Peritoneal Mesothelioma: The Site of Origin Matters

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OVERVIEW

The etiology, gender distribution, pathology, natural history, and treatment options for mesothelioma (MM) differ substantially depending on the site of origin. Peritoneal mesothelioma (MPeM) is a rare disease, comprising only approximately 10% to 15% of the 2,500 cases of MM diagnosed in the United States each year. Patients with MPeM are younger than patients with pleural MM, and a higher proportion, mostly women, are long-term survivors. Most MPeM is caused by asbestos exposure. Germ-line mutations of BAP1 (BRCA associated protein 1) can predispose to MM, uveal melanoma, and potentially other cancers. MPeM can be challenging to diagnose, and cytology is rarely helpful. Review by an experienced pathologist using a panel of at least two positive and two negative immunohistochemical stains is essential. The three major pathologic subtypes are epithelial, sarcomatoid, and biphasic. Most cases are epithelial; the others have a dismal prognosis. Two indolent subtypes of borderline malignant potential—well-differentiated papillary mesothelioma and benign multicystic mesothelioma—are more common in the peritoneum and are treated surgically. In highly selected patients receiving treatment at experienced referral centers, an aggressive locoregional strategy that combines cytoreductive surgery to remove all gross disease and hyperthermic intraperitoneal chemotherapy to treat residual microscopic tumors yields a 3-year survival of 60% and a median survival approaching 5 years, far better than expected from historic controls. This approach also provides durable palliation of malignant ascites in nearly all patients. Pemetrexed is the only U.S. Food and Drug Administration (FDA)–approved systemic chemotherapy for pleural MM. Largely on the basis of data from pharmaceutical registry studies, the activity of pemetrexed-based chemotherapy appears to be similar in pleural MM and MPeM.

Peritoneal mesothelioma (MPeM) is a rare malignancy, comprising only 10% to 15% of the approximately 2,500 cases of malignant mesothelioma (MM) diagnosed in the United States each year. In the Surveillance, Epidemiology, and End Results (SEER) database, 10.5% of the MM identified between 1973 and 2005 was MPeM. MM is a heterogeneous disease, and the etiology, gender distribution, pathology, natural history, and treatment options can differ markedly depending on the site of origin. The vast majority of MM (85%) develop in the pleura; MM of the pericardium and tunica vaginalis are exceedingly rare.

Patients with MPeM are significantly younger than those with pleural MM (mean age, 63.3 vs. 70.8 years, respectively; \( p < 0.001 \)). In historic series, patients with MPeM also have a shorter median survival, and women with MPeM live significantly longer than men (13 vs. 6 months; \( p < 0.001 \)). There is greater variability in the survival of patients with MPeM compared to those with pleural MM, however, and a higher proportion of patients with MPeM, mostly women, are long-term survivors.

Although men have a higher overall incidence of MPeM, a larger proportion of women develop MM that originates in the peritoneum. In the SEER database, women accounted for only 19% of pleural MM cases but comprised 44% of peritoneal MM cases. Most MM in males is caused by asbestos, with a 20- to 50-year latency following exposure. The attributable risk due to asbestos exposure is lower in women. MPeM may be associated with more prolonged, heavy asbestos exposure than pleural MM. In asbestos miners and insulators, for example, the proportion of MPeM is highest in those who have had the greatest cumulative asbestos exposure. Other potential causes of MPeM include thorotrast, erionite, therapeutic radiation, familial Mediterranean fever, and other causes of chronic peritonitis.

Only a small fraction (< 5%) of those heavily exposed to asbestos will develop MM, yet the disease has been observed to cluster within families. This may be due to a newly described MM genetic susceptibility syndrome, in which germ-line mutations of BAP1 (BRCA associated protein 1) predispose to MM (including MPeM), uveal melanoma, other melanocytic tumors, and potentially other malignancies. MM is thought to predominate with asbestos exposure. Somatic mutations of BAP1 are also observed in approximately 23% of MM.
PRESENTATION, IMAGING, AND DIAGNOSIS

Most patients with MPeM present with vague, nonspecific abdominal symptoms, including increased abdominal girth, abdominal pain or discomfort, and weight loss. An umbilical or inguinal hernia may be present. Systemic symptoms can include fevers, night sweats, asthenia, nausea/vomiting, constipation, anorexia, and early satiety. Laboratory studies may reveal thrombocytosis.6,9-10

CT scan is the preferred initial imaging study, although it may underestimate the disease burden. It can demonstrate moderate to extensive ascites, diffuse peritoneal thickening, and nodular involvement of the omentum and mesentery.9-11 Most patients have diffuse peritoneal involvement, although localized MPeM can occur. Calcified pleural plaques can be observed in individuals with asbestos exposure. Liver metastases are exceedingly rare despite extensive intra-abdominal involvement. Pleural effusions and pleural-based tumors may develop later in the course of the disease, but other distant metastases are infrequent. MM may implant along needle tracts and surgical sites to produce painful subcutaneous nodules. Combined diffusion-weighted and gadolinium-enhanced magnetic resonance imaging may be more accurate than CT in quantifying the volume and extent of peritoneal tumor before surgical resection.12 There are limited data on the role of PET/CT in the management of MPeM, although it may be useful for the detection of recurrent disease.13

Ca-125 is commonly elevated in MPeM. Although it has no role in diagnosis, Ca-125 can be helpful in monitoring the disease course, particularly in patients without measurable tumor.6 There is less data for MPeM than for pleural MM regarding the utility of the recently described biomarkers serum mesothelin-related peptide (SMRP), osteopontin, and fibrin-3.14

Cytology is rarely helpful for diagnosis because the sensitivity of fluid cytology is low (32% to 76%),15 and the distinction between benign and malignant MM often depends on the degree of invasion, which cannot be ascertained by cytology. CT or ultrasound-guided needle biopsy or laparoscopy is generally required to establish the diagnosis.

Similar to pleural MM, the three principal histologic subtypes of MPeM are epithelial, sarcomatoid, and mixed (biphasic). In MPeM, however, biphasic tumors are infrequent, and pure sarcomatoid tumors are rare; both have a substantially worse prognosis than epithelial MPeM.15 The differential diagnosis of MPeM includes metastatic adenocarcinomas of the ovary, lung, or GI tract, as well as reactive mesothelium. No single immunohistochemical stain is pathognomonic of MM. Review by an experienced pathologist using a panel of at least two positive and two negative immunohistochemical stains is required to make a definitive diagnosis; the specific panel depends on the differential diagnosis. Common positive markers include calretinin, D2–40, CK 5/6, and WT-1; some frequently used negative markers include MOC-31, PAX8, BG8, Ber-EP4, B72.3, CEA, and CDX-2.15

Two distinct pathologic subtypes of borderline malignant potential are much more common in the peritoneum than in the pleura: well-differentiated papillary mesothelioma (WDPM) and benign multicystic mesothelioma (BMM).15-17 Both have relatively indolent behavior, are treated primarily with surgery, occur principally in women, and are not attributed to asbestos. WDPM commonly presents as an asymptomatic, incidental finding that can often be cured with resection alone. BMM, which consists of large grape-like cystic clusters, generally presents with an abdominal mass and abdominal pain, often in reproductive-age women with a history of endometriosis. Both entities can be locally recurrent, although this is much more common with BMM. Rare transformation to malignant mesothelioma has been reported for both WDPM and BMM, although in the case of WDPM this may reflect initial misdiagnosis or sampling error.

KEY POINTS

- Mesothelioma (MM) is a heterogeneous disease, and the etiology, gender distribution, pathology, natural history, and treatment options can differ markedly depending on the site of origin. There is greater variability in the survival of patients with peritoneal mesothelioma (MPeM) compared to those with pleural MM, and a higher proportion of patients with MPeM, mostly women, are long-term survivors.
- A MM genetic susceptibility syndrome, in which germ-line mutations of BAP1 predispose to MM, uveal melanoma, other melanocytic tumors, and potentially other malignancies has recently been described.
- MM can be challenging to diagnose, and cytology is rarely helpful. Review by an experienced pathologist using a panel of at least two positive and two negative immunohistochemical stains is required for definitive diagnosis. It is important to recognize the two indolent subtypes of borderline malignant potential, well-differentiated papillary mesothelioma (WDPM) and benign multicystic mesothelioma, which are treated with surgery.
- An aggressive locoregional approach that combines cytoreductive surgery with hyperthermic intraperitoneal chemotherapy can achieve median survival approaching 5 years in highly selected patients at experienced referral centers, and can palliate symptomatic ascites in nearly all patients.
- Pemetrexed is the only FDA-approved systemic chemotherapy for pleural MM. Largely on the basis of data from pharmaceutical registry studies, the activity of pemetrexed-based chemotherapy appears similar in pleural MM and MPeM.

NATURAL HISTORY AND TREATMENT OPTIONS

A standard therapeutic approach is not well defined. Most treatment algorithms are extrapolated from data derived from highly selected patients in small, retrospective, single-center series at referral institutions with expertise in MPeM.
and other peritoneal malignancies, and from a few recent multicenter databases. There are infrequent clinical trials in MPeM; all are small and nonrandomized.

Compounding these inherent selection biases, the heterogeneous natural history of MPeM (especially by gender and histology), makes it even more challenging to determine the impact of a therapeutic intervention. Women with MPeM present with earlier-stage disease, have more favorable histology, and have a better prognosis regardless of stage, which may be related in part, to differences in causation. The prognosis of MPeM, particularly in women, is also quite variable. Although MPeM often behaves as aggressively as pleural MM, unlike in pleural MM, a substantial proportion of MPeM in women is fairly indolent. In one small series, patients otherwise similar in terms of age, symptoms, initial tumor burden, tumor morphology, and treatment were divided into those with survival less than 4 years (60%) and those with survival more than 4 years (40%). In the short-term survivors, median survival was 12 months, and 1-year survival was 67%, quite similar to survival for pleural MM. By contrast, median survival in the long-term survival group was 7 years (range, 5 to 15 years), which would not be expected in pleural MM.2

The median survival of untreated MPeM is about 6 months. The median survival of patients with MPeM in the 1980s and ’90s who received systemic chemotherapy or palliative surgery was less than 1 year (range, 9 to 15 months). This contrasts markedly with more contemporary series in patients who underwent aggressive locoregional treatment, in whom median survival approaches 5 years (range, 34 to 92 months).19,20

**Surgery**

MPeM remains confined to the abdominopelvic cavity, with little invasion of the underlying organs and no metastatic spread until it is quite advanced. This natural history suggests that aggressive locoregional treatment may be appropriate, and in the absence of level 1 evidence, this is a preferred strategy that appears to improve survival over historic controls.19,20 Although the specifics of patient selection, surgical techniques, and chemotherapy agent, dose, and method of delivery differ by institution, the cardinal principle is that aggressive cytoreductive surgery (CRS) is required to remove all gross peritoneal disease. Residual microscopic tumors are treated intraoperatively with hyperthermic intraperitoneal chemotherapy (HIPEC). This is sometimes followed by early postoperative intraperitoneal chemotherapy (EPIC) or, less commonly, whole-abdominal radiation or adjuvant systemic chemotherapy.9,19,20

At laparotomy, the preoperative disease extent is determined by the peritoneal cancer index (PCI), which divides the abdomen into a grid of nine squares and the small bowel mesentery into quadrants. Tumor burden in each area is scored on a scale of 0 to 3 (e.g., no involvement to extensive), up to a cumulative score of 39.9

The completeness of cytoreduction (CC) score quantifies residual disease after resection on the basis of the size of the remaining tumor nodules (CC-0: none, CC-1: < 2.5 mm, CC-2: 2.5 mm to 2.5 cm, and CC-3: > 2.5 cm or a confluence of tumor nodules at any site).9 Preoperative CT scan findings predictive of an adequate cytoreduction include the absence of a larger than 5-cm epigastric mass and no loss of normal architecture of the small bowel and its mesentery.11

In a complete gross cytoreduction, the surgeon removes all visible abdominal and pelvic tumors and involved solid organs, performing a complete diaphragmatic, parietal, and pelvic peritonectomy, greater and lesser omentectomy, and when necessary, splenectomy, bowel resection, hysterectomy, salpingectomy, or oophorectomy.9 A complete peritoneectomy is superior to partial peritonectomy, even when an area seems grossly uninvolved.21 Small tumor implants on the bowel serosa and mesentery are treated with electrofulguration. The morbidity of CRS in MPeM even in experienced centers ranges from 25% to 40% and mortality from 0% to 8%.19 Common complications include intestinal fistula, bleeding, embolism, wound infection, electrolyte abnormalities, and sepsis. Thus, selection of fit patients likely to achieve a complete cytoreduction is essential; they should be referred to experienced centers.

The optimal time to achieve uniform distribution of chemotherapy to the peritoneum is after the majority of tumor has been resected but before adhesions develop. Thus, once maximal cytoreduction is attained, HIPEC is administered intraoperatively, delivering a high drug concentration directly to microscopic residual disease. Hyperthermia can be tumoricidal and augments chemotherapy cytotoxicity.6 Cisplatin, mitomycin, carboplatin, and doxorubicin are most commonly used.

Although selection criteria and treatment specifics vary widely between institutions, experienced investigators using this approach report an impressive median overall survival that seems superior to the expected natural history of MPeM (Table 1).19,20 The overwhelming majority of patients (86% to 94%) also achieve substantial, durable palliation of malignant ascites.6

The largest surgical series in MPeM is a retrospective registry established in 2008 to collect data from 405 patients with MPeM at eight institutions in six countries between 1989 and 2009.22 Eligible patients were deemed candidates for CRS/HIPEC. As expected from a registry that spanned multiple continents and two decades, there was considerable variation in the HIPEC technique, specifically in the choice of cytotoxic agent, the degree of hyperthermia (40 to 43°C), the duration of the perfusion (30 to 120 minutes), and the exposure technique (open or closed). Nonetheless, this data set provides a wealth of valuable information about the toxicities and outcomes with CRS/HIPEC in selected patients with MPeM at experienced centers, establishing a benchmark against which other treatments can be compared.

HIPEC was administered in 92% of cases, 23% of patients received EPIC (usually with paclitaxel), and 5% of patients received adjuvant systemic pemetrexed-based chemotherapy. The median age was 50 years, 56% of patients were male, and 79% of patients had epithelial histology. Only 6% had lymph node metastases. The mean PCI was 20; 46% of
patients achieved a CC-0/1. The mean surgical duration was 8 hours; the median length of hospital stay was 22 days. Perioperative complications occurred in 46% of all patients; 31% of all patients had grade 3/4 complications. Perioperative mortality was 2%. With a median follow-up of 33 months, the overall median survival was 53 months (range, 1 to 235 months). The 3- and 5-year survival rates were 60% and 47%, respectively. On multivariate analysis, epithelial histology, lymph node–negative disease (CC-0/1), and HIPEC treatment were independently associated with superior survival. There was no difference in outcome between chemotherapeutic regimens. As expected, women had substantially longer survival than did men (119 vs. 36 months; p < 0.001).

A more recent analysis of 294 patients from this registry confirmed that female gender is a favorable prognostic factor. Three- and 5-year survival rates for women were 76% and 68%, respectively, compared to 50% and 39% for males. Women had a substantially lower PCI, lower-stage disease, and more favorable histology. Women older than age 55 had an inferior survival rate compared with younger women (p = 0.019); there was no difference in outcome by age in men.

There is no official Tumor, Node, Metastasis (TNM) staging system for MPeM. A preoperative staging system has recently been proposed on the basis of this registry data. Seven prognostic variables were identified on univariate analysis: age 50 years or younger, female gender, epithelial subtype, PCI 1 to 10, absence of lymph node metastases, absence of extra-abdominal metastases (defined as penetrating the diaphragm or invading an abdominal wall scar), and CC-0/1. Because age, gender, and pathologic subtype are intrinsic, and CC score can be obtained only after surgery, these were not considered for preoperative staging; the three remaining prognostic determinants (PCI, lymph node status, and extra-abdominal metastases) were therefore selected. T stage is derived intraoperatively from the PCI (T1: PCI 1 to 10, T2: PCI 11 to 20, T3: PCI 21 to 30, T4: PCI 31 to 39). The N stage (N0, N1) and M stage (M0, M1) are defined as in other malignancies. This system successfully stratified survival by stage. One-year survival for patients with stage I (T1N0M0), stage II (T2–3N0M0), and stage III (T4 or N1 or M1) disease was 94%, 87%, and 66%, respectively; 5-year survival was 87%, 53%, and 29%, respectively.

**Systemic Chemotherapy**
Chemotherapy for MPeM is administered principally in patients with recurrent disease, and in those who are not appropriate candidates for aggressive surgery. At some centers, adjuvant chemotherapy is offered to patients with disease that is not optimally debulked or who are otherwise at a high risk for recurrence. Neoadjuvant chemotherapy is most commonly used in patients who are not candidates for immediate cytoreduction as a result of their disease burden, as well as in those with a poor prognosis (including those with nonepithelial histology, and, in some centers, male patients) to spare those with potentially aggressive disease from major surgery.

Most of what we believe about the activity of chemotherapy in MPeM is extrapolated from trials performed exclusively in patients with pleural MM because it is generally presumed, although certainly not proven, that most systemic chemotherapy drugs have similar efficacy in both sites. Because of the different natural history of pleural MM and MPeM, however, patients with MPeM are generally excluded from clinical trials of new agents in MM. Even the occasional trial that permits patients with MPeM enrollment very few. Patients with MPeM are frequently ineligible for clinical trials because their diffuse peritoneal disease is generally not measurable by Response Evaluation Criteria in Solid Tumors (RECIST). Available data on the activity of chemotherapy for MPeM come from several small retrospective analyses, a few case reports, and a few prospective observational series including two large pharmaceutical registry studies. The few prospective clinical trials are small, and there are no randomized studies.

The only FDA-approved drug for pleural MM is pemetrexed, an antifolate that inhibits thymidylate synthase, dihydrofolate reductase, and glycaminamide ribonucleotide formyltransferase. The best level 1 evidence of the activity of any agent in pleural MM comes from a pivotal single-blind, placebo-controlled phase III trial, in which 456 patients were randomly assigned to receive cisplatin (75 mg/m²) with or without pemetrexed (500 mg/m²) every 21 days for up to six cycles. No patients with MPeM were enrolled. Patients who received pemetrexed/cisplatin experienced a longer median overall survival (12.1 vs. 9.3 months; p = 0.020), a superior time to progression (5.7 vs. 3.9 months; p = 0.001), a higher objective response rate (41% vs. 17%; p < 0.001), and a superior quality of life compared to cisplatin alone. In a similar phase III trial, cisplatin with or without the antifolate raltitrexed achieved comparable outcomes in patients with pleural MM (median overall survival 11.4 vs. 8.8 months;
p = 0.048).26 This combination is approved for MM in some European countries; it has not been studied in MPeM.

Most of the available information on the activity of pemetrexed in MPeM is derived from Eli Lily and Company’s (Indianapolis, IN) U.S. and International Expanded Access Programs (EAP) performed before regulatory approval.27,28 Although these provide valuable data, they should be interpreted cautiously; there is far greater heterogeneity in patient populations and less rigorous assessment and reporting of adverse events and clinical activity than in prospective clinical trials. Nonetheless, these data suggest that pemetrexed-based regimens have comparable activity in pleural MM and MPeM, as shown in Table 2.24

Of the 1,056 patients with MM in the U.S. EAP, 98 (9.3%) had MPeM. Most (58%) had received prior chemotherapy. Sixty-six patients received pemetrexed/cisplatin; the remainder, pemetrexed alone. The 73 patients assessable for response were a heterogeneous group: 28 were chemotherapy naïve and 43 were previously treated; 47 received pemetrexed/cisplatin and 26 received pemetrexed. The overall response rate was 26%, and 45% of patients had stable disease, yielding a disease control rate of 71%. Response rates were similar in chemotherapy-naïve (25%) and previously treated patients (23%). Pemetrexed/cisplatin yielded a higher response rate (30%) than did pemetrexed alone (19%). Progression-free survival was not reported. Median overall survival had not been reached in the chemotherapy-naïve patients; it was 13.1 months in those previously treated.27

The International EAP demonstrated the activity and tolerability of pemetrexed alone or with cisplatin or carboplatin (area under the curve [AUC] 5) in an equally heterogeneous group of 109 patients with MPeM, who were evenly distributed among the three treatment regimens. Most of the patients who received platinum doublets were chemotherapy naïve, compared with only 21% of those who received single-agent pemetrexed. Although RECIST criteria were recommended, SWOG (formerly Southwest Oncology Group) or WHO response criteria were permitted. Response rates for pemetrexed, pemetrexed/cisplatin, and pemetrexed/carboplatin were 12.5%, 20%, and 24%, respectively; disease control rates were 50%, 80%, and 76%, respectively. For those receiving pemetrexed alone, the median time to progression was 6.2 months and the median overall survival was 10.3 months; these values could not be determined in the other treatment arms due to a high censoring rate.28

As part of the International EAP in Germany, 22 patients with MPeM received treatment at a single-center. Most (68%) were chemotherapy naïve; 95% received pemetrexed/cisplatin. The objective response rate in 10 assessable patients was 36%; the disease control rate was 77%. Mean time to progression was 11.5 months, and mean overall survival was 13.7 months.29 In a tiny series typical of MPeM studies, Greek investigators treated six patients with MPeM with pemetrexed/cisplatin. All had undergone an exploratory laparotomy during which a cytoreductive surgery was attempted, but none had a complete cytoreduction. Two patients (33%) achieved a complete response (defined as resolution of all measurable disease or ascites and normalization of Ca-125), three patients (50%) had partial responses, and one had stable disease. Mean time to disease progression was 9.5 months, median overall survival was 24 months, and three patients were alive at 40+ months.30

Pleural MM patients who obtain durable disease control with first-line pemetrexed are commonly retreated with a pemetrexed-based regimen, since about two-thirds of those who achieve a progression-free survival lasting longer than 6 months from first-line pemetrexed have disease control upon retreatment, and 17% will have an objective response.31 It

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**TABLE 2. Activity of Pemetrexed-Based Chemotherapy in Pleural and Peritoneal Mesothelioma**

<table>
<thead>
<tr>
<th>Author</th>
<th>Regimen</th>
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Abbreviations: EAP, Expanded Access Program; NR, not reported.
may be reasonable to assume similar activity for pemetrexed in previously treated MPeM. Only a few other agents or combinations have even modest activity in pleural MM, including single-agent vinorelbine, and gemcitabine with cisplatin; none of these have been tested prospectively in MPeM.

The combination of gemcitabine (1250 mg/m² days 1 and 8) plus pemetrexed (500 mg/m², day 8) was evaluated in one of the largest prospective chemotherapy trials ever reported in MPeM. Twenty patients with MPeM were enrolled at 10 centers during a period of 17 months as part of a trial evaluating this combination in pleural MM. The primary endpoint was objective response rate, which was only 15%, comparable to single-agent pemetrexed. The disease control rate was 50%. Median time to progression was 10.4 months; median overall survival was 26.8 months. This combination produced substantial grade 3/4 toxicity, including neutropenia (60%), febrile neutropenia (10%), fatigue (20%), vomiting (10%), and dehydration (10%).

Although current data suggest that cytotoxic chemotherapy has similar activity in pleural MM and MPeM, this may not be the case with targeted agents, potentially reflecting differences in the biology of the two diseases. Epidermal growth factor receptor (EGFR) tyrosine kinase inhibitors, for example, are inactive in pleural MM, and EGFR mutations are rare (<2%). EGFR mutations occur in 31% of MPeM, however. An ongoing University of Chicago phase II trial administers erlotinib to patients with MPeM who have activating EGFR tumors. Other potential therapeutic targets that are the subject of ongoing or planned clinical trials in MM include mesothelin, PI3 kinase, MET, EphB4, and FAK.

CONCLUSION

MPeM is an uncommon but deadly disease with a variable natural history that remains localized to the abdominal cavity for most of its course. Select patients receiving treatment at specialized centers with an aggressive locoregional strategy of cytoreductive surgery and HIPEC can achieve prolonged survival. Pemetrexed-based chemotherapy appears to have similar activity in pleural MM and MPeM. A concerted international collaborative effort is essential to make further progress in the management of this rare malignancy.

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References