

Modern management of malignant pleural mesothelioma

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Abstract: Malignant pleural mesothelioma (MPM) is a deadly disease that produces a significant worldwide health care burden. The majority of cases are associated with prior asbestos exposure, but recent studies have identified a possible genetic predisposition in a minority of patients. Historically, obtaining a pathologic diagnosis of MPM was challenging, but with current pathological techniques, a secure diagnosis is possible in the majority of patients. Curative therapy for MPM remains elusive, and the primary treatment option for fit patients is platinum-based chemotherapy. Encouraging recent reports suggest that there may be a benefit to the addition of bevacizumab to standard chemotherapy as well as with the use of immune checkpoint inhibitors in MPM. Selected patients may be considered for aggressive surgical approaches, but there is considerable controversy regarding the true benefit of surgery and multimodality therapy in this disease.

Keywords: mesothelioma, asbestos, chemotherapy, surgery

Introduction

Malignant pleural mesothelioma (MPM) is a rare and aggressive malignancy arising from the mesothelial cells lining the pleural cavity. There is a clear association between occupational or environmental asbestos and mineral fiber exposure and the development of MPM. An exposure is identified in up to 80% of cases. The latency period from exposure to development of disease can range from 20 to 70 years and appears to be dose dependent with heavily exposed patients presenting earlier.¹ Ionizing radiation has also been implicated as a risk factor for MPM. Population studies show an increased risk of MPM in patients exposed to mediastinal irradiation for treatment of prior lymphoma as well as those exposed to occupational radiation. Patients with MPM associated with therapeutic irradiation for lymphoma typically present at a younger age and have longer overall survival compared to those with asbestos-associated MPM.^{2,3}

The incidence of MPM began to rise in the USA in 1975 and peaked in 1995 coinciding with diminishing occupational asbestos exposure.⁴ Currently, there are an estimated 2,500 new cases in the USA annually. MPM is a disease of elderly males with an average age at diagnosis of 74 years and 80% of cases occurring in men. The incidence in females is fourfold lower and has remained mostly unchanged over the past 4 decades. In Europe, Australia, and Japan, the projected peak incidence will be between 2015 and 2025. The rising incidence worldwide is expected to result in substantial health and economic burden.^{5,6}

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Genetic predisposition

Up to 20% of MPM patients have no prior asbestos exposure, and the majority of individuals with exposure do not develop disease. This suggests that asbestos exposure is not necessary or sufficient to cause mesothelioma. These observations have led to a growing interest in identifying whether genetic mutations result in disease susceptibility and whether they can serve as potential therapeutic targets.

Mutations in the *BAP1* tumor suppressor gene have been associated with a variety of malignancies, and *BAP1* is frequently mutated in MPM. In recent small case series, somatic *BAP1* mutations have been reported in 57%–63% of MPM tumor samples.^{7,8}

Germline *BAP1* mutations coupled with somatic loss of the second *BAP1* allele were discovered in mesothelioma tumor samples from affected families, in which up to 50% of family members developed MPM despite modest levels of environmental asbestos exposure.⁹

Germline and somatic *BAP1* mutations resulting in a loss of heterozygosity have been associated with a novel tumor predisposition syndrome associated with various other malignancies. Uveal melanoma, cutaneous melanoma, renal cell carcinoma, cholangiocarcinoma, and basal cell carcinoma are most frequently described, but a variety of other tumors have also been associated with the syndrome. The prevalence of germline *BAP1* mutations was 6% in a large asbestos-exposed cohort with both mesothelioma and a family history of cancer. Two-thirds of this group had two or more primary cancers. These patients were also noted to have a significantly lower age of onset with a higher occurrence of peritoneal involvement.¹⁰ In addition, somatic loss of the *NF2* and *CDKN2A/ARF* tumor suppressor genes has also been associated with MPM but appears to be less prevalent than *BAP1* mutations.⁸

Approximately 2% of mesothelioma patients are young (<40 years) and comprise a subgroup with unique clinical characteristics, such as improved overall survival and balanced sex distribution.¹¹ It is unclear if genetic susceptibility is the driver of the pathogenesis in these younger patients.

Clinical presentation

Patients with MPM present with the triad of pleural effusion, dyspnea, and chest wall pain in 60% of cases. Dyspnea may be a result of pleural fluid accumulation or lung encasement by tumor, which results in decreased chest wall expansion predisposing patients to pneumonia. MPM is typically extensive at presentation, and complications of local invasion are common. This includes superior vena cava obstruction,

cardiac tamponade, spinal cord compression, phrenic nerve or recurrent laryngeal nerve paralysis, diaphragmatic dysfunction, Horner's syndrome, dysphagia, subcutaneous involvement, and direct extension through the chest wall. Spread to the contralateral pleural cavity and across the diaphragm is seen in 10%–20% of cases. Peritoneal involvement may manifest as ascites or bowel obstruction and results in significant morbidity. Onset of local symptoms typically leads to diagnostic evaluation. Late features of MPM include constitutional symptoms and hematogenous metastases to virtually any organ.^{5,12–15}

Diagnostic evaluation

Accurate diagnosis of MPM can be challenging, since it is uncommon and often difficult to distinguish from benign conditions. The diagnosis of MPM is based on an adequate tissue sample in the context of appropriate clinical, radiographic, and surgical findings. A definitive morphologic diagnosis is typically confirmed with immunohistochemistry.

Pathology

The three primary histologic subtypes of MPM include epithelioid (50%–70%), sarcomatoid (10%–20%), and mixed (biphasic) categories. The epithelioid histology is the most common and has a better prognosis than the other histologies.^{1,16} Under the heading of sarcomatoid mesothelioma are two additional rare subtypes, the desmoplastic and lymphohistiocytic variants, which account for <5% of all MPM diagnoses. Differentiating MPM from benign conditions and other malignancies is a frequent diagnostic problem. Histologic features and immunohistochemical (IHC) panels can be used to make these distinctions in both scenarios. In distinguishing MPM from carcinoma, the International Mesothelioma Interest Group (IMIG) recommends the use of at least two mesothelioma IHC markers and two carcinoma markers to confirm the diagnosis. If there are discordant findings, additional markers should be used. Common malignant mesothelioma IHC markers include Wilm's tumor 1, calretinin, cytokeratin 5/6, and D2-40 (podoplanin), and frequently utilized IHC markers for carcinoma are MOC-31, BG8 (Lewis^x), and Ber-EP4.¹⁷ In addition, it is recommended that the pathologist should not consider the presence or absence of a history of asbestos exposure when making a diagnosis of MPM. While the prior standards suggested that tissue biopsy for histology was required to render a diagnosis of MPM, more recent guidelines from the IMIG have established highly effective diagnostic criteria for MPM based on cytology alone. While the sensitivity of cytology may

be lower, the accuracy is excellent (with positive predictive values approaching 100%) when these criteria and appropriate ancillary techniques are applied.^{18–21}

Diagnostic specimen

There are no large prospective studies comparing the optimal technique for obtaining a diagnostic specimen for MPM. Common methods include cytologic analysis and pleural biopsy (Abrams needle, computed tomography (CT)-guided, thoracoscopy, and open biopsy).

Although tissue biopsy is generally preferred, cytologic analysis of the pleural fluid is often an initial consideration, since patients commonly present with a pleural effusion. The sensitivity of cytology alone ranges widely between 32% and 76%.¹⁷ This is likely due to sampling rather than interpretation; therefore, an adequate amount of fluid is necessary to ensure sufficient cell concentration. The addition of immunohistochemistry enhances the diagnostic accuracy.

The diagnostic sensitivity of thoracoscopy for MPM is as high as 94%–98% in case series.^{22–24} This is in contrast to diagnostic rates of 21%–71% with blind pleural biopsy and 83%–88% with CT-guided needle biopsy.^{23,25–29} Thoracoscopy also has the advantage of allowing additional staging information to be obtained in those patients being considered for surgery.

Pretreatment evaluation

Staging

Patients are staged according to the IMIG TNM staging system, which was approved by the American Joint Committee on Cancer and the International Union for Cancer Control (Table 1).

Imaging

CT imaging of the chest and abdomen is recommended in all patients. Fluoro-deoxyglucose positron emission tomography is reserved for patients being considered for surgery to exclude extrathoracic spread. It is not used universally for staging, since there can be false positivity from nonmalignant processes including pleural inflammation from pleurodesis. Magnetic resonance imaging can be helpful in evaluating patients with suspected vascular, diaphragmatic, or spine invasion.

Candidates for surgical resection will also undergo additional procedures to exclude contralateral pleural disease, extrathoracic spread, or peritoneal involvement. Mediastinoscopy or endobronchial ultrasound fine needle aspiration of mediastinal lymph nodes is recommended. Additional studies

include video-assisted thoracoscopy to exclude extension into the contralateral lung and laparoscopy to exclude transdiaphragmatic extension into the peritoneal cavity. In a series of 118 possible surgical candidates with MPM, laparoscopy was performed in 109 patients, and ten (9.2%) had incidental peritoneal involvement.³⁰

Prognosis

MPM is a highly aggressive disease with a dismal prognosis with reported median survivals of 6–12 months and <5% of patients surviving >5 years.^{5,15,31} Both the European Organization for the Research and Treatment of Cancer (EORTC) and the Cancer and Leukemia Group B (CALGB) have published prognostic scoring systems for this disease.^{32,33} Both scoring systems were established in cohorts of previously untreated patients enrolled in Phase II trials of chemotherapy and have been subsequently validated in independent cohorts.^{34,35} In a multivariate analysis, the CALGB identified the following as independent predictors of poor outcome: pleural primary site, lactate dehydrogenase >500 IU/L, Eastern Cooperative Oncology Group (ECOG) performance status >0, platelet count >400,000/ μ L, non-epithelial histology, and age >75 years. Six prognostic subgroups were identified with median survivals that ranged from 1.4 to 13.9 months (Table 2). The best prognostic subgroup included patients with either an ECOG performance status of 0 and age <49 years or an ECOG performance status of 0, age >49 years, and a hemoglobin >14.6 g/dL. The worst survival was seen in patients with an ECOG performance status of 1 or 2 and a white blood cell count >15.6/ μ L. The EORTC model also identified ECOG performance status >0 and sarcomatoid histology along with an elevated white blood cell count, male sex, and possible/probable diagnosis of mesothelioma (as opposed to a definite diagnosis) as independent predictors of poor outcome in multivariate analysis. This model classified patients into two groups: a low-risk group with a median survival of 10.8 months and a high-risk group with a median survival of 5.5 months (Table 3). In addition to the clinical factors reviewed, multiple groups have attempted to evaluate potential molecular predictors of prognosis, including gene expression analyses.³⁶ However, to date, none have shown enough promise to be in routine clinical use.

Treatment

Patients with MPM should be managed by an experienced multidisciplinary team. Treatment options include surgery, radiation therapy (RT), and chemotherapy. Selected patients with clinical stages I–III with operable disease and a good

Table 1 International Mesothelioma Interest Group staging system for diffuse malignant pleural mesothelioma

| T | Primary tumor | N | Regional lymph nodes |
|----------|---|--|---|
| TX | Primary tumor cannot be assessed | NX | Regional lymph nodes cannot be assessed |
| T0 | No evidence of primary tumor | N0 | No regional lymph node metastasis |
| T1 | Tumor limited to the ipsilateral parietal pleura with or without mediastinal pleural and with or without diaphragmatic pleural involvement | N1 | Metastasis to the ipsilateral bronchopulmonary or hilar lymph nodes |
| T1a | No involvement of the visceral pleura | N2 | Metastases in the subcarinal lymph node or the ipsilateral mediastinal lymph nodes including the ipsilateral internal mammary and peridiaphragmatic nodes |
| T1b | Tumor also involving the visceral pleura | N3 | Metastasis in contralateral mediastinal, contralateral internal mammary, ipsilateral, or contralateral supraclavicular lymph nodes |
| T2 | Tumor involving each of the ipsilateral pleural surfaces (parietal, mediastinal, diaphragmatic, and visceral pleura) with at least one of the following: – Involvement of the diaphragmatic muscle – Extension of tumor from visceral pleura into the underlying pulmonary parenchyma | M M0 M1 | Distant metastasis No distant metastasis Distant metastasis |
| T3 | Locally advanced but potentially resectable tumor. Tumor involving all of the ipsilateral pleural surfaces (parietal, mediastinal, diaphragmatic, and visceral pleura), with at least one of the following: – Involvement of the endothoracic fascia – Extension into the mediastinal fat – Solitary, completely resectable focus of tumor extending into the soft tissue of the chest wall – Nontransmural involvement of the pericardium | Stage I Stage II Stage III Stage IV | T1aN0(IA); T1bN0(IB) T2N0 Any T3, any N1, or any N2 Any T4, any N3, or any M1 |
| T4 | Locally advanced technically unresectable tumor. Tumor involving all the ipsilateral pleural surfaces (parietal, mediastinal, diaphragmatic, and visceral pleura) with at least one of the following: – Diffuse extension or multifocal masses of tumor in the chest wall, with or without associated rib destruction – Direct transdiaphragmatic extension of the tumor to the peritoneum – Direct extension of tumor to the contralateral pleura – Direct extension of the tumor to mediastinal organs – Direct extension of tumor into the spine Tumor extending through to the internal surface of the pericardium with or without a pericardial effusion or tumor involving the myocardium | | |

Table 2 CALGB prognostic groups

| | Prognostic groups | Group prognostic variables | Median survival (months) | 95% CI (months) |
|-------------|--------------------------|--|---------------------------------|------------------------|
| CALGB index | Group 1 | PS =0, age <49 years PS =0, age ≥49 years, Hgb ≥14.6 | 13.9 | 11.1–31.4 |
| | Group 2 | PS =1/2, WBC <8.7, no chest pain | 9.5 | 6.9–14.7 |
| | Group 3 | PS =0, age ≥49 years, Hgb <14.6 PS =1/2, WBC count <15.6, chest pain, no weight loss, Hgb ≥12.3 | 9.2 | 7.5–10.5 |
| | Group 4 | PS =1/2, WBC 8.7–15.5, no chest pain | 6.5 | 3.7–9.4 |
| | Group 5 | PS =1/2, WBC <15.6, chest pain, no weight loss, Hgb <12.3 PS =1/2, WBC 9.8–15.5, chest pain, weight loss, Hgb <11.2 | 4.4 | 3.4–5.1 |
| | Group 6 | PS =1/2, WBC <9.8, chest pain, weight loss PS =1/2, WBC ≥15.6 | 1.4 | 0.5–3.6 |

Note: Adapted from *Chest*, 113/3, Herndon JE, Green MR, Chahinian AP, et al, Factors predictive of survival among 337 patients with mesothelioma treated between 1984 and 1994 by the Cancer and Leukemia Group B, 723–731, Copyright (1998), with permission from Elsevier.³²

Abbreviations: CALGB, Cancer and Leukemia Group B; CI, confidence interval; PS, Eastern Cooperative Oncology Group performance status; Hgb, hemoglobin (g/dL); WBC, white blood cell (10⁹/L).

Table 3 EORTC prognostic groups

| | Poor prognostic factors | Prognostic groups | Median survival | One-year OS (95% CI) | Two-year OS (95% CI) |
|--------------------|--|-------------------------------------|-----------------|----------------------|----------------------|
| EORTC index (1998) | ECOG performance status 1–2 | Low risk ^a (0–2 poor PF) | 10.8 months | 40% (30%–50%) | 14% (6%–22%) |
| | White blood cell count >8.3×10 ⁹ /L | | | | |
| | Male sex | High risk ^b (≥3 poor PF) | 5.5 months | 12% (4%–20%) | 0% |
| | Probable/possible histologic diagnosis | | | | |
| | Sarcomatoid subtype | | | | |

Notes: ^aLow risk equivalent to EPS <1.27. ^bHigh risk equivalent to EPS >1.27. Curran D, Shamoud T, Therasse P, et al, Prognostic factors in patients with pleural mesothelioma: the European Organization for Research and Treatment of Cancer experience. *J Clin Oncol*, 16, 1, 145–152. Adapted with permission. © (1998) American Society of Clinical Oncology.³³

Abbreviations: EORTC, European Organization for the Research and Treatment of Cancer; OS, overall survival; CI, confidence interval; ECOG, Eastern Cooperative Oncology Group; PF, prognostic factors; EPS, EORTC prognostic score.

performance status may be candidates for multimodality therapy.

Chemotherapy

Most patients with MPM are not candidates for aggressive surgery due to the extent of disease or an inadequate functional status. In those patients unable or unwilling to have surgery, and with an acceptable performance status, chemotherapy is a reasonable treatment option. Platinum analogs, selected anti-metabolites (pemetrexed [Eli Lilly and Company, Indianapolis, IN, USA], raltitrexed [AstraZeneca, London, UK], methotrexate [multiple manufacturers]), gemcitabine (Eli Lilly and Company), vinorelbine (Pierre Fabre, Parsippany, NJ, USA), and doxorubicin (multiple manufacturers) have activity in MPM with single-agent response rates of 7%–20%.³⁷ Only one randomized trial has evaluated the impact of first-line single-agent chemotherapy on survival in this disease. A Phase III comparison of weekly vinorelbine with best supportive care in patients with previously untreated MPM closed early due to poor accrual, and was therefore underpowered, but demonstrated a trend toward improved progression-free and overall survival in the vinorelbine arm.³⁸

The role of combination chemotherapy has also been evaluated in MPM. Vogeang et al performed a randomized Phase III comparison of cisplatin and pemetrexed versus cisplatin (multiple manufacturers) alone in 456 treatment-naïve patients with MPM who were not surgical candidates. There was a statistically significant improvement in median overall survival (12.1 versus 9.3 months, $P=0.02$) and progression-free survival (5.7 versus 3.9 months, $P=0.001$) that favored the combination arm.³⁹ As a result of this trial, the combination of cisplatin and pemetrexed received the US Food and Drug Administration (FDA) approval as first-line treatment for MPM and has been the preferred regimen over the past decade in the USA. A similar Phase III trial performed in Europe compared the combination of cisplatin and raltitrexed with cisplatin alone. The primary end point

was median overall survival, and a statistically significant improvement was seen in the combination arm (11.4 versus 8.8 months, $P=0.048$).⁴⁰

The combination of carboplatin (Bristol-Myers Squibb, Princeton, NJ, USA) and pemetrexed has also been evaluated in three Phase II trials in patients with untreated MPM with reported median overall survivals of 12.7–14 months.^{41–43} In addition, in a non-randomized comparison of 1,704 patients treated with cisplatin and pemetrexed or carboplatin and pemetrexed as part of an expanded access program, the median time to progression (7 versus 6.9 months) and 1-year survival rates (63.1% and 64%) were similar between the two regimens.⁴⁴ The combination of carboplatin and pemetrexed is therefore a reasonable alternative for those patients unable to receive cisplatin. In addition, the combination of cisplatin and gemcitabine has been assessed in two Phase II trials with reported median survivals of 9.6 and 11.2 months, suggesting that it may be a useful option for MPM patients who cannot receive pemetrexed.^{45,46}

The benefit of second-line chemotherapy in MPM has only been evaluated to a limited extent. Jassem et al randomized 243 patients with previously treated MPM who had not received prior pemetrexed to pemetrexed or best supportive care. A significant improvement in median time to progression was seen in the pemetrexed arm (3.7 versus 1.5 months, $P=0.0002$), but no difference in overall survival or mean change in quality of life was observed.⁴⁷ The authors speculated that the lack of improvement in overall survival may have resulted from a significant imbalance in post-discontinuation chemotherapy between the two arms. Nonetheless, these results suggest that pemetrexed is a reasonable second-line option for those patients who did not receive it first-line. Additional second-line options in MPM include vinorelbine and gemcitabine, but both have demonstrated limited activity in this setting.^{48,49}

Until recently, prior studies of molecularly targeted therapy in MPM had failed to demonstrate significant promise. Specifically, multiple prior attempts to target the vascular endothelial

growth factor pathway in MPM had met with limited success.^{50,51} However, a recent multicenter Phase III trial (IFCT-CFPC-0701 MAPS) compared the addition of the vascular endothelial growth factor monoclonal antibody bevacizumab (Genentech Inc., South San Francisco, CA, USA) to cisplatin and pemetrexed followed by maintenance bevacizumab with cisplatin and pemetrexed alone in 448 untreated, unresectable MPM patients with a good performance status. A statistically significant increase in the median overall survival was observed in the bevacizumab-containing arm compared with the chemotherapy-only arm (18.8 versus 16.1 months, $P=0.012$). Higher rates of grade 3 hypertension, proteinuria, and arterial thrombotic events were also observed in the bevacizumab arm.⁵² Though not yet formally approved for use in MPM, this regimen could be considered an emerging standard of care for appropriately selected patients who are candidates for bevacizumab.

Immunotherapy

Targeting immune checkpoints with immunomodulatory monoclonal antibodies has been shown to be effective in pretreated patients with a variety of solid tumors. A recent Phase II study evaluated the CTLA-4 monoclonal antibody tremelimumab (AstraZeneca) in 29 chemotherapy-resistant malignant mesothelioma patients (28 patients with MPM). The median overall survival was 11.3 months, and 52% of patients had disease control at a median follow-up of 23.1 months.⁵³ Tremelimumab has recently been granted orphan drug approval by the FDA; however, AstraZeneca reported a follow-up phase IIb trial of tremelimumab monotherapy versus placebo as second or third line treatment for mesothelioma (both pleural and peritoneal) and tremilimumab did not improve overall survival in this setting. There is now interest in investigating tremelimumab in combination with additional immunotherapy in this setting. In addition, monoclonal antibodies directed against PD-L1 or PD1 are also currently being investigated in Phase I/II trials in MPM. Prior preclinical series demonstrated that PD1 and PD-L1 are expressed in a significant percentage of MPM and that expression may identify patients with a worse prognosis.^{54,55} Alley et al recently reported early promising results from their Phase I/II trial of pembrolizumab, a monoclonal antibody against PD1, in pretreated patients with MPM. In the 25 patients with PD1 expressing tumors, there was a 28% overall response rate (7 patients) and a 6 month progression free survival rate of 49.4% at a median follow-up of 8.6 months.⁵⁶

Radiation

RT is used as a part of a multimodality approach with the appropriate timing determined by a multidisciplinary team

(described in the “Multimodality therapy” section). RT alone is typically not performed as MPM is not sensitive to RT. Radiation can be used to palliate chest wall pain as well as subcutaneous extensions from mesothelioma. Currently, there is no evidence to support routine use of prophylactic radiation, which is at times given to prevent seeding of surgical incisions and port sites.⁵⁷

Surgery

Surgical treatment is occasionally performed in carefully selected patients with the intent to resect all visible tumor resulting in macroscopic complete resection, eliminate pleural effusion, improve local symptoms, and to increase the efficacy of adjuvant therapy.⁵⁸

With regard to palliation of pleural effusion in MPM, Rintoul et al⁵⁹ performed a Phase III trial of video-assisted thoracoscopic partial pleurectomy (VAT-PP) versus talc pleurodesis in 196 MPM patients with a pleural effusion (the MesoVATS trial). The primary end point was overall survival at 12 months, which was 52% in the VAT-PP group and 57% in the talc pleurodesis group ($P=0.81$). Surgical complications (31% versus 14%) and length of hospital stay (7 versus 3 days) were significantly greater in the VAT-PP patients, whereas the rate of complete resolution of the effusion at 12 months and the quality of life measures were similar in both treatment arms.

Additional surgical approaches for MPM include either pleurectomy/decortication (P/D) or extrapleural pneumonectomy (EPP). P/D is a complete visceral and parietal pleurectomy with the intent of extirpation of all gross disease. Removal of the ipsilateral diaphragm and/or pericardium may be required if those areas are involved. EPP is an en bloc resection of the lung, visceral and parietal pleura, diaphragm, and adjacent pericardium. The true value of these procedures in mesothelioma is debated extensively in the literature for the following reasons. There have been no definitive comparisons of EPP and P/D or comparisons of these procedures against nonsurgical treatment of mesothelioma. In addition, as will be detailed in the following paragraph, both procedures have significant associated morbidity and mortality. Lastly, neither EPP nor P/D results in a complete R0 resection (ie, a curative intent resection with no remaining macro- or microscopic tumor). They are, therefore, not curative as a single modality of treatment.

A recent systematic literature review of EPP in MPM identified 34 relevant studies from 26 institutions that included over 3,700 patients.⁶⁰ The reported median overall survivals from these series ranged from 9.4 to 27.5 months,

and the 5-year survival rates were from 0% to 24%. If the middle two quartiles were analyzed alone to exclude the outliers, the median survivals were 12–20 months, and 5-year survival rates were 10%–19%. Perioperative mortality rates ranged from 0% to 11.8% with major morbidity seen in 12.5%–48% of patients. The most common complications were atrial arrhythmias, respiratory infections, respiratory failure, pulmonary embolus, and myocardial infarction.

A separate review of 17 articles from 13 centers sought to identify prognostic factors and patient selection criteria for EPP.⁶¹ The two factors that consistently predicted for poor outcome with EPP were non-epithelioid histology and N2 nodal involvement. The reviewers concluded that patients in either of these categories should not be considered candidates for EPP.

A comprehensive analysis of the available literature assessing outcomes with partial pleurectomy and complete P/D in MPM has also been performed.⁶² If the analysis is restricted to those patients who underwent complete P/D, resultant median survivals ranged from 11.5 to 18.1 months, and 5-year survival rates from 0% to 23% were reported. Operative mortality rates were 0%–6%, and morbidity rates were not consistently stated. A recent systematic review of the literature to evaluate perioperative and long-term outcomes with EPP and P/D in MPM patients was conducted by Cao et al. Seven studies including 632 EPP patients and 513 P/D patients were analyzed. Perioperative mortality rates were significantly higher with EPP (6.8% versus 2.9%, $P=0.02$) as were perioperative morbidity rates (62% versus 27.9%, $P<0.0001$). Median survivals ranged from 13 to 29 months for P/D patients and from 12 to 22 months for EPP patients, with a trend in favor of P/D. The authors cautioned that while these results are based on non-randomized comparisons of the two procedures, the available data suggest lower rates of perioperative morbidity and mortality and similar (and possibly superior) long-term survival with P/D.⁶³ At the present time, there is not complete agreement on the role of aggressive surgery in this disease or the most appropriate surgical procedure. All would agree that patients considered for these procedures require rigorous staging (as outlined earlier) to evaluate for mediastinal nodal involvement and to exclude extrathoracic spread. An extensive cardiac and pulmonary evaluation is also necessary to insure the patient's ability to tolerate surgery. In addition, there is general agreement that patients with involvement of mediastinal lymph nodes or non-epithelioid histology do not appear to benefit from EPP, and current consensus guidelines from a number of international organizations also advocate that these procedures be

restricted to centers with extensive experience in the management of this disease.^{64–68}

Multimodality therapy

Following either EPP or P/D, the rates of both local and distant recurrence are high.^{14,69,70} This provides a logical rationale for the evaluation of adjuvant therapy in this setting. Rusch et al reported their single-institution experience in 57 patients who received postoperative hemithoracic radiation to 54 G following EPP. They observed that this approach was feasible and appeared to decrease local recurrence rates in comparison to historical controls.⁷⁰ More recently, neoadjuvant intensity-modulated RT to 25 G followed by a 5 G boost to “areas of risk” delivered prior to EPP was also shown to be safe and feasible in 25 patients with MPM.⁷¹ The role of adjuvant chemotherapy has also been evaluated to a very limited degree. The largest series includes 183 patients who underwent EPP at a single institution between 1980 and 1997.⁷² Postoperatively, they received a variety of different chemotherapy regimens (doxorubicin and cyclophosphamide with or without cisplatin or carboplatin and paclitaxel) followed by RT. For the 176 patients who survived EPP, the median survival was an encouraging 19 months. However, no firm conclusions can be drawn regarding the benefit of adjuvant therapy based on this single-arm study.

Several centers have evaluated the feasibility of pre-operative chemotherapy followed by EPP followed by postoperative hemithoracic radiation. As shown in Table 2, 37%–71% of patients successfully completed all therapy, and in the intent-to-treat analyses, median survivals ranged from 14 to 25.5 months.^{73–79} While these survivals appear superior to those reported for patients receiving either surgery or chemotherapy alone, the impact of patient selection is likely significantly influencing these results. This is best illustrated by the MARS randomized feasibility study.⁸⁰ In this trial, patients determined to be medically fit and eligible for EPP after a comprehensive evaluation received three cycles of platinum-based chemotherapy. Those who completed chemotherapy and were felt to still be candidates for EPP following restaging were randomized to EPP followed by radiation or no EPP. The first 50 patients were enrolled in the feasibility portion of the study to determine if accrual would allow for successful completion of a larger Phase III trial. While the accrual end point was not met, results from these 50 patients demonstrated median survivals in the EPP and no-EPP groups of 14.4 and 19.5 months, respectively. The hazard ratio for overall survival in the EPP group versus the no-EPP group was 1.9 ($P=0.082$). When one considers that overall survival

Table 4 Phase II trials of trimodality therapy in mesothelioma

| Trial | N | Epithelioid | Stage | Regimen | EPP | PORT | EPP mortality | Median survival, ITT (months) |
|-------------------------------|----|-------------|----------------|-----------|----------|----------|---------------|-------------------------------|
| Weder et al ⁷³ | 19 | 14 (74%) | T1–3, N0–2, M0 | Cis Gem | 16 (84%) | 13 (68%) | 1 (6%) | 23 |
| Flores et al ⁷⁴ | 19 | 14 (74%) | T3–4, N0–2, M0 | Cis Gem | 8 (42%) | 7 (37%) | 0 | 19 |
| Rea et al ⁷⁵ | 21 | 20 (95%) | T1–3, N0–2, M0 | Car Gem | 17 (81%) | 15 (71%) | 0 | 25.5 |
| Weder et al ⁷⁶ | 61 | 42 (69%) | T1–3, N0–2, M0 | Cis Gem | 45 (74%) | 36 (59%) | 1 (2%) | 19.8 |
| de Perrot et al ⁷⁷ | 60 | 44 (73%) | T1–3, N0–2, M0 | Cis based | 45 (75%) | 30 (50%) | 3 (7%) | 14 |
| Krug et al ⁷⁸ | 77 | 62 (81%) | T1–3, N0–2, M0 | Cis Pem | 54 (70%) | 44 (57%) | 2 (4%) | 16.8 |
| Van Schil et al ⁷⁹ | 58 | NS | T1–3, N1, M0 | Cis Pem | 46 (79%) | 38 (66%) | 3 (7%) | 18.4 |

Note: Cis based, cisplatin/vinorelbine (n=26), cisplatin/pemetrexed (n=24), cisplatin/raltitrexed (n=6), and cisplatin/gemcitabine (n=4).

Abbreviations: N, number of patients enrolled; EPP, extrapleural pneumonectomy; PORT, postoperative radiation therapy; ITT, intention-to-treat population; Cis Gem, cisplatin and gemcitabine; Car Gem, carboplatin and gemcitabine; Cis Pem, cisplatin and pemetrexed; NS, not stated; Cis, cisplatin.

in this trial was measured from the time of randomization (following the completion of preoperative chemotherapy), the median survivals for those patients in the no-EPP arm compare favorably with those shown in Table 4. In addition, Stahel et al recently reported a randomized Phase II trial of hemithoracic radiation versus observation in 54 MPM patients with complete macroscopic resection after EPP. All patients had also received neoadjuvant chemotherapy with cisplatin and pemetrexed for three cycles prior to EPP. There was no difference in median locoregional relapse-free survival between the two treatment arms, and the authors concluded that their findings did not support the routine use of hemithoracic radiation in MPM patients following neoadjuvant chemotherapy and EPP.⁸¹ Both the MARS and Stahel et al studies provide further evidence that patient selection is heavily influencing the outcomes reported in the single-arm multimodality trials and that definitive randomized trials will be necessary to truly delineate the role of multimodality therapy in MPM.

Conclusion

The management of MPM remains a significant challenge, and the prognosis for the vast majority of patients afflicted with this disease remains poor. While the decreased use of asbestos in industry will gradually reduce the worldwide burden of MPM, it is predicted that the incidence of the disease across the world will continue to rise for several decades before the effects of decreased asbestos use are realized. In addition, up to 20% of patients with MPM do not have clear prior asbestos exposure, arguing that the disease will not be eliminated completely in the “post-asbestos” era. Therefore, it is imperative that novel and improved therapies for MPM continue to be developed. At present, most fit patients with MPM are offered platinum-based chemotherapy combinations that modestly improve survival. Surgery and multimodality therapy are offered to selected patients at experienced centers but without clear evidence to truly define the magnitude of

benefit of that approach. Recent successes with the addition of bevacizumab to standard chemotherapy and with the possibility of antitumor effects with the immune checkpoint inhibitors in MPM give hope that a better understanding of the biology of this disease will gradually lead to improved outcomes for these patients.

Disclosure

Jonathan Dowell has disclosed that he has received research support from MedImmune, LLC and Verastem, Inc. Shivani Patel has no relevant financial interests to disclose. The authors report no conflicts of interest in this work.

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