Malignant mesothelioma

Shirish M. Gadgeel, MD,[1] and Harvey I. Pass, MD[2]

[1] Barbara Ann Karmanos Cancer Institute, Wayne State University, Detroit, MI, and [2] NYU Medical Center/School of Medicine, New York, NY.

Malignant mesothelioma is an aggressive tumor that is increasing in incidence all over the world, even though its incidence has leveled off in the United States. Asbestos exposure is considered the main risk factor for mesothelioma. Some experts believe that exposure to simian virus 40 may also play a role. Pleural mesothelioma accounts for 90% of all tumors, although mesotheliomas can occur in other serosal surfaces. Histopathology, immunohistochemistry, and sometimes electron microscopy are required to distinguish mesothelioma from other tumors involving the pleura. Performance status and sarcomatoid histology are among the most important prognostic factors. Median survival for pleural mesothelioma is 12 months from diagnosis. Recent data have demonstrated the benefits of chemotherapy in patients with good performance status. The role of aggressive surgery, such as extrapleural pneumonectomy, remains ill defined, though it should be considered in early-stage disease. Multimodality regimens are being evaluated to improve upon the current outcome of these patients. With greater understanding of the molecular mechanisms underlying the pathogenesis of mesothelioma, there is hope of developing novel agents that are more effective.

Malignant mesotheliomas are tumors that arise from the mesothelial cells of serosal surfaces, such as the pleura and peritoneum. Although the tumor is rare, its incidence is increasing in many parts of the world and is expected to do so for many years.[1] In the United States, about 2,500 cases occur annually, and its incidence is leveling off or even decreasing.[2] This review will focus primarily on pleural mesothelioma, which accounts for 90% of all malignant mesotheliomas. We will also discuss peritoneal mesothelioma briefly at the end of this article.

Case history

R.W. is a 73-year-old male patient. Fifteen months ago, he noticed some difficulty in breathing. His primary care physician observed that air entry in the right lung field was reduced compared with the left and ordered a chest x-ray to evaluate the patient's symptoms. The chest x-ray revealed a right-sided pleural effusion. R.W. was referred to a pulmonologist, who performed a thoracentesis and bronchoscopy. The bronchoscopy did not reveal any abnormal findings, and bronchial washings did not reveal any abnormal cells. Cytologic analysis of the pleural fluid revealed malignant cells that were positive for cytokeratin and negative for Leu M1, TTF-1 (thyroid transcription factor-1), and CEA (carcinoembryonic antigen). The pathologic diagnosis was malignant pleural mesothelioma.

The pathology slides were reviewed at our center, and our pathologist concurred with the primary diagnosis of pleural mesothelioma. Our pathologist opined that it was of the epithelioid variety.

On the advice of the pulmonologist, R.W. underwent pleurodesis. He then sought an opinion at our center. The patient was doing well clinically and had no symptoms. His past medical history was significant for hypertension, a history of cerebrovascular accident with no residual deficit, and a history of bilateral knee-replacement surgeries. His medications included hydrochlorothiazide, fosinopril, and aspirin. He had no known drug allergies.

R.W. was married. He had retired from his job as a technician in an automobile manufacturing plant and was unaware of any prior asbestos exposure. He had smoked cigarettes for 30 years (a pack a day) and stopped smoking 19 years prior to diagnosis. The patient's family history was significant for one sister who died of oral cancer.

Clinical course

The patient was initially evaluated at our center by thoracic surgery, and a computed tomographic

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Correspondence to: Shirish M. Gadgeel, MD, Department of Internal Medicine, Division of Hematology and Oncology, Karmanos Cancer Institute, Wayne State University, 4100 John R, 4HWCRC, Detroit, MI 48201; telephone: 313-745-8389; fax: 313-745-9355; e-mail: gadgeels@karmanos.org.

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(CT) scan of the chest was ordered. The CT scan revealed diffuse pleural thickening on the right side, particularly at the lung base. A 1.5-cm lymph node was found in the aortopulmonary window, but all other lymph nodes were normal in size. Pulmonary function tests revealed an FEV_1 (forced expiratory volume in 1 second) of 2.77 L, an FEV_1/FVC (forced vital capacity) ratio of 76%, an $FEF_{25\%–75\%}$ (forced expiratory flow) rate of 2.06, and a DL_{CO} (lung diffusion capacity) of 77% of predicted.

A lung perfusion scan revealed that the right lung contributed 40% of the total lung ventilation. The patient also underwent an evaluation by a cardiologist, who conducted an exercise stress test and echocardiography. The cardiologist felt that his cardiac status was adequate for thoracic surgery. All of the patient's laboratory tests were normal, including his white blood cell count, platelet count, and renal function.

R.W. was enrolled on a clinical trial evaluating 4 cycles of cisplatin and pemetrexed (Alimta) followed by extrapleural pneumonectomy and hemithoracic radiotherapy. He received the first cycle of pemetrexed (500 mg/m²) and cisplatin (75 mg/m²) about 3 months after the original diagnosis and subsequently underwent the remaining 3 planned chemotherapy cycles on schedule. During chemotherapy, he developed a mild elevation in his serum creatinine level and a mild decline in his serum magnesium level. He complained of grade 2 fatigue, which generally lasted for 4–5 days after each cycle of chemotherapy. A CT scan performed after the 4 cycles of treatment demonstrated stable disease.

Six weeks after the start of the last cycle of chemotherapy, R.W. underwent an extrapleural pneumonectomy that included resection of the right lung with the pleura, diaphragm, and pericardium. Pathologic analysis revealed that the tumor had not involved the diaphragm or the pericardium but was infiltrating the underlying lung. Four of 14 hilar lymph nodes were positive for tumor, but none of the mediastinal lymph nodes was positive. Thus his pathologic stage was T2, N1, M0 (stage III).

The patient was in the hospital for a week. Pain at the surgical site was managed by epidural analgesia. He required analgesics at home to control postoperative pain for about 3 months. He also required oxygen at home for about 6–7 weeks after surgery.

About 6 weeks after surgery, R.W. was started on external-beam radiation therapy to the right hemithorax. He received a total dose of 54 Gy over a 6-week period. During this period, he developed fatigue and dysphagia. Between the surgery and radiation therapy, the patient lost approximately 14% of his baseline weight.

Since the completion of all of the planned treatment, the patient's activity level is gradually improving. He does not require any oxygen at home and is not on any pain medications. He has gained some weight, but his current weight is still 10% less than his baseline weight. A recent CT scan showed no evidence of tumor progression.

TABLE 1

Industries associated with asbestos exposure

- Ship building
- Insulation
- Railroad
- Auto parts
- Paper mill
- Ceramics
- Construction

Epidemiology

Malignant mesothelioma is more common in males than in females, and it typically occurs in the fifth to seventh decade of life. Almost 90% of malignant mesotheliomas occur in the pleura; only about 250 cases of peritoneal mesothelioma are diagnosed each year in the United States.

Asbestos exposure

Asbestos is the principal carcinogen implicated in the pathogenesis of mesothelioma. This tumor was even less common before the widespread use of asbestos. In 1960, the first convincing evidence of a link between mesothelioma and asbestos was described from data on patients who worked or lived in the vicinity of South African asbestos mines.[3] This link was confirmed by other observations, which suggested that there is a 20- to 40-year latency period between exposure to asbestos and occurrence of the malignancy.[4,5] In about 20% of patients, asbestos exposure cannot be identified, although this frequency varies in different parts of the United States.[6–8]

Asbestos regulations do appear to have an impact on the incidence of mesothelioma, as suggested by the leveling off of its annual incidence in the United States.[2] However, since heavy use of asbestos occurred later in many parts of the world than that in the western world, the incidence of mesothelioma is expected to rise worldwide for many years. Some of the common occupations associated with asbestos exposure are listed in Table 1. The risk of malignant mesothelioma extends also to those who are in proximity of asbestos handlers, such as household members.[9,10]

There are two principal forms of asbestos: long, thin fibers known as amphiboles and serpentine fibers known as chrysotile. Chrysotile fibers are more easily broken down by phagocytes and transported out of the lungs than are amphibole fibers. These data have led some to consider that mesothelioma associated with chrysotile exposure is almost completely explained by amphibole contamination of chrysotile deposits.[11] However, recent evidence from electron microscopy studies support the view that chrysotile asbestos fibers can cause mesothelioma, although not as frequently as amphibole fibers.[12,13]

Other risk factors

Despite the large number of individuals exposed to asbestos, malignant mesothelioma remains rare, leading some experts to suggest that additional factors are required to cause the disease. Simian virus 40 (SV40), a DNA virus, has been implicated as a carcinogen in the formation of mesotheliomas. Carbone et al[14] reported that SV40 sequences could be found in up to 60% of mesotheliomas. Bocchetta et al[15] reported that human mesothelial cells are susceptible to SV40 infection and that 100% of the infected cells express SV40 T antigen (Tag), but the infected cells are not lysed by SV40. The mechanism for this appears to be related to abnormally high levels of p53 expression in mesothelial cells, which binds Tag and limits the replication of SV40. This probably sets up a situation where the mesothelial cells infected with SV40 can acquire genetic mutations and a malignant phenotype.

There is evidence that SV40 may have been transmitted in humans through injectable polio vaccines until 35–40 years and in other countries, such as Russia, as late as 20 years ago.[16,17] Intermediate follow-up of individuals who received the vaccine has shown no evidence of increased numbers of mesotheliomas.[17] The role of SV40 in causation of mesotheliomas remains uncertain.

Molecular biology of mesothelioma

Compared with the etiology of mesotheliomas, the pathogenesis and molecular factors involved in their formation are much better understood. This increasing knowledge base is expected to lead to more effective treatment options for patients with mesothelioma.

Cytogenetics

Most malignant mesotheliomas have complex karyotypes, with extensive aneuploidy and rearrangements of many chromosomes.[18,19] Loss of one copy of chromosome 22 is the single, most common karyotypic change in malignant mesothelioma. Other chromosomal changes commonly observed are rearrangements of 1p, 3p, 9p, and 6q. Karyotypic changes differ according to the histologic subtype of malignant mesotheliomas. For example, deletion in 3p21 is common in the epithelioid subtype of malignant mesothelioma but rare in sarcomatoid or biphasic tumors. Analysis of the chromosomes altered in malignant mesotheliomas reveals that many changes affect known tumor suppressor genes, such as p16 *(CDKN2A)* and p14 *(ARF).* In addition loss of function of neurofibromin 2 *(NF2),* or merlin, a gene present on chromosome 22, may be involved in the pathogenesis of malignant mesothelioma.

Thus, cytogenetic and molecular genetic studies suggest that mesotheliomas result from the step-by-step accumulation of numerous somatic genetic events, most of which are deletions of tumor suppressor genes. The identification of the critical somatic genetic events will likely lead to a better understanding of the pathogenetic mechanisms involved in the development of malignant mesotheliomas.

Growth factors

It is well recognized that abnormalities in growth factors and their pathways can have an impact on various aspects of cancer formation and progression. The growth of normal human mesothelial cells is regulated by many growth factors, including epidermal growth factor (EGF), platelet-derived growth factor, transforming growth factor β, and hepatocyte growth factor.[20–22] Alterations in the activity of these growth factors and their pathways have been observed in malignant mesothelioma cells, and these alterations may confer a growth and survival advantage to mesothelioma cells.

Angiogenesis

Angiogenesis plays an important role in the growth, progression, and metastasis of solid tumors, and angiogenesis, as assessed histologically by intratumoral microvascular density, correlates with poor prognosis in many tumor types.[23–25] Mesotheliomas have a high intratumoral microvessel density, and this property is significantly related to survival, even after adjusting for other known prognostic factors, such as histologic type, stage, and age.[26]

Vascular endothelial growth factor (VEGF) is considered the most important regulator of tumor angiogenesis and vascular permeability.[27] In malignant mesotheliomas, VEGF overexpression is well documented, and its expression has been associated clinically with poor prognosis.[28] This knowledge has formed the basis of evaluating anti-VEGF therapy in malignant mesotheliomas.

Pathology

Three major histologic subtypes of mesothelioma have been described: epithelial, sarcomatoid, and mixed or biphasic. The epithelial form is the most common subtype and can occur in papillary, vacuolated, solid, or tubular patterns. The sarcomatoid subtype consists predominantly of spindle-shaped cells and resembles fibrosarcoma. The presence of both spindle-shaped cells and epithelioid cells characterizes the mixed type of mesothelioma. The pathologic subtypes have prognostic relevance with sarcomatoid tumors demonstrating an aggressive phenotype.[6]

Clinical presentation

The clinical course of mesothelioma is related almost exclusively to local progression of the tumor. Clin-

TABLE 2

Clinical features of pleural malignant mesothelioma

Symptoms	Laboratory abnormalities
Chest pain	Thrombocytosis
Dyspnea	Elevated white blood cell count
Cough	SIADH
Palpitations (from arrhythmia)	Hypoglycemia
Fever	Hypercalcemia
Night sweats	
Fatigue	
Dysphagia	
Ascites (from tumor extension)	

SIADH = syndrome of inappropriate antidiuretic hormone secretion

ically or radiologically apparent distant metastatic disease is uncommon, although in autopsy series, over 50% of patients have evidence of distant metastases.[29,30] In pleural mesotheliomas, the right side is more commonly involved than the left. This disparity may be related to the greater inhalation of asbestos fibers in the right lung.

Symptoms (Table 2)

Typically, the onset of symptoms is insidious, and the symptoms are related to tumor growth at the visceral surface (eg, pleural mesothelioma patients have dyspnea, chest pain, and cough). Dyspnea is primarily related to pleural effusion, which occurs in > 95% of patients. The chest pain in pleural mesothelioma is a steady pain involving the affected hemithorax, rather than a pleuritic type of pain.[29,30] Patients with pleural mesothelioma may also experience dysphagia due to compression of the esophagus by the pleura-based tumor.

Systemic complaints include fever, fatigue, and weight loss. Mesothelioma patients may have fevers with night sweats, raising the suspicion of an infective etiology for the observed effusion. In advanced stages, patients may develop symptoms from continued growth of the tumor. Thus, patients may develop arrhythmia from extension of the tumor to the pericardium and ascites or abdominal pain from extension to the peritoneum.

Ninety percent of patients at diagnosis or during the course of their disease may develop thrombocytosis. This development has been correlated with high levels of interleukin-6 produced by the tumor cells.[31] Patients may also experience a leukemoid reaction and thrombotic episodes. Other, less often observed, metabolic abnormalities include SIADH (syndrome of inappropriate antidiuretic hormone secretion), hypoglycemia, and hypercalcemia.

Malignant mesothelioma patients may have associated lymphoproliferative disorders, such as lymphomas, myeloma, and chronic lymphocytic leukemia.[32] Interestingly, a case-control study showed an association between asbestos exposure and lymphomas of the gastrointestinal tract.[33]

TABLE 3

Differential diagnosis of pleural malignant mesothelioma

Pathologic marker	Malignant mesothelioma	Adenocarcinoma
PAS stain	Rare	Positive
Cytokeratin	Positive	Positive
CEA	Rare	Positive
Calretinin	Positive	Rare
Leu M1	Rare	Positive
Electron microscopy	Long, thin, branched microvilli	Short, thick, non-branched microvilli

PAS = periodic acid-Schiff; CEA = carcinoembryonic antigen

Diagnosis

Radiology

A chest x-ray is usually the first radiology test done after the onset of symptoms. Typically, a pleural effusion is observed, requiring additional studies. Chest x-ray may show evidence of asbestos exposure in the form of pleural plaques and calcifications, but these deposits are not common. CT of the chest will typically show evidence of a circumferential tumor that grows as a pleural rind, restricting and compressing the ipsilateral hemithorax. In addition, CT scanning can determine whether the mediastinal lymph nodes are enlarged, an adverse prognostic sign. Magnetic resonance imaging (MRI) of the chest can help define invasion of the tumor into the surrounding structures, particularly into areas such as the mediastinum and spine. However, in most cases, MRI scans do not add more information to that obtained from CT scans.

Emerging data suggest that positron emission tomography (PET) scans may offer additional information regarding tumor extent, mediastinal lymph node involvement, and involvement of extrathoracic sites.[34,35] Further, PET scan may provide prognostic information based on the standardized uptake value.[36] However, the appropriate role of PET scans in the management of pleural mesothelioma remains to be defined.

TABLE 4

Staging of pleural mesothelioma

Primary tumor	
TX	Primary tumor cannot be assessed
T0	No evidence of primary tumor
T1	Tumor involves ipsilateral parietal pleura, with or without focal involvement of visceral pleural
T1a	Tumor involves ipsilateral parietal (mediastinal, diaphragmatic) pleura; no involvement of the visceral pleura
T1b	Tumor involves ipsilateral parietal (mediastinal, diaphragmatic) pleura, with focal involvement of the visceral pleura
T2	Tumor involves any of the ipsilateral pleural surfaces with at least one of the following: Confluent visceral pleural tumor (including fissures) Invasion of the diaphragmatic muscle Invasion of lung parenchyma
T3	Tumor involves any of the ipsilateral pleural surfaces with at least one of the following: Invasion of the endothoracic fascia Invasion into mediastinal fat Solitary focus of tumor invading the soft tissues of the chest wall Nontransmural involvement of the pericardium
T4	Tumor involves any of the ipsilateral pleural surfaces with at least one of the following: Diffuse or multifocal invasion of soft tissues of the chest wall Any involvement of rib Invasion through the diaphragm to the peritoneum Direct extension of any mediastinal organs Direct extension to the contralateral pleura Invasion of the spine Extension to the internal surface of the pericardium Pericardial effusion with positive cytology Invasion of the myocardium Invasion of the brachial plexus
Regional lymph nodes	
NX	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastases
N1	Metastases in the ipsilateral bronchopulmonary and/or hilar lymph nodes
N2	Metastases in the subcarinal lymph nodes and/or ipsilateral internal mammary or mediastinal lymph nodes
N3	Metastases in the contralateral mediastinal, internal mammary or hilar lymph nodes, and/or ipsilateral or contralateral supraclavicular or scalene lymph nodes
Distant metastasis	
MX	Distant metastases cannot be assessed
M0	No distant metastasis
M1	Distant metastasis present

Stage grouping

Stage I	T1	N0	M0
Stage IA	T1a	N0	M0
Stage IB	T1b	N0	M0
Stage II	T2	N0	M0
Stage III	T1,2	N1	M0
	T1,2	N2	M0
	T3	Any N	
Stage IV	T4	Any N	M0
	Any T	N3	M0
	Any T	Any N	M0

Adapted from Rusch[40]

Pathologic differentiation of malignant mesothelioma

An important aspect of diagnosis of malignant mesothelioma is differentiating it from other pleura-based tumors, particularly metastases from other tumors to the pleura (Table 3). Histologic analysis, immunohistochemistry, and electron microscopy are relevant in making this differentiation.[37–39]

On histologic analysis, malignant mesotheliomas are rarely positive on periodic acid-Schiff staining or mucicarmine staining, whereas adenocarcinomas are frequently positive. On immunohistochemistry, mesothelioma cells generally are calretinin and WT1 (Wilms' tumor antibody) positive, EMA (epithelial membrane antigen) positive, mesothelin positive, CEA negative, and Leu M1 negative. On electron microscopy, mesotheliomas possess long, branched microvilli with cells that lack mucin granules and have giant desmosomes.

It is also important to differentiate sarcomatoid mesothelioma from sarcoma involving the pleura. Cytokeratin expression is most useful in making this distinction, with sarcomatoid mesotheliomas demonstrating strong expression of cytokeratin.

Staging and prognostic features

Several systems have been used for staging malignant mesotheliomas over the past 30 years. The currently accepted staging system was developed by the International Mesothelioma Interest Group and is accepted by the American Joint Committee on Cancer (Table 4).[40]

Based on many clinical factors, two separate groups, the Cancer and Leukemia Group B (CALGB) and European Organization for Research and Treatment of Cancer have developed prognostic systems.[6,41] In both systems the most important prognostic factor is the patient's performance status. Other poor prognostic factors that are present in one or both systems are sarcomatoid histology, male gender, high white blood cell count, chest pain, and weight loss (Table 5).

The median survival in the different prognostic groups in the CALGB system ranges from 1.4 months to 13.6 months, and 1-year survival ranges from 0% to 63%.

TABLE 5

Factors associated with poor prognosis

- Performance status (ECOG status ≥ 2)
- Non-epithelial histology
- Chest pain
- Age > 75 years
- Male gender
- High platelet count
- Lactate dehydrogenase level > 500 IU/L
- Low hemoglobin level
- High white blood cell count
- Weight loss

ECOG = Eastern Cooperative Oncology Group

Therapeutic options

Surgery

The role of surgery in the management of malignant mesotheliomas remains ill defined owing to the rarity of this disease and the highly selected nature of the patients who have been included in published surgical series. Nonetheless, surgical excision—especially when performed by an experienced surgeon—is a reasonable strategy in patients with disease confined to the pleural space (T1–T3 tumors), since local tumor progression is an important aspect of this disease.

The surgical procedures used to remove the tumor include pleurectomy and extrapleural pneumonectomy (EPP). EPP involves resecting the parietal pleura, lung pericardium, and diaphragm en bloc, whereas pleurectomy consists of stripping the pleura from the apex to the diaphragm and removing the pericardium and the parietal pleura. There are no comparative studies of either approach. However, excluding stage I tumors, EPP is required to achieve complete resection of all gross tumor. The operative mortality of EPP is 5%, median survival is 2 years, and only 10%–20% of patients who have undergone this procedure survive 5 years.[42]

Results from surgical series suggest that certain factors have prognostic value. These factors include histologic subtype, preoperative tumor bulk, and mediastinal lymph node involvement.[43,44] Based on these data, some experts have suggested that EPP should not be considered in patients with sarcomatoid histology and for resecting stage III or stage IV tumors.

Mesothelioma patients can also undergo palliative surgical procedures, such as pleurodesis. This procedure can be done alone or with partial pleurectomy, using video-assisted thoracoscopic surgery (VATS) and insufflation of agents such as talc.

Radiation therapy

The role of radiation therapy in the treatment of mesothelioma is limited, since the pleura encompasses the entire hemithorax and thus involves such vital structures as the ipsilateral lung, heart, pericardium, and liver on the right side. Despite some reports of long-term survival after irradiation, most reviews of radiotherapy for malignant mesothelioma report no significant effect on disease control or survival.[45,46] Radiation therapy is primarily used to palliate chest pain resulting from local extension of the tumor into the chest wall.

Radiotherapy also has been used as adjuvant therapy following EPP or pleurectomy. In the postoperative setting, radiation therapy does appear to reduce the risk of local recurrence.[47] Brachytherapy has also been used in the postoperative setting to minimize the toxicity of external-beam irradiation and provide better local control.[48] However, the paucity of data regarding this technique limits the ability to

TABLE 6

Single-agent chemotherapy of malignant mesothelioma

Agent	Response rate	Reference
Doxorubicin	0%–9%	Sorensen et al,[55] Lerner et al[56]
Liposomal doxorubicin	0%–6%	Oh et al,[57] Baas et al,[58] Skubitz[59]
Cisplatin	14%	Mintzer et al,[60] Zidar et al[61]
Carboplatin	7%–16%	Vogelzang et al,[62] Raghavan et al[63]
Methotrexate	37%	Solheim et al[50]
Edatrexate	25%	Kindler et al[51]
Pemetrexed	14%	Scagliotti et al[52]
Gemcitabine	0%–7%	Kindler et al,[64] van Meerbeeck et al[65]
Paclitaxel	0%	van Meerbeeck et al,[66] Vogelzang et al[67]
Docetaxel	10%	Vorobiof et al[68]

define the role of brachytherapy.

Systemic therapy

The benefits of chemotherapy in the management of malignant mesothelioma were not well defined until recently, owing to the small nature of the trials, lack of consistency in assessing response, and absence of appropriate staging systems and prognostic scales, which precluded comparison of results across trials.

Monotherapy. Clinical trials of single-agent therapy have shown that responses are limited, with most agents demonstrating a response rate of not more than 15%.[49] One class of agents that has shown consistent antitumor activity is the antimetabolite group, particularly antifolates.[50–52] Antifolates, such as methotrexate and pemetrexed, are transported into tumor cells through various folate receptors, and preclinical data suggest that mesothelioma cells express high levels of folate receptors.[53] In addition, mesotheliomas commonly are deficient in methylthioadenosine phosphorylase (MTAP), an enzyme that makes them more dependent upon de novo purine biosynthesis and thus more susceptible to the effects of antifolates.[54]

Table 6 summarizes the response rates observed in a variety of published clinical trials[50–52,55–68] of single-agent chemotherapy in malignant mesothelioma.

Combination chemotherapy, primarily doxorubicin-based and platinum-based regimens, has been evaluated in the management of malignant mesotheliomas. Even though combination therapy does produce higher response rates, it has not consistently shown an improvement in survival over single-agent therapy. In the past few years, two phase III studies evaluating a combination of cisplatin with an antifolate (pemetrexed and raltitrexed) showed superior response rate and survival compared with cisplatin alone.[69,70] In the United States, pemetrexed, when used in combination with cisplatin, is the only approved drug for the management of malignant mesotheliomas.

With the acceptance of the combination of cisplatin and pemetrexed as the current standard, there is considerable interest in second-line treatment of malignant mesothelioma. However, the information available to guide physicians in the post-pemetrexed era is greatly limited. In reviewing the post-study chemotherapy given to patients enrolled in a phase III trial of pemetrexed, Manegold et al[71] found that second-line therapy—most commonly gemcitabine (Gemzar) or doxorubicin—was significantly associated with improved survival, suggesting the value of second-line treatment.

Targeted therapy

Coming on the heels of our increasing knowledge of the pathogenesis of this disease is a great deal of interest in developing drugs that target specific molecules controlling the growth and survival of mesothelioma cells. Two separate epidermal growth factor receptor/tyrosine kinase inhibitors, erlotinib (Tarceva) and gefitinib (Iressa), have been evaluated in malignant mesothelioma patients and produced disappointing results.[72,73] Similarly, imatinib (Gleevec), a platelet-derived growth factor receptor inhibitor, showed no response among 25 patients.[74]

Based upon the high levels of VEGF found in malignant mesothelioma, several groups are evaluating anti-VEGF therapy to block angiogenesis. Recently, a randomized phase II study evaluating the benefits of adding bevacizumab (Avastin), an anti-VEGF monoclonal antibody, to a combination of cisplatin and gemcitabine completed accrual.[74] Other anti-VEGF agents, such as the VEGF-receptor inhibitors PTK787 and AZD2171, are undergoing evaluation in this disease. Interest also exists in evaluating proteasome inhibitors, such as bortezomib (Velcade), and histone deacetylase inhibitors, such as suberoylanilide hydroxamic acid (SAHA, vorinostat).

Multimodality therapy

Survival of mesothelioma patients following single-modality therapy in most series is poor. This has led to investigations of a multimodality approach. As stated earlier, postoperative irradiation, both as brachytherapy and external-beam radiation therapy, has been somewhat successful in reducing the risk of local relapse. Postoperative chemotherapy, given either intracavitorily or postoperatively, has also been evaluated.[75,76] Combined modality therapy for malignant mesothelioma is challenging, due to the difficulty patients have in tolerating all aspects of treatment.

With the advent of drugs such as gemcitabine and pemetrexed that are well tolerated, there is an interest in delivering chemotherapy prior to planned surgery. In a Swiss study, 19 patients received 3 cycles of cisplatin and gemcitabine followed by surgery. Radiation therapy was considered after surgery for areas at risk. The median survival in this study was 23 months, with a 2-year survival of 42%.[77] A similar study evaluating the combination of cisplatin and pemetrexed as induction therapy and including postoperative hemithoracic irradiation is ongoing in the United States. It was alluded to in the case history described in this report.

These data suggest that, in appropriately selected patients, a multimodality approach may offer patients with malignant mesothelioma better control of their disease and longer survival.

Peritoneal mesothelioma

Peritoneal mesothelioma is much less common than pleural mesothelioma, with only 250 cases diagnosed each year in the United States.[2] Asbestos exposure is also believed to play a role in the development of peritoneal mesothelioma. Insulation workers appear to be at particularly higher risk of developing peritoneal mesothelioma.[78] Histologic subtypes of peritoneal mesothelioma are similar to those for pleural mesothelioma. The sarcomatoid subtype is much less common in peritoneal mesothelioma than in pleural mesothelioma.

Clinical manifestations consist of abdominal pain, bloating, alterations in bowel habits, and weight loss. Ascites is present in most patients at the time of diagnosis. The differential diagnosis includes ovarian cancer, colon cancer, and metastases to the peritoneum. An immunohistochemical panel similar to that used in differentiating pleural mesothelioma from other tumors is utilized for differentiating peritoneal mesothelioma.

Management of peritoneal mesothelioma varies based on the patient's ability to tolerate aggressive surgical procedures. Several investigators have reported using aggressive cytoreduction followed by intraoperative hyperthermic perfusion of chemotherapeutic agents or early postoperative intraperitoneal chemotherapy.[79,80] The agents used, their dose, duration of treatment, and the degree of hyperthermia have varied in the different series.

For peritoneal mesothelioma patients who are not surgical candidates, intraperitoneal combined with systemic chemotherapy is considered. In an expanded access program offered by Eli Lilly & Company, cisplatin and pemetrexed were administered to previously untreated patients and pemetrexed alone was given to patients who had received prior therapy. The objective response rate among the 73 patients evaluated for response was 26%.[81] Other regimens that have been studied in peritoneal mesothelioma are doxorubicin-containing regimens and a combination of cisplatin and irinotecan (Camptosar).[82]

The prognosis of peritoneal mesothelioma patients is more varied than that of pleural mesothelioma patients, which is uniformly poor. In a retrospective analysis of 25 patients, two distinct groups were found.[83] One group of patients survived ≥ 4 years and had a median survival of 7 years, whereas the other group had a median survival of only 12 months. Thus, unlike patients with pleural mesothelioma, a distinct proportion of patients with peritoneal mesothelioma may have long-term survival.

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ABOUT THE AUTHORS

Affiliations: Dr. Gadgeel is Assistant Professor, Department of Internal Medicine/Division of Hematology and Oncology, Barbara Ann Karmanos Cancer Institute, Wayne State University, Detroit, MI. Dr. Pass is Professor of Cardiothoracic Surgery and Division Chief for Thoracic Surgery and Thoracic Oncology, NYU Medical Center/School of Medicine, New York, NY.

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