Recent Advances in the Treatment of Malignant Pleural Mesothelioma

Suresh S. Ramalingam, MD, and Chandra P. Belani, MD†*

Malignant pleural mesothelioma clinically manifests after decades of initial exposure to etiologic agents, such as asbestos, and presents with nonspecific symptoms such as dyspnea, pain, or weight loss. In patients with limited, resectable disease, surgical therapy with extrapleural pneumonectomy or pleurectomy is recommended, although, it is unclear which approach is superior. Radiation has a limited role and is used primarily for palliation. The palliative efficacy of traditional chemotherapeutic agents and combination regimens is modest at best. The combination of cisplatin and pemetrexed, a novel multitargeted antifolate agent, is the approved "standard of care" for patients with unresectable malignant pleural mesothelioma. A number of molecularly targeted agents are currently under evaluation for mesothelioma such as the Histone deacetylase (HDAC) inhibitors that have demonstrated promising anticancer activity. Vorinostat, a small molecule inhibitor of HDAC, which targets select members of class I and II HDACs, has shown early evidence of activity and is currently being evaluated in a randomized study for patients who progress with standard therapy for advanced mesothelioma. It is hoped that the HDAC inhibitors and other novel targeted agents will pave the way for improved outcomes for patients with this disease.

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Malignant pleural mesothelioma (MPM) is a rare malignancy, which has been the subject of much attention because of its long recognized link to asbestos and poor outcome.[1] Because of the 30- to 40-year lag time between exposure to asbestos and the development of MPM, the incidence of the disease is expected to continue to increase over the next decade.[2,3] Most patients with MPM are diagnosed in the sixth or seventh decade of life. Although there is no evidence that tobacco causes MPM, it does, in combination with asbestos, seem to synergistically increase the risk of MPM. Other etiologies have also been proposed including radiation and Simian Virus (SV40).[4]

There are three primary histologic subtypes: epithelial, sarcomatous or fibrosaracomatous, and mixed.[5] The first is generally considered to have the best prognosis, whereas the sarcomatous type portends a poor prognosis. Death from MPM typically results from local invasion, rather than distant metastases. Indeed, few patients have distant metastases at the time of diagnosis. Nevertheless, autopsy studies have reported that as many as 80% of patients have widespread disease on examination.[6]

Computed tomography (CT) and magnetic resonance imaging (MRI) scans are considered the most accurate radiographic studies in the evaluation of MPM at this time.[7,8] In both, the most characteristics findings are pleural thickening, often focal, and pleural effusion. However, it is unclear if one or the other is the superior imaging method. Two separate reports comparing the accuracies of CT and MRI have been published by Heelan et al.[9] and Patz et al.,[10]respectively, and the authors concurred that they are equivalent. Although MRI may be slightly superior in evaluating chest wall invasion, CT is favored for assessment of mediastinal involvement.

The clinico-pathologic factors most commonly linked with a better outcome are histology (epithelial), performance status (Eastern Cooperative Oncology Group 0 or 1), and stage.[11,12] Other variables that have been reported, but not confirmed, to influence survival or response are duration of symptoms, gender, leukocyte and platelet count, and age.

THERAPEUTIC OPTIONS

Surgery

Complete surgical resection has a curative potential in selected patients with MPM. However, not all patients with MPM present with early stage disease that is amenable to surgical resection. The two surgical procedures that are generally considered are extrapleural pneumonectomy (EPP) and pleurectomy with dectorication. EPP entails the en bloc resection of the lung, as well as relevant lymph nodes, adherent pericardium, and involved diaphragm. Though initial reports noted promising survival with surgical intervention in patients with stage I disease, particularly with epithelial histology, the operative mortality and morbidity was high at 10 to 20%.[13] Combined with improvements in postoperative care, data from experienced centers, have noted the mortality rate in recent times to be approximately 5 to

*Emory University School of Medicine, Winship Cancer Institute, Atlanta, Georgia; and †Penn State Hershey Medical Center, Penn State Hershey Cancer Institute, Hershey, Pennsylvania.

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Address for correspondence: Chandra P. Belani, MD, Penn State Hershey Medical Center, Penn State Cancer Institute, H072, 500 University Drive, Hershey, PA 17033. E-mail: cbelani@psu.edu

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10%.[14,15] Schipper et al.[16] reported a large series of patients treated with MPM treated at their institution ($N = 285$ patients). Seventy-three patients underwent EPP of whom approximately 50% had major complications. The median survival for patients who underwent EPP was 16 months and the 3-year survival rate was only 14%. Pleurectomy and decortication is associated with a lower postoperative complications rate but has a higher rate of local recurrence.

It is unclear whether EPP or pleurectomy with decortication is clearly superior, as no prospective randomized comparisons have been performed.[17] A report from the Lung Cancer Study Group demonstrated in a nonrandomized study that patients who were treated with EPP had similar survival to those treated with nonradical surgery.[18] Similarly, Allen et al.,[19] reported comparable outcomes for patients treated with EPP and pleurectomy. Although these reports suggest that there is no benefit to EPP, they also note that local recurrence was substantially lower with EPP. Recently, Flores et al.[20] studied data from 663 consecutive patients who underwent either EPP or pleurectomy with decortication across three institutions. The postoperative mortality rate was higher for EPP (7%) compared with pleurectomy (4%). The hazard ratio for survival favored the use of pleurectomy over EPP. The overall survival with EPP was inferior based on an univariate analysis, when compared with pleurectomy with decortication. Female gender and the use of multimodality therapy were associated with a better outcome. EPP was associated with a lower rate of local recurrence. Interpretation of these results is limited by potential variations in eligibility criteria for the two procedures at the three participating institutions.

Thus several questions remain unanswered regarding the role of surgery in the treatment of MPM. Appropriate patient selection criteria, the type of surgery, and the timing of surgery are often chosen based on individual institutional protocols.

MULTIMODALITY THERAPY

An active avenue of exploration in MPM is the role of multimodality therapy in an attempt to minimize the occurrence of local, and distant metastasis after, if possible, resection, or at least maximal reduction of the tumor. The largest experience reported to date is that of Sugarbaker and Norberto,[21] who treated 183 patients over nearly 2 decades. Patients who underwent EPP were subsequently treated with combination chemotherapy regimen of cyclophosphamide, doxorubicin, and cisplatin, and later paclitaxel and carboplatin followed by 3000 cGy of radiation. In their experience, operative mortality was less than 4%, and major morbidity, primarily cardiac arrhythmia, respiratory failure, aspiration, pulmonary embolism, and infection was noted in approximately 30% of patients. The median survival was 19 months, and 2-year survival rate was 38%. Fifteen percent of patients survived 5 years. The use of tri-modality therapy has also been studied by other groups. Batirel et al.[22] studied the strategy of EPP followed by hemithoracic radiation (54 Gy). Subsequently, all patients were treated with platinum-based chemotherapy. Though this was a small study with only 20 patients, the approach was safe and was associated with a median survival of 20 months.

The use of intracavitary chemotherapy after pleurectomy was studied by Richards et al.[23] in a phase I/II study. Forty-four patients with MPM underwent pleurectomy and were given intrapleural hyperthermic cisplatin with an exposure time of 1 hour. The dose of cisplatin was escalated in sequential cohorts of patients. The procedure was tolerated well and was associated with a median survival of 13 months. The major adverse events reported included atrial fibrillation and venous thrombosis. The postoperative mortality rate was 11%. The study had a higher proportion of patients with sarcomatoid histology, which is generally resistant to chemotherapy. These results are promising, but can only be recommended in the presence of an experienced team of surgeons and oncologists.

The availability of an efficacious combination chemotherapy regimen (cisplatin-pemetrexed) provides the opportunity for improved multidisciplinary care. In a phase II study, Krug et al.[24] treated 77 MPM patients with four cycles of cisplatin-pemetrexed. EPP followed by hemithoracic radiation was administered to patients with objective response or stable disease with chemotherapy. Overall, 83% of the patients received all four cycles of chemotherapy. Out of 54 patients who underwent surgery, 87% were able to undergo EPP. The median survival was promising at 17 months, based on a preliminary report. This study demonstrates the feasibility of neoadjuvant chemotherapy in patients with resectable MPM, and further studies are essential to define patient subpopulations that derive benefit from combined-modality therapy.

RADIATION

Radiotherapy has been evaluated for palliation, primary therapy or after surgical intervention in patients with MPM. Because MPM is a diffuse disease with frequent involvement of neighboring organs such as the lung, esophagus, heart, and liver, the use of radiation as primary therapy is not feasible in a majority of the patients. In a small study of 12 patients who underwent primary radiation therapy, two fatal complications of hepatitis and myelopathy were noted.[25] In another study by Linden et al.,[26] radiation was used alone or in combination with chemotherapy for the treatment of MPM. Thirty-one patients received radiation therapy alone to a dose of 40 Gy. There was one partial response and the median survival was 6 months. Nearly, all patients developed radiation induced pulmonary fibrosis. For these reasons, radiation is not recommended as primary therapy for mesothelioma. Nevertheless, radiation can be used for palliation of chest pain or painful chest wall recurrences after surgical therapy. In a prospective study by Bissett et al.,[27] 22 MPM patients with chest pain were treated with 30 Gy of external beam radiation to the involved hemithorax. Though improvement in pain was noted in 13 out of 19 evaluable patients at 1 month after therapy, the benefit was short lived. Majority of the patients had worsening pain by 3 months. The use of a slightly higher dose of radiation was reported to be associated with a greater degree of benefit in another study.[28] Out of 19 patients who received palliative radiation, the use of 40 Gy over 4 weeks appeared to be associated with the best results.

Radiotherapy has also been evaluated as part of multimodality therapy for patients with MPM. Patients who underwent

