

## Malignant Pleural Mesothelioma—A Current Review

a report by

Marc S Ballas, MD,<sup>1</sup> Abraham Chachoua, MD,<sup>2</sup> Jessica Donington, MD<sup>3</sup> and Harvey I Pass, MD<sup>4</sup>

1. Medical Oncologist; 2. Associate Professor of Medicine and Urology; 3. General Thoracic Surgeon; 4. Professor of Cardiothoracic Surgery and Surgery, and Division Chief, Thoracic Surgery and Thoracic Oncology, New York University School of Medicine

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Malignant pleural mesothelioma (MPM) is a locally aggressive cancer that arises from the multipotential mesothelial cells of the pleura. MPM has a uniformly poor prognosis with a median survival from diagnosis of nine to 12 months.<sup>4</sup> Limited treatment options are available for those diagnosed with MPM or at risk for developing MPM from past or ongoing asbestos exposure. While rare, MPM is responsible for approximately 0.6% of all cancer-related deaths.<sup>5</sup> MPM poses an increasing public health, medical, and economic problem. This is due to the peak commercial use of asbestos in industrialized countries between the 1930s and the 1960s and the latency in developing MPM from the time of first exposure, which ranges from 15 to 40 years.<sup>6,7</sup> In addition, asbestos continues to pose a public health hazard throughout the world due to the need for its disposal and its current and increasing use in industrializing nations. Recent estimates report an expected incidence of 2,000–3,000 cases per year in the US, 1,950–2,450 cases per year in the UK, and 250,000 deaths caused by MPM in Western Europe over the next few decades.<sup>1,8,9</sup>

In addition to the direct costs to the healthcare system, defendant companies in the US have already paid \$54 billion in legal claims and are expected to face upwards of \$200 billion in future liabilities, thus representing a significant socioeconomic burden.<sup>5</sup> Interestingly, only 5% of asbestos mine workers who have experienced heavy exposure to asbestos go on to develop MPM, a fact that illustrates the complex relationship between environment, biology, and genetics in MPM.<sup>10</sup> In addition, the characteristically long latency time for developing MPM suggests that the multiple somatic abnormalities common in MPM accumulate within the mesothelial cells over time and contribute substantially to the pathogenesis of MPM. Recent research has implicated multiple molecular pathways and genetic loci that are abnormal in MPM, and has increased our understanding of the pathogenesis of the disease. These insights may provide possible therapeutic targets for treatment and prevention.

### Pathogenesis

The mechanism of asbestos-induced MPM is unclear. Genomic and molecular analyses have elucidated multiple cytogenetic and molecular abnormalities that contribute to the development of MPM. It is commonly believed that asbestos inhalation leads to the deposition of fibres deep in the lung parenchyma and eventual migration and implantation of fibers into the pleural lining. Repeated episodes of inflammation and healing, oxygen free radical production from inflammatory cells and the iron moiety within asbestos,<sup>11–13</sup> and direct damage to DNA by the fibers are generally accepted pathogenic features of asbestos exposure.<sup>4</sup> Interestingly, dose-dependent cytotoxicity of asbestos is not lethal to the asbestos-sensitive mesothelial cells.<sup>14,15</sup> The inflammatory response to asbestos deposition in the pleura is mediated by macrophages and mesothelial cells, with both cell types secreting tumor necrosis factor (TNF)- $\alpha$  and the mesothelial cell expressing TNF- $\alpha$  receptor (TNF-R1) in an autocrine and paracrine interaction. TNF- $\alpha$  then stimulates the nuclear factor kappa B (NF- $\kappa$ B) pathway, which regulates pro-survival cellular mechanisms and may allow asbestos-induced DNA-damaged cells to divide rather than undergo apoptosis. This response imparts a survival advantage that permits the asbestos-injured cells to transform and progress into malignant mesothelioma.<sup>16</sup> Based on these findings, high-risk cohorts in Turkey will be treated with ranpirnase, a ribonuclease (RNase) that inhibits NF- $\kappa$ B activation, which will hopefully block this pathway and help prevent the development of MPM.

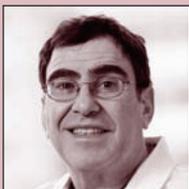
Considerable controversy regarding the role of simian virus 40 (SV40) in the pathogenesis of MPM persists today. SV40 is a rhesus monkey DNA virus, likely introduced to humans from contaminated Salk polio vaccines produced between 1955 and 1978.<sup>17</sup> SV40 has been associated with the development of MPM in humans and animal models.<sup>18,19</sup> Overall, the role of SV40 in MPM is a controversial topic.



Marc S Ballas, MD, is a Medical Oncologist at New York University (NYU) School of Medicine and NYU Cancer Center. He is on the Faculty of Medicine at NYU School of Medicine, with a clinical research interest in thoracic tumors and sarcoma. His main focus is the diagnosis and treatment of non-small-cell lung cancer, including the investigation of novel agents of therapeutic and preventive potential in clinical trials. Dr Ballas completed his medical oncology training at the Medical Oncology Branch of the National Cancer Institute in Bethesda, Maryland.



Jessica Donington, MD, is a General Thoracic Surgeon at New York University (NYU) School of Medicine. She is Director of the NYU Thoracic Oncology Translational Laboratory at Bellevue Hospital, and her clinical and research interests are focused on the diagnosis and treatment of non-small-cell lung cancer. Her areas of clinical expertise include the use of multimodality therapy for lung cancer and lung cancer in women. Her laboratory work looks at the detection of biomarkers for the early diagnosis of lung cancer and at the role of osteopontin, an ubiquitous protein, in lung cancer development.



Harvey I Pass, MD, is a Professor of Cardiothoracic Surgery and Surgery and Division Chief for Thoracic Surgery and Thoracic Oncology at New York University (NYU) School of Medicine. He is internationally recognized as an expert in the multidisciplinary management of lung cancer, mesothelioma, and esophageal cancer, and the management of pulmonary metastases. Dr Pass has co-authored over 300 original reports and edited various editions of oncological publications. He has received the National Institutes of Health (NIH) Directors' Award, the President's Award for Clinical Research at Karmanos Cancer Institute, and the Wagner Medal from the International Mesothelioma Interest Group.

E: harvey.pass@nyumc.org

### Presentation

A person with MPM will usually be male and between 50 and 70 years of age, and will report a significant history of asbestos exposure. The most common symptoms upon presentation include dyspnea and chest pain. More than 50–70% of patients report dyspnea and 60% present with non-pleuritic chest pain that is typically located in the posterolateral thorax. Physical findings are directly related to the extent and natural progression of disease. Eighty percent of patients will present with a pleural effusion and dyspnea, and 95% will develop an effusion at some point during the course of their disease.<sup>10</sup> Extension of the tumor through the diaphragm can result in malignant ascites.

### Laboratory Analysis and Serum Markers

Laboratory findings are generally non-specific and can include hypergammaglobulinemia, an elevated erythrocyte sedimentation rate (ESR), anemia, and, most strikingly, thrombocytosis (>400,000), which is seen in upwards of 30–40% of patients. Recent research has identified serum mesothelin-related protein (SMRP) and osteopontin as promising new serum markers for identifying and following patients with MPM. A Mesothelin enzyme-linked immunosorbent assay (ELISA) (MesoMark™) is currently available for clinical use in Europe and Australia and through reference laboratories in the US.

### Imaging

Computed tomography (CT) of the chest remains the most useful imaging study in MPM. CT can identify pleural changes associated with asbestos exposure and MPM such as pleural thickening, calcified plaques, and pleural effusions, localized nodular mass with pleural effusion, and intrapulmonary nodules in 60% of cases, but is not sensitive in diagnosing chest wall or diaphragmatic involvement.<sup>20</sup> MRI has recently been proved to be more sensitive in diagnosing chest wall invasion and diaphragmatic invasion.<sup>21</sup> Positron emission tomography (PET) has been used at multiple centers in the US, and early data suggest PET is helpful in identifying benign and malignant pleural disease (MPM in particular) in individuals exposed to asbestos.<sup>22</sup> PET may be useful in determining the extent of distant metastatic disease, but had a sensitivity of only 11% in detecting metastatic lymph node disease.<sup>23</sup>

### Diagnostic Approach

Since pleural effusion is such a common presenting sign in MPM, thoracentesis is routinely the first diagnostic procedure attempted and succeeds in diagnosing approximately 30–50% of cases.<sup>24</sup> Video-assisted thoracoscopy (VATS) is useful when thoracentesis results are negative, can provide a diagnosis in 80% of patients, and provides excellent visualization of the extent of disease.<sup>25</sup> When tumor volume precludes thoracoscopy, open biopsy should be performed in an intercostal space that can later be excised with a more definitive operation. There are three main histological subtypes of MPM: epithelial tumors account for 50–60% of MPMs and carry a better prognosis; sarcomatoid MPMs account for 10% of cases and are the most resistant to therapy, with a mean survival less than one year; and mixed (or biphasic) tumors account for 35% of MPMs. MPM is generally positive for cytokeratin, calretinin, and WT1 and negative for CEA, CD15, TTF-1, and B72.<sup>3</sup> It is generally accepted that positive staining for cytokeratin and calretinin with negative staining for three epithelial markers is sufficient to make the diagnosis of MPM. In difficult diagnostic circumstances, electron microscopy usually makes the definitive diagnosis.

### Staging

Historically, staging for MPM used non-standardized criteria that resulted in substantial differences in the reported rates of survival and treatment efficacy. In response, the International Mesothelioma Interest Group (IMIG) published their guidelines for the staging of MPM that more accurately documented the progression of disease and the importance of nodal involvement.<sup>26</sup> The American Joint Commission on Cancer (AJCC) has adopted these guidelines, and the current tumor, node, metastasis (TNM) staging system used is generally accepted. Staging is essential for operative planning. Patients with

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stage I–III disease are candidates for surgical cytoreduction. In an effort to stratify patients for survival, Cancer and Leukemia Group B (CALGB) and European Organization for Research and Treatment of Cancer (EORTC) studies found that performance status is the best predictor of survival, while age, histological subtype, and gender are other important prognostic factors.<sup>27,28</sup>

### Treatment Modalities

To date, there are no generally accepted or published treatment guidelines for MPM.<sup>29</sup> Recently, the standard treatment regimen for unresectable MPM has been cisplatin plus pemetrexed. This followed a well-powered phase III trial demonstrating longer median survival time and longer time to progression with combined therapy versus cisplatin alone.<sup>30</sup> For these patients, control of pleural effusions can be accomplished by thoracoscopic or chest tube pleurodesis with 90% efficacy. PleureX® catheters can be used for poor surgical candidates or recurrent effusions. The main goals of treatment are to control local disease, treat symptoms, and prevent progression and metastasis. Surgery, radiation, chemotherapy, and immunotherapy (generally in combination) have become the common treatment strategies.

### Surgery

The common operations used to treat MPM include thoracoscopy for diagnosis or symptomatic control, and extrapleural pneumonectomy (EPP) or pleurectomy/decortication (PD) for curative intent and cytoreduction for adjuvant therapy. Significant debate exists as to whether EPP or PD offers any survival advantage over each other or other treatments. No randomized, controlled trials comparing EPP versus PD or surgery versus non-surgical treatments have been performed, but recent data from Flores et al. point to the efficacy of PD in early-stage mesothelioma compared with EPP.<sup>31</sup> The Mesothelioma and Radical Surgery Trial (MARS) trial in the UK, which randomizes patients after chemotherapy to either EPP with radiation or non-surgical therapy, currently aims to determine whether EPP offers any survival advantage. EPP is an *en bloc* resection of pleura, underlying lung parenchyma, ipsilateral hemidiaphragm, and pericardium. PD attempts to remove all pleural disease without underlying lung and may also include the ipsilateral hemidiaphragm and pericardium in the resection.

## Radiation

Thoracic radiotherapy for MPM is limited mainly by the radiosensitivity of the surrounding vital structures of the chest and by the volume of tumor. Curative doses (greater than 60Gy) pose a serious risk to normal tissues including the neighboring lung, heart, esophagus, and spinal cord. Several studies have shown that definitive radiotherapy does not increase median survival past 10 months.<sup>32–35</sup> However, Boutin et al. demonstrated that radiotherapy was an effective prophylactic treatment after thoracoscopy to prevent port-site seeding.<sup>36</sup>

## Chemotherapy

Historically, anthracyclines, platinum agents, and antimetabolites have been used as single agents against MPM with poor response rates—ranging from 30 to 40%—and median survival times of less than one year. Combination chemotherapies have had marginally better response rates and median survival times. Platinum-based regimens demonstrated the best response and survival results.<sup>37</sup> Symptomatic relief was seen in 40–50% of patients

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treated with a combination of mitomycin C, vinblastine, and cisplatin.<sup>38</sup> Recently, studies using the antimetabolic vinca alkaloid vinorelbine as a single agent have shown similar benefit.<sup>39</sup> Pemetrexed is a novel antifolate that showed extensive antitumor activity in phase I and II trials.<sup>40</sup> A phase III trial enrolled and randomized 456 patients to receive either cisplatin or cisplatin in combination with pemetrexed. The combined regimen proved superior with a three-month longer average survival time and almost a two-month increase in disease-free interval (both statistically significant).<sup>30</sup> In addition, the same study noted that vitamin B<sub>12</sub> and folate supplementation provided better tolerance and a decreased side effect profile, and thus gave a better response rate.

While no drugs have demonstrated efficacy in the relapsed setting, milataxel, a novel taxane analog that can be administered orally, is being studied in a phase II open-label trial in patients with refractory mesothelioma to the pemetrexed cisplatin combination.

## Multimodality Therapy

The most promising survival data have been generated in studies that combined surgery with radiation or chemotherapy, or all three modalities.<sup>41</sup> Multiple studies in selected patients have confirmed that durable survival could be achieved in early-stage patients without nodal disease, and that EPP could be performed with acceptable operative mortality.<sup>42</sup> One benefit of EPP is that post-operative radiation therapy can be given without concern for ipsilateral pulmonary toxicity.<sup>43</sup> In a phase II trial of EPP followed by radiation therapy completed at Memorial Sloan-Kettering Cancer Center, Rusch and colleagues demonstrated that some patients could have a

durable survival—27% at three years—and a decreased local recurrence of only 13%.<sup>44</sup> In an effort to boost the amount of radiation delivered to the post-operative field, researchers have utilized intensity-modulated radiation therapy (IMRT).<sup>45</sup> Intrapleural chemotherapy at the time of surgery is an intriguing method of treatment that has yet to show any improvement in local control or survival rates.

Recently, several studies have reported encouraging results using induction chemotherapy. Weder et al. showed in a small pilot study that neoadjuvant chemotherapy with cisplatin and gemcitabine followed by EPP and post-operative radiation could produce a median survival of 23 months. One- and two-year survival rates were 79 and 37%, respectively.<sup>46</sup> In another small study, Flores et al. found that early-stage MPM patients successfully completing a course of neoadjuvant chemotherapy with cisplatin and gemcitabine followed by EPP and 54Gy of radiotherapy had a median survival of 33.5 months.<sup>47</sup> A more recent Swiss multicenter phase II trial of induction therapy followed by EPP and radiation that included 61 patients reported the same 23-month median survival in patients who underwent EPP. These data suggest that induction therapy may prolong survival compared with upfront surgery. Post-operative morbidity was 62% and mortality was 3.2%, which is similar to the Brigham experience.<sup>48</sup>

A multicenter US trial of neoadjuvant pemetrexed and cisplatin (PC) followed by EPP and hemithoracic radiation for resectable MPM that included 77 patients illustrated that trimodality therapy was feasible and that chemotherapy could be successfully delivered to patients in a neoadjuvant setting. However, preliminary median survival was only 16.6 months, below the median survival reported in the aforementioned single-institution studies. However, these results could be explained by the high censorship rates experienced early in this study.<sup>49</sup>

## Targeted Therapies

Epidermal growth factor receptor (EGFR), vascular endothelial growth factor (VEGF), and platelet-derived growth factor (PDGF) are important growth factors involved in MPM pathogenesis that are currently being treated with targeted therapy in several studies. Unfortunately, trials with the EGFR tyrosine kinase inhibitors erlotinib and gefitinib have shown no efficacy.<sup>50,51</sup> In addition, imatinib mesylate, an inhibitor of tyrosine kinase activity, has had similar treatment failure.<sup>52</sup> Recently, a multicenter, double-blind, randomized, placebo-controlled phase II trial that included gemcitabine and cisplatin with either bevacizumab (Avastin), an anti-VEGF receptor monoclonal antibody, or placebo concluded that the addition of bevacizumab did not affect progression-free survival or median overall survival.<sup>53</sup> Other studies with antiangiogenic therapies including thalidomide and PTK787 have had no clinical benefit.<sup>54,55</sup> Bortezomib, a proteasome inhibitor, is currently being tested in a multinational, multicenter, phase II study and has shown activity against MPM in pre-clinical studies.<sup>56</sup> Furthermore, in phase I trials of oral and IV formulations of vorinostat, suberoylanilide hydroxamic acid (SAHA), a novel histone deacetylase inhibitor, two patients had partial response, prompting a placebo-controlled, randomized phase III study of oral SAHA in relapsed mesothelioma patients.<sup>57</sup>

## Expert Opinion/Five-year Review

MPM continues to impart a dismal prognosis to those diagnosed with the disease. Currently, no standard therapy or consensus exists regarding

treatment. The number of MPM cases will likely rise over the next two decades and clinicians specializing in thoracic malignancies will increasingly be called upon to treat these patients. For non-surgical candidates, cisplatin plus pemetrexed is now considered to be the standard of care. Based on the previous success of radical surgery and adjuvant chemoradiation, current trimodality therapy has focused on induction therapy followed by surgery and radiation. The encouraging results of this treatment strategy warrant

larger confirmatory trials. The utilization of newer technologies such as PET and gene expression microarray may enable better staging and risk stratification of patients, and thus appropriately directed therapies. Basic science and translational research have led to substantial advances in understanding MPM pathogenesis and molecular mechanisms. The use of proteomics and serum analysis may lead to earlier diagnosis of MPM, earlier treatment, and thus better survival. ■

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