of a pathologic PCI (pPCI) has been proposed; this is determined based on a thorough pathologic assessment of the specimens sent from a CRS/HIPEC. A recent study noted that pPCI resulted in lower PCI scores as compared to the intra-operative surgeon's assessment (sPCI) in 65% of patients, suggesting there may be over-estimation of disease at the time of surgery (40). The concordance between the pPCI and the sPCI varied among the different histologies assessed. Of particular interest, the concordance was markedly lower in peritoneal mesothelioma as compared to the population as a whole (6.7% versus 19.4% in all patients) (40). This recently developed concept of a pPCI requires future investigation to determine its clinical significance and if it can be used prognostically.

Imaging

Cross-sectional imaging is an integral part of the pre-operative assessment and operative planning for patients with newly diagnosed or recurrent MPM. Computer tomography (CT) has traditionally predominated in the work-up for patients with carcinomatosis due to its wide availability and accessibility, but increasingly magnetic resonance imaging (MRI) has begun to play a more substantive role. However, much of the data supporting the use of these modalities in the assessment of MPM is extrapolated from literature on carcinomatosis from colorectal carcinoma and other etiologies (41-44).

CT is frequently the first diagnostic imaging modality performed to evaluate patients with suspected or confirmed carcinomatosis. CT findings consistent with peritoneal mesothelioma include thickening of the peritoneum or mesentery (often with an irregular or nodular fashion), solid masses, omental thickening with or without masses, scalloping of adjacent organs, and ascites (45-47). Unlike in pleural mesothelioma, calcified plaques are uncommon and should elicit concern for an alternative diagnosis (46). The use of intravenous (IV) contrast can be helpful as MPM tumors typically enhance with contrast (48). The lack of a primary tumor with no lymph node involvement or distant metastases can help add primary peritoneal malignancy to the differential (49). Positron emitting tomography (PET)/CT, as compared to diagnostic laparoscopy, has very low sensitivity for the diagnosis of peritoneal disease in patients with pleural mesothelioma, likely related to the small peritoneal implants often being below the resolution of the imaging (50).

MRI has become increasingly utilized, alone and in conjunction with CT scan, based on data demonstrating an enhanced ability to detect and more accurately assess the extent of disease (41,42,51). Proponents of MR suggest that CT may under-stage patients: one study demonstrated upstaging in approximately half of the patients from the pre-operative evaluation based on CT alone to the surgical PCI based on operative findings (41,43). Furthermore, MRI has been shown to have greater accuracy for lesions <0.5 cm compared to CT, which is relevant since MPM often presents with many, smaller tumors (42). A combination of the two imaging modalities may have greater accuracy in the pre-operative analysis of tumor burden than CT alone (52). The greater sensitivity and specificity of MRI leads to a more accurate pre-operative PCI assessment as compared to CT for patients who underwent CRS and HIPEC (44,53). With the increased sensitivity and specificity that MRI and diffusion weighted imaging add to pre-operative evaluation and the ability to evaluate the retroperitoneum, it can potentially provide an alternative and

non-invasive method to surgical planning as compared to laparoscopy (53,54).

While invasive, diagnostic laparoscopy is still performed to stage the abdomen prior to, or at the time of, a planned CRS/HIPEC. It permits biopsy of lesions for pathologic confirmation and provides accurate staging to help to guide candidate selection for CRS and HIPEC (55,56). The finding of unresectable disease at the time of diagnostic laparoscopy can help to prevent non-therapeutic laparotomies at CRS and HIPEC when the tumor burden is not amenable to complete cytoreduction. Diagnostic laparoscopy is also considered a safe and useful tool in patients with pleural mesothelioma who are suspected of having bicompartmental disease (50,57).

All patients with MPM should undergo cross-sectional imaging as part of their diagnostic work-up, the choice of CT versus MR is at the discretion of the treating surgeon and their/institutional practices, as is the decision for a diagnostic laparoscopy.

Surgical management

The surgical management of peritoneal mesothelioma entails two primary principles: surgical debulking and intraperitoneal chemotherapy. The extent of surgical debulking, or cytoreduction, is measured by the CCR. CCR scores are based on the degree to which the disease burden has been surgically removed (36,38,58). Similar to other peritoneal surface malignancies, a CCR score of 0 corresponds to no gross disease after CRS, CCR of 1 indicates nodules <2.5 mm persisting after cytoreduction, CCR of 2 is residual lesions measuring 2.5 mm to 2.5 cm, and CCR of 3 indicates residual lesions are >2.5 cm. CCR of 2 and 3 are commonly considered incomplete cytoreduction and portend a poor prognosis, while CCR scores of 0 and 1 are associated with improved survival (36). Due to its often diffuse involvement of the peritoneal surfaces, cytoreduction in MPM can require extensive peritonectomy to achieve a favorable CCR. A CCR of 0 or 1 may not be achieved if there is a significant disease burden in the porta hepatis and/or bowel serosa; in these cases, HIPEC is typically not performed.

Intraperitoneal (IP) chemotherapy can be given in several different settings for patients with peritoneal surface malignancies. The most common administration method is HIPEC upon completion of debulking, but early postoperative chemotherapy (EPIC) after CRS and adjuvant/long-term normothermic intraperitoneal chemotherapy (NIPEC) have also been investigated. Previous data demonstrates a survival benefit with HIPEC after CRS for patients with peritoneal mesothelioma and it is widely accepted as the standard of care in appropriately selected patients (10,31,59-62). CRS and HIPEC or EPIC are associated with improved long-term survival in select patients with MPM (63,64). An overall survival of 34–96 months has been reported in patients who are undergoing combination of surgical and chemotherapeutic therapy (22,65).

Based on experience in the treatment of disseminated ovarian cancer, EPIC has been evaluated in other peritoneal surface malignancies, including MPM, colorectal, and appendiceal malignancies. In several studies investigating EPIC after CRS and HIPEC in non-ovarian histologies, no survival benefit was seen and there was greater morbidity in the immediate post-operative period (66-68). However, Sugarbaker *et al.* demonstrated a survival benefit with the addition of six months of adjuvant IP paclitaxel or pemetrexed plus IV cisplastin based on a retrospective analysis of their patients with epithelioid peritoneal mesothelioma. The 5-year survival for patients who received long-term IP chemo in addition to HIPEC and EPIC was 75%, while 5-year survival for patients who underwent CRS and HIPEC alone was 44% and 52% with the addition of EPIC to HIPEC (69). A follow-up single-institution randomized control study was performed, which again demonstrated improved survival associated with their regimen of long-term IP chemotherapy or NIPEC (70). The use of adjuvant NIPEC deserves future investigation to determine if the survival benefit can be replicated without undue morbidity.

The most frequently used IP chemotherapy agents for HIPEC are cisplatin and mitomycin C. Small single institutional and retrospective data demonstrate a benefit to cisplatin over mitomycin C, but data is limited due to the rarity of this disease. A non-randomized study from Wake Forest in 2010 evaluated the use of mitomycin C versus cisplatin in 38 patients with MPM and found median survivals of 10.8 and 40.8 months respectively and a trend toward improved disease-free and progression-free survival using cisplatin (71). A retrospective analysis of over 200 patients from three high-volume academic centers reinforced the improved outcomes with the use of cisplatin compared to mitomycin C for HIPEC (22). Carboplatin has also been investigated as an alternative to mitomycin C and has been shown to have significantly improved overall survival, in addition to reduced hospital and ICU length of stay and lower requirement for blood products (72). International guidelines currently support the use of either

Table 2 Summary of clinical trials involving immunotherapy, photodynamic therapy, and oncolytic virus therapy evaluated

ClinicalTrials.gov identifier/ authors	Year	Phase	Cancers	Intervention	Region
Simon *et al.*/NCT00061477	2002–2004	II	Malignant peritoneal mesothelioma	Premetrexed + gemcitabine	USA
NCT00128102	2005–2011	III	Malignant pleural mesothelioma	Premetrexed + carboplatin/cisplatin with or without vorinostat	International
	2001–2002	II	Pleural of peritoneal mesothelioma	Gefitinib	USA
NCT01907100	2016–2018	II/III	Malignant pleural mesothelioma	Nintedanib + premetrexed & cisplatin	International
NCT01843374	2013–2014	IIb	Unresectable pleural or peritoneal mesothelioma	Tremelimumab	International
NCT02588131	2015–2016	II	Unresectable pleural or peritoneal mesothelioma	Tremelimumab + durvalumab	International
NCT01772004	2014–2015	Ib	Unresectable pleural or peritoneal mesothelioma after chemotherapy	Avelumab	International
Hahn *et al.*	1997–2004	II	Peritoneal carcinomatosis and sarcomatosis	PDT + CRS	USA
NCT01362790	2011–2017	II	Malignant mesothelioma	SS1P + pentostatin + cyclophosphamide	USA
NCT01119664	2011–2013	I	Unresectable malignant pleural mesothelioma	Ad.IFN & celecoxib + premetrexed or premetrexed + gemcitabine	USA
NCT02879669	2016–2020	I	Unresectable malignant pleural mesothelioma	ONCOS-102 + premetrexed/ cisplatin (carboplatin) + cyclophosphamide	International

PDT, photodynamic therapy; CRS, cytoreductive surgery; Ad.IFN, adenoviral vector containing human interferon-a2b.

cisplatin or mitomycin C and the decision regarding the agent of choice is at the discretion of the treating physician and/or institutional guidelines (73).

Bicompartmental disease is rare and presents an additional treatment challenge due to the morbidity of treating both intra-thoracic and -abdominal disease. In post-mortem data, synchronous disease was found in 1.8% of patients (9/500) but these incidences were primarily related to a mesothelioma diagnoses along with a different type of cancer (74). The description of how to treat bicompartmental disease was mostly limited to case reports until a recent single-institution study described the outcomes of 50 patients with pleural and peritoneal mesothelioma with surgical treatment in at least one cavity, most of which had surgery in the abdominal cavity (75). Patients were first diagnosed with peritoneal mesothelioma (70%), while 26% presented first with pleural disease and 4% had simultaneous disease diagnoses. Progression to bicompartmental disease occurred within 1 year in over half of the patients. The median overall survival of the entire cohort was 33.9 months from initial intervention, but in the few patients with a simultaneous presentation of peritoneal and pleural disease, the median survival was an impressive 66 months. Furthermore, in patients who progressed to bicompartmental disease in <1 *vs.* >1 year, median survival was 26 *vs.* 59 months respectively. The survival rates from this paper far exceed the historical numbers for patients having non-operative management, suggesting that a more substantial role for surgery in this population may exist than previously thought.

Systemic therapy for patient with MPM

There is no clear consensus on the optimal systemic therapy of MPM and given the rarity of this tumor, much of the data that guide management of MPM is based on retrospective series and small, single center, open-label trials (*Table 2*). As a result, new therapies for MPM are often based on data extrapolated from studies in pleural mesothelioma.

Systemic chemotherapy for MPM is typically considered

in patients who are deemed to be poor surgical candidates or in those with metastatic, locally unresectable, or bicompartmental mesothelioma. A number of different chemotherapeutic regimens have been explored and much of the evidence supporting current clinical practice is derived from data in the US Expanded Access Program (76). Two open-label, non-randomized studies from this program investigated the efficacy of pemetrexed, an anti-folate agent, and a platinum agent (cisplatin or carboplatin) in patients with advanced MPM who are chemotherapy-naïve or previously treated (76,77). Collectively, over one thousand patients, including those with pleural mesothelioma, were treated for six cycles or until disease progression. In the subset of peritoneal mesothelioma patients (98 and 109 patients respectively) the overall response rates were up to 26%, with stable disease in up to 45% (76,77). As a result of these landmark studies, most patients today are treated with pemetrexed, either alone or in combination with platinum-based agents.

Alternative treatment regimens have also been explored including a phase II clinical trial which investigated the efficacy of pemetrexed in combination with gemcitabine for chemotherapy naïve patients with MPM (78). The study demonstrated disease control rates of 50%, with response rates of 15% and overall survival time of 26.8 months. A limitation of this study is that it only included 20 patients with peritoneal mesothelioma, without sufficient power for a subgroup analysis, and considerable hematologic toxicity. Given the overall low response rate (15%), it is unclear whether this regimen confers enough clinical benefit to warrant routine use in patients with peritoneal mesothelioma only.

Targeted therapeutic approaches to MPM

Advances in DNA sequencing technology, gene expression analyses and methylation studies over the last decade have greatly expanded our knowledge of the molecular landscape that characterize most solid tumors. An extensive analysis of molecular alterations in mesothelioma was recently reported by the Cancer Genome Atlas consortium (79). In this study, the genetic and epigenetic features of 74 mesothelioma tumors were evaluated using whole-exome sequencing, gene expression analyses, and methylation profiling (79). The authors confirmed the presence of frequent alterations in *BAP1*, a tumor-suppressor gene mutated in more than 50% of all mesotheliomas, and in a number of other key genes and pathways including *CDKN2A*, *NF2*, *TP53*, *LATS2*, and *SETD2*.

Mutations in *BAP1* are of interest not only because of their high prevalence in mesothelioma, but also because the potential to provide therapeutic targets. Knowledge of a familial BAP1 mutation should prompt early screening for uveal and cutaneous melanoma, renal cell carcinoma, other skin cancers and several other cancers since patients with familial BAP1 mutations are more at risk of dying from these other cancers (80). Several ongoing clinical trials are evaluating the efficacy of screening and surveillance and comparing the role of cross-sectional imaging and early surgical resection for detection of disease (80). *BAP1* encodes a deubiquitinase that regulates the activity of multiple genes involved in key processes such as DNA replication, DNA repair, cell metabolism, and death (81,82). Histone deacetylases (HDAC), HDAC1 and HDAC2, are epigenetic regulators of gene expression and are modulated by *BAP1*. Upon *BAP1* loss of function, HDAC1 is increased and HDAC2 is reduced, an effect observed *in vitro* across several cancer cell lines, including mesothelioma lines (83). These observations raised the possibility of using *BAP1* status as a biomarker to identify mesotheliomas with dysregulated HDAC activity, which could then be targeted using specific HDAC inhibitors, such as vorinostat (84). Those studies led to a multi-institution, double-blind phase 3 trial (VANTAGE-014 study) comparing vorinostat with placebo in 661 patients with pleural mesothelioma (85). The authors found no difference in median overall survival for patients treated with vorinostat versus placebo (30.7 *vs.* 27.1 weeks; hazard ratio =0.98; P=0.86), unfortunately highlighting that promising preclinical data does not always translate into a therapeutic reality. Olaparib, a monoclonal PARP-inhibitor, and tazemetostat, a EZH2 inhibitor, are two therapies specific to BAP1 loss mutations, both with limited response (86,87).

Another relevant molecular alteration which has been targeted for therapeutic purposes is the epidermal growth factor receptor (EGFR) tyrosine kinase, which is over-expressed in 44–97% of malignant mesotheliomas (88). The Cancer and Leukemia Group B conducted a phase II study of gefitinib, an EGFR inhibitor in 43 patients with mesothelioma (42 had pleural disease and only 1 had peritoneal) (89). Although the vast majority of the patients enrolled had EGFR overexpression based on immunohistochemistry (97%), only 1 patient (2%) had a complete response, 1 patient (2%) had a partial response, and 21 (49%) had stable disease lasting two to eight cycles.

A recent phase II study sought to investigate the activity of nintedanib, a multi-kinase inhibitor that targets

vascular endothelial growth factor (VEGF) receptors, platelet-derived growth factors, fibroblastic growth factor receptors, and Src and Abl kinases, in patients with pleural mesothelioma. Patients who received a combination of nintedanib with pemetrexed and cisplatin had improved progression-free survival (hazard ratio =0.56; 95% CI: 0.34–0.91; P=0.017) compared with controls who received pemetrexed/cisplatin only, although no difference was found in overall survival (90).

Bevacizumab, an anti-VEGF therapy was first investigated as an addition to the combination of pemetrexed and carboplatin in a phase II trial and noted to result in a partial response in 34% and stable disease in 58% of pleural mesothelioma patients treated (91). Further evidence supporting the use of bevacizumab in addition to pemetrexed and a platinum agent (cisplatin in this trial) was provided by a large phase III clinical trial in pleural mesothelioma where the triplet therapy was found to result in significantly longer median overall survival than patients treated with Pemetrexed and cisplatin alone (18.8 *vs.* 16.1 months) (92). Based on these two trials, Bevacizumab became a preferred regimen in the treatment of both pleural and peritoneal mesothelioma. Presently, it continues to be an area of on-going investigation in mesothelioma (*Table 3*), particularly in conjunction with immunotherapy, as 3 out of the 4 trials listed on ClinicalTrials.gov website as of Fall 2022 are using bevacizumab with immunotherapy. In a rare peritoneal mesothelioma-specific trial, bevacizumab with atezolizumab, an anti-PD-L1 monoclonal antibody, has been shown to elicit durable overall survival and is well tolerated in patients with advanced, treatment-resistant MPM, showing excellent promise as a potential future regimen (93).

Immunotherapy in MPM

Over the last decade, cancer immunotherapy has revolutionized the field of oncology by prolonging survival and in some instances providing sustained remission of cancers once considered rapidly fatal. The role of immunotherapy in MPM is being actively evaluated. Akin to the targeted therapy arena, most studies on immunotherapy in mesothelioma have primarily focused on pleural mesothelioma with a limited number of patients with peritoneal mesothelioma participating. One such study is the DETERMINE trial, a phase IIb randomized trial, that included 26 patients who had previously progressed on systemic therapy with pleural or peritoneal mesothelioma and were randomized to receive tremelimumab, an anti CTLA-4 antibody, or placebo (94). The study did not show a significant difference in overall survival between treatment and placebo, and due to the small numbers, no subgroup analysis of peritoneal mesothelioma patients was performed.

Anti PD-1 and anti PD-L1 therapies have rationale for investigation in peritoneal mesothelioma. A recent study found that PD-L1 was expressed by almost a third of mesothelioma cells, with significantly higher expression of PD-L1 in peritoneal mesothelioma than in pleural mesothelioma (95). Although potentially promising, there were only 13 patients with peritoneal mesothelioma in the study. Additionally, recent studies have demonstrated that PD-L1 expression in mesothelioma cells may be influenced by prior exposure to systemic therapy and could be more heterogeneous than initially thought (96,97).

A small number of studies exploring the efficacy of anti PD-1 or PD-L1 agents in mesothelioma have been published. One such study is the JAVELIN trial, a phase Ib trial included 53 patients with pleural and peritoneal mesothelioma who were treated with avelumab, a monoclonal antibody targeting PD-L1. All patients had progressed after at least one line of treatment with a combination of pemetrexed and platin based regimens (98). The authors noted a 9% objective response rate, with more responses in PD-L1 positive as compared to PD-L1 negative cancers. Disease control was achieved in 58% of patients and overall, the responses were durable (median response 15.2 months) suggesting this may be a worthy option in some patients who have progressed on pemetrexed and platinum therapy. Unfortunately, this data may not directly translate to MPM given the small number of patients enrolled and inability to perform a subgroup analysis.

Another open label, non-randomized study examined the efficacy of combining Tremelimumab, an anti-CTLA-4 antibody with durvalumab, an anti PD-L1 antibody, in 40 patients with unresectable pleural or peritoneal mesothelioma (99). In this study, 28% of patients had an immune-related objective response, 63% had clinical disease control, and a median response duration of 16.1 months was demonstrated. Tumor PD-L1 expression did not correlate with response or survival parameters. This dual checkpoint blockade regimen may have a promising role in pleural and/or peritoneal mesothelioma, though additional investigation is warranted.

New therapeutic avenues in MPM

MPM is characterized by unique biology compared with

Table 3 A summary of the clinical trials studying mesothelioma and bevacizumab

ClinicalTrials.gov identifier	Recruitment status	Phase	Cancer types	Intervention	Country
NCT00604461	Terminated	I/II	Mesothelioma	Carboplatin + bevacizumab + premetrexed	USA
NCT00295503	Completed	II	Mesothelioma	Cisplatin + bevacizumab + premetrexed	USA
NCT03762018	Active, not recruiting	III	Malignant Advanced Pleural Mesothelioma	Carboplatin + bevacizumab + premetrexed + atezolizumab	Belgium
NCT00407459	Completed	II	Mesothelioma	Bevacizumab + premetrexed + carboplatin	Italy
NCT00137826	Completed	II	Mesothelioma	Erlotinib + bevacizumab	USA
NCT00651456	Completed	II/III	Mesothelioma	Premetrexed and cisplatin + bevacizumab *vs.* premetrexed and cisplatin	France
NCT05001880	Recruiting	II	Malignant perionteal mesothelioma	Atezolizumab + bevacizumab, CRS & HIPEC, premetrexed, PET scan	USA
NCT00027703	Completed	II	Mesothelioma	Gemcitabine, cisplatin, bevacizumab *vs.* placebo	USA
NCT03654833	Recruiting	II	Malignant mesothelioma	Rucaparib, abemaciclib, pembrolizumab, bemcentinib atezolizumab + bevacizumab, dostarlimab + niraparib	UK
NCT03074513	Active, not recruiting	II	Appendiceal cancer, anal cancer, gynecologic squamous cell carcinoma, pancreatic neuroendocrine tumors, recurrent Merkel cell carcinoma, recurrent nasopharyngeal carcinoma, recurrent pleural mesothelioma	Atezolizumab + bevacizumab	USA
NCT05042557	Recruiting		Malignant pleural mesothelioma		China
NCT04430842	Active, not recruiting	I	Brain cancer, bladder cancer, breast cancer, cervical cancer, cholangiocarcinoma, colorectal cancer, esophageal cancer, gastric cancer, head and neck cancer, kidney cancer, liver cancer, melanoma, ovarian cancer, pancreatic cancer, pleural mesothelioma, prostate cancer, sarcoma, tongue cancer, thymic cancer, urinary tract cancer	QBS10072S	Australia

CRS, cytoreductive surgery; HIPEC, hyperthermic intraperitoneal chemotherapy; PET, positron emitting tomography.

most other cancers that originate in the abdomen, namely tumor progression is characterized by diffuse peritoneal involvement and local invasion, while tumor spread to lymph nodes and distant organs is less frequent. As a result, many treatment strategies for MPM are largely focused on controlling local disease. As discussed earlier, cytoreductive surgery and HIPEC represent the most effective treatment in patients with localized disease, extending overall survival by several years (22). Nonetheless, new therapeutic strategies (*Table 2*) continue to be explored for the treatment of localized MPM.

Photodynamic therapy (PDT)

PDT is a form of non-ionizing radiation treatment that uses a drug, called a photosensitizer, combined with light to exert its therapeutic effect (100). When the photosensitizer is exposed to specific luminous wavelengths it releases energy, which is then transferred to oxygen to generate reactive oxygen species; these in turn can cause cell death by inducing apoptosis, necrosis or autophagy (101). The

light required to activate common photosensitizing agents has a depth of penetration into tissues up to only 10 mm. As a result, PDT has been commonly used to treat superficial lesions, such as endobronchial or mucosal lesions of the gastrointestinal tract, or skin lesions.

Given the typically superficial growth of mesothelioma, several studies have explored the use of PDT as a therapeutic adjunct in the treatment of pleural mesothelioma, typically after debulking surgery. No published studies have demonstrated the safety and/or efficacy of PDT specifically in peritoneal mesothelioma. A phase II trial of PDT on 100 patients with peritoneal carcinomatosis from sarcoma, gastrointestinal and ovarian cancers demonstrated feasibility of PDT in the peritoneal cavity. However, no significant objective responses or tumor control was achieved in this study and volume overload resulted in toxicity to patients (102).

Targeted immunotherapy

Perhaps the most important challenge in cancer drug development is the identification of therapeutic targets that are truly specific for malignant cells without targeting healthy tissue. One strategy is to identify antigens that are highly expressed by cancer cells and minimally expressed by normal tissues. A prototypical example of such an antigen in mesothelioma is mesothelin. Mesothelin was first discovered by researchers at the National Cancer Institute (NCI) in 1992 in an attempt to identify new surface targets for immunotherapy (103). Mesothelin is expressed at low levels in healthy mesothelial cells of the pleura, pericardium and peritoneum, whereas almost all mesotheliomas express mesothelin at high level (104). The physiological role of mesothelin in healthy tissues remains unclear but appears to be non-essential, as knock-out mice for the gene encoding for mesothelin still develop normally (105).

Given these findings, a number of strategies have been developed in order to target mesothelin for therapeutic purposes. SS1P is an anti-mesothelin immunotoxin that was evaluated in a phase I trial of patients with mesothelioma (106). Although the treatment had acceptable safety profile, antitumor activity was limited due to the development of neutralizing antibodies against the toxin portion of SS1P. Given the concern for immunogenicity to the SS1P immunotoxin, a follow up study enrolled 10 patients with chemotherapy-refractory mesothelioma pretreated with pentostatin, a lymphoablative drug, and cyclophosphamide (107). Remarkably, three of the patients had major tumor regression, and two others responded to chemotherapy after discontinuing immunotoxin therapy, suggesting the mesothelin pathway may have therapeutic potential and warrants additional investigation.

Chimeric antigen receptor (CAR)-T cell therapy

Substantial progress in cellular engineering and *ex-vivo* culture has led to the creation of modified T-cells which are *ex vivo* manipulated to recognize specific antigens expressed by cancer cells. CAR-T cells represent the most successful of such approaches. Autologous T-cells are engineered to express a CAR constituted by an antigen-binding domain, typically in the form of a single chain variable fragment (scFv) derived from the variable fragment of antibodies, connected with a transmembrane domain and a cytoplasmatic portion, which contains the signaling domain (108). Initial trials of CAR-T cell targeting CD19 on acute B-cell leukemias and lymphomas with high CD19 expression produced impressive results and led to an exponential growth in research within the field (109,110).

Given its constitutively high expression in most mesotheliomas, mesothelin is an attractive target for CAR-T therapy and CAR-T constructs have been developed in recent years that specifically target mesothelin. A first study led by the NCI evaluated the activity of anti-mesothelin CAR-T cells in tumors expressing high levels of mesothelin, including mesothelioma (NCT01583686, unpublished). Patients were administered CAR-T cells in combination with a lymphodepleting chemotherapeutic regimen and IL-2, given to stimulate T-cell expansion. Although the treatment was well tolerated with minimal toxicity profile, the study was terminated early due to lack of efficacy and insufficient patient accrual. Subsequent studies have focused on newer generation CAR-T constructs. The best overall response so far comes from a study from investigators at the University of Pennsylvania, in which 11 out of 15 patients treated with anti-mesothelin CAR-T cells demonstrated stable disease at 1 months from infusion, with acceptable toxicity (111).

As more preclinical and clinical data on CAR-T cell therapies emerge, novel CAR designs are being developed to overcome some of the challenges associated with this therapeutic approach, such as T-cell exhaustion, poor CAR-T persistence in circulation, on target/off tumor toxicity, and immunosuppression by tumor microenvironment (112). A number of clinical trials (*Table 4*) are actively testing the activity of newer generations of CAR-T constructs in the treatment of mesothelioma and will hopefully translate into improved survival for patients affected by this deadly cancer.

Table 4 Ongoing clinical trials evaluating CAR-T cell therapy in mesothelioma

ClinicalTrials.gov identifier	Recruitment status	Phase	Cancer types	Intervention	Country
NCT04577326	Active, not recruiting	I	Malignant pleural mesothelioma	Cyclophosphamide + CAR-T cells	USA
NCT04489862	Recruiting	I	NSCLC; mesothelioma	Anti-PD1 + MSLN-CAR T cells	China
NCT02159716	Completed	I	Metastatic PDAC	CAR-T-MSLN	USA
			Epithelial ovarian cancer		
			Malignant pleural mesothelioma		
NCT03054298	Recruiting	I	Lung adenocarcinoma; ovarian cancer	huCART-meso cells	USA
			Peritoneal carcinoma; fallopian tube cancer; mesothelioma		
NCT03638206	Recruiting	I/II	B-cell ALL; lymphoma; myeloid leukemia; MM; HCC; gastric cancer	CAR-T/TCR-T cells	China
			PDAC, mesothelioma; CRC; esophageal cancer; lung cancer		
			Glioma; melanoma; synovial sarcoma; ovarian cancer; RCC		
NCT02414269	Active, not recruiting	I/II	Malignant pleural disease; mesothelioma; metastases; lung cancer; breast cancer	iCasp9M28z T cell infusions	USA
NCT01355965	Completed	I	Malignant pleural mesothelioma	Anti-MSLN autologous T cells	USA
NCT01722149	Completed	I	Malignant pleural mesothelioma	Adoptive transfer of re-directed T cells	Switzerland

CAR, chimeric antigen receptor; NSCLC, non-small cell lung cancer; PDAC, pancreatic ductal adenocarcinoma; ALL, acute lymphoblastic leukemia; MM, multiple myeloma; HCC, hepatocellular carcinoma; CRC, colorectal cancer; RCC, renal cell carcinoma; MSLN, mesothelin; huCART-meso, human chimeric antigen receptor modified T-cells targeting mesothelin; iCasp9M28z, autologous T-lymphocytes transduced with a retroviral vector encoding a chimeric antigen receptor specific for mesothelin linked to the signaling domains for the co-stimulatory molecules CD28 and CD3 zeta, as well as the suicide gene inducible caspase 9.

Oncolytic viruses

Oncolytic viruses constitute another class of immunotherapy agents in which viruses are engineered to contain cancer cell targets and express antibody fragments, cytokines, and/or costimulatory molecules to induce local and systemic antitumor immunity (113,114). A recent phase I study evaluated the safety and feasibility of a replication-defective adenovirus engineered to express the human IFNα2b gene (Ad.IFN) in combination with a 14-day course of celecoxib followed by chemotherapy in 40 patients with unresectable malignant pleural mesothelioma (115). Approximately half of the patients received first-line pemetrexed-based chemotherapy, whereas the others received second-line chemotherapy with either pemetrexed or gemcitabine. Notably, patients in the first-line cohort had median overall survival of 12.5 months. In patients treated with second-line chemotherapy, the median overall survival was 21.5 months with 32% of patients alive after 2 years, exceeding historical controls (115).

Another phase I/II trial recently evaluated a granulocyte macrophage colony stimulating factor (GMCSF)-expressing oncolytic adenovirus (ONCOS-102), in patients with malignant pleural mesothelioma, all of whom had been refractory to conventional treatments. Twenty patients enrolled and received ONCOS-102 intratumorally under CT or ultrasound guidance in combination with pemetrexed and cisplatin and were compared to a matched control group (n=11) who received only standard of care treatment. A preliminary report showed strong immune activation, with increased tumoral T-cell infiltration (116). Interestingly, intra-tumoral upregulation of PD-L1 was also noted, suggesting that treatment with ONCOS-102 may play a complementary role to that of checkpoint inhibitors.

Discussion

Narrative

The surgical management of patients with MPM has not changed substantially over the past two decades with the mainstay of treatment remaining complete cytoreduction and HIPEC for eligible patients, though investigations into alternative methods to deliver intraperitoneal chemotherapy are being explored in several peritoneal surface malignancies. Advances in the preoperative evaluation of patients, namely improvements in cross-sectional imaging, are helping to identify proper patients for surgical intervention. Clinical trials in new systemic therapies for pleural mesothelioma are the main drivers of progress in MPM since the rarity of MPM makes it challenging to study as a distinct entity. Hopefully therapeutic advances in pleural mesothelioma will continue to translate into improved outcomes for patients with pleural and peritoneal mesothelioma alike.

Strengths and limitations

In this article, we reviewed over 110 articles which comprehensively span the treatment, diagnosis, history and characteristics of MPM. The strengths of this article stem from the extensive breadth of content summarized from the available literature. We organized the information into categories to guide clinicians in their ability to monitor, detect, and treat MPM. There are a few limitations of this study as well. Foremost this is a review article, not a meta-analysis nor an experimental study, therefore data from this review are exclusively descriptive. Secondly, the limited clinical trial data, from low patient enrollment and trials ending prior to their intended conclusion, hampers our ability to have a more complete view of treatment specific to MPM.

Future directions

To expedite progress in the field, collaboration between centers that treat MPM is necessary since MPM is such an uncommon disease. We hope that partnerships will allow adequate accrual to allow clinical trials focused on MPM alone to be developed since this is a distinct entity from pleural mesothelioma with its own unique therapeutic challenges.

Conclusions

Despite advances in medical therapy, MPM remains a challenge to diagnose and treat. However, with improvements in detection and new developments in targeted therapy, earlier intervention of MPM can hopefully lead to improved outcomes.

Acknowledgments

Funding: None.

Footnote

Provenance and Peer Review: This article was commissioned by the Guest Editors (Abbas E. Abbas and Stacey Su) for the series "Mesothelioma" published in *AME Surgical Journal*. The article has undergone external peer review.

Reporting Checklist: The authors have completed the Narrative Review reporting checklist. Available at https://asj.amegroups.com/article/view/10.21037/asj-22-37/rc

Peer Review File: Available at https://asj.amegroups.com/article/view/10.21037/asj-22-37/prf

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://asj.amegroups.com/article/view/10.21037/asj-22-37/coif). The series "Mesothelioma" was commissioned by the editorial office without any funding or sponsorship. The authors have no other conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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doi: 10.21037/asj-22-37
Cite this article as: Newland JJ, Dal Molin M, Terhune JH. An update in malignant peritoneal mesothelioma diagnosis and treatment—a narrative review. AME Surg J 2023;3:36.