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.

Key Words: Mesothelioma, Novel Therapies, Multimodality Management.

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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

surgical resection for MPM were treated with 54 Gy of hemithoracic external beam radiation in a phase II study.[29] Out of the 57 patients who received postoperative radiotherapy, the median survival was 34 and 10 months, respectively, for patients with early stage (I and II) and advanced stage (III and IV) disease, respectively. The treatment was tolerated well overall with one case of tracheo-esophageal fistula being the most severe toxicity reported. There was excellent local control with postoperative radiotherapy, and majority of the recurrences occurred at systemic sites. High-dose intraoperative radiotherapy has also been evaluated in patients in an effort to improve the local control rate for patients with surgically resectable MPM. However, this approach was associated with a high degree of toxicity and has not been evaluated further.[30]

More recently, intensity-modulated radiotherapy (IMRT) has been studied for therapy for MPM. This technique allows for improved dose distribution to areas at risk for recurrence and a lower exposure of adjacent organs to the radiation. In a cohort of 100 patients who underwent EPP, IMRT with a median dose of 45 Gy was administered to 63 patients.[31] The median overall survival was higher (14.4 months) for patients who received IMRT, whereas patients without IMRT had a median survival of 10 months. Only three patients had in-field recurrences with IMRT. Although these results are encouraging, the results from another small study of 13 patients urge caution with this approach.[32] There was one case of fatal pulmonary toxicity in a patient who received IMRT after EPP. This study also documented a low rate of local recurrence, though the follow-up duration was short. Allen et al.[33] documented, noted fatal pulmonary toxicity in 6 out of 13 patients treated with IMRT after chemotherapy and EPP for MPM. Therefore, it is important that IMRT be used as part of clinical trials for the treatment of MPM.

CHEMOTHERAPY

A wide array of chemotherapeutic agents has been evaluated for the treatment of MPM.[34] Initial studies noted anticancer activity with older agents such as methotrexate, doxorubicin, and platinum compounds.[35–38] More recently, newer agents such as taxanes, gemcitabine, pemetrexed, and raltitrexed have been noted to have promising anticancer activity with a favorable tolerability profile (Table 1 and 2).[39–44] Until recently, studies that evaluated combination of these agents had failed to demonstrate a substantial increase in survival, although response rates were often improved. In a recent trial, pemetrexed, a multitargeted antifolate, in combination with cisplatin resulted in improved survival for patients with mesothelioma.[45] The results of this large clinical trial, have established a "new standard" for the treatment of patients with advanced MPM.

TABLE 1. Gemcitabine for Mesothelioma

Author	Treatment	*N*	RR (%)	Median Survival
Van Meerbeeck et al.[76]	Gem	27	7	8 mo
Kindler et al.[77]	Gem	17	0	4.7 mo
Nowak and Byrne[78]	Gem + Cis	53	33	11.2 mo
Byrne et al.[52]	Gem + Cis	21	48	41 wk
Van Haarst et al.[79]	Gem + Cis	29	16	9.6 mo
Favaretto et al.[53]	Gem + Carbo	50	26	66 wk

RR, Response rate.

TABLE 2. Taxanes in Mesothelioma

Author	Regimen	*N*	RR	Median Survival
Van Meerbeeck et al.[40]	Paclitaxel	25	0	39 wk
Vogelzang et al.[41]	Paclitaxel (high dose)	39	95	5 mo
Vorobiof et al.[80]	Docetaxel	30	10%	12 mo
Belani et al.[81]	Docetaxel	20	5%	4 mo

RR, Response rate.

ANTIFOLATE AGENTS

High-dose methotrexate has demonstrated anticancer activity in MPM. Administered at 3 g/m^2 every 10 to 21 days, with leucovorin rescue, methotrexate demonstrated responses in 37% of 60 patients including one complete response, with a median survival of 11 months.[35] Other antifolates such as edatrexate and trimetrexate are less active in MPM in trials conducted by the Cancer and Leukemia Group B (CALGB). Kindler et al.[46] reported 2 series of patients with trimetrexate for unresectable MPM. Patients received 5 days of trimetrexate at doses of 6 or 10 mg/m^2 IV. Responses were noted in 12% of patients at both administered doses, though the higher dose level resulted in a greater proportion of patients with stable disease, and longer time to treatment failure, and duration of median survival. The main side effects were hematologic in nature, with dose dependent nausea, vomiting, and stomatitis. Subsequently, edatrexate with or without leucovorin was evaluated by the CALGB. Administered at 80 mg/m^2 iv on a weekly schedule, edatrexate generated responses in 25% of 20 treated patients. Meanwhile, the same dose and schedule of edatrexate in combination with leucovorin rescue caused tumor regression in 6 of 38 (16%) of patients. The median survival was 9.6 and 6.6 months, respectively, on these two schedules. The toxicity, however, was substantially greater in the regimen without leucovorin, primarily mucositis, nausea and vomiting, and a macular rash. Raltitrexed, another novel antifolate compound has also demonstrated anticancer activity in the treatment of mesothelioma. In a phase II study conducted by Baas et al.,[44] a promising response rate of 20% was noted. This led to further evaluation of this agent, in combination with cisplatin in a phase III trial sponsored by the European Organisation for Research and Treatment of Cancer Lung Cancer Group and the National Cancer Institute (NCI) of Canada.[47]

ANTHRACYCLINES

Doxorubicin has been evaluated in multiple trials for the treatment of MPM.[37,43] When administered at 60 mg/m^2 iv every 3 weeks, responses have been demonstrated in 10 to 15% of patients, with a median survival of 8 to 10 months. Other anthracyclines, such as epirubicin and mitoxantrone have also yielded similar results.[48,49] Another anthracycline, detorubicin, had promising results in a phase II study, includ-

ing a 43% response rate in 21 patients, and a median survival of 17 months, with a 60% 1-year-survival.[50] Unfortunately, serious cardiac toxicity was common, and no further research with this agent has been conducted.

PLATINUM COMPOUNDS AND OTHER NOVEL AGENTS

Cisplatin and carboplatin have been evaluated in a number of trials and have demonstrated response rates of 10 to 20%. Both cisplatin and carboplatin seem to have comparable efficacy. The taxanes have yielded modest efficacy, with disease stabilization being the best response in most studies.[40,41] Multiple phase II studies have demonstrated anticancer activity for gemcitabine in the treatment of MPM.[39] Response rates of approximately 0 to 31% have been reported in the setting of advanced stage disease. This has prompted the evaluation of gemcitabine in combination of a platinum compound for front-line therapy for MPM.

COMBINATION CHEMOTHERAPY

Combination chemotherapy is now the standard treatment approach for advanced MPM. A number of combination regimens have been evaluated in phase II studies.[37,51,52] Both the platinols and doxorubicin exhibit preclinical synergy with multiple chemotherapeutic agents for the treatment of MPM. Hence, combination regimens that include a platinum compound and an anthracycline have been extensively evaluated in several phase II studies.[37] The combination of doxorubicin and cisplatin with or without cyclophosphamide administered every 3 weeks resulted in response rate of less than 25%. The median survival was approximately 8 to 10 months. The Gemcitabine when combined with cisplatin or carboplatin has also been reported to be effective, with responses in 47% and 20% of patients, respectively.[52,53] In the former study, median survival was 41 weeks, and 40% of patients were alive 1 year after therapy. In addition, the regimen was well tolerated in this group of patients who often are older, and with comorbidities.

PEMETREXED

Pemetrexed is an antifolate that exerts anticancer effect by inhibiting three different enzymes that are necessary for folate metabolism, purine, and pyrimidine synthesis.[54] These enzymes are dihydrofolate reductase, thymidine synthase (TS), and glycinamide ribonucleotide formyl transferase. A unique folate transport mechanism with a high affinity for pemetrexed has been identified in mesothelioma cell lines. This could, at least in part, explain the higher degree of antitumor activity noted with pemetrexed in MPM. Polyglutamated pemetrexed is a potent inhibitor of TS and glycinamide ribonucleotide formyl transferase. Preliminary evidence of anticancer activity against mesothelioma with pemetrexed was observed in phase I trials.[55] In a phase I study of the combination of cisplatin and pemetrexed, partial responses were observed in 5 out of 11 patients with MPM.[56] This was further substantiated in a study by Calvert and colleagues who reported 8 responses in 25 patients with MPM treated with the combination of carboplatin and pemetrexed as part of a phase I trial. This formed the rationale for evaluation of this combination for patients with MPM.

A phase II study evaluated the antitumor activity of pemetrexed in patients with previously untreated mesothelioma.[57] Sixty-four patients were treated with pemetrexed at a dose of 500 mg/m^2 IV administered every 3 weeks. Nine patients (14%) experienced partial response. The median survival was 10.7 months. Forty-three patients in the study received supplementation with vitamin B12 and folic acid to reduce the toxicity associated with the use of pemetrexed. Patients treated with vitamin supplementation had a better overall survival than those who did not receive vitamin supplementation (13 versus 8 months). The incidence of both hematological and nonhematological toxicities was lower in patients who received vitamin supplements. Vitamin supplementation was instituted based on a study that evaluated the predictive factors for severe toxicity in patients treated with pemetrexed. This multivariate analysis of data from 246 patients treated with pemetrexed demonstrated a higher incidence of diarrhea, mucositis, neutropenia, and thrombocytopenia in patients with higher pretreatment plasma levels of total homocysteine and methylmalonic acid.[58] Supplementation of vitamin B12 and folic acid was done to decrease the levels of H and methylmalonic acid in an effort to decrease toxicity.

Vogelzang et al.[45] conducted a randomized phase III trial to evaluate the efficacy of the combination of cisplatin and pemetrexed. Patients with previously untreated MPM were randomized to either treatment with cisplatin and pemetrexed or therapy with pemetrexed alone. A total of 456 patients participated in the study, which was conducted at multiple institutions from several countries the world over. The primary end point of the study was overall survival and secondary endpoints included response rate, time to progression, and duration of response. The first 117 patients treated in the study did not receive vitamin supplementation. The remainder of the patients were treated with folic acid 350 to 1000 μg daily (orally) and vitamin B12 1000 μg every 9 weeks (intramuscularly). Patients in the pemetrexed-cisplatin arm received a median of six cycles of chemotherapy compared with four cycles in the cisplatin arm. Grades 3/4 neutropenia (28%) and leukopenia (18%) were the most common hematological toxicities. Nonhematological toxicities (grade 3) included nausea (15%), fatigue (10%), and vomiting (13%). In general, toxicities were reported more frequently in the combination arm. Nevertheless, there was a marked reduction in toxicity for patients who received vitamin supplementation. All efficacy parameters were superior in the combination arm (response rate 42% versus 17%, $p < 0.001$; median time to progression 5.7 versus 3.9 months, $p < 0.001$). The median survival was 12.1-month with cisplaitn-pemetrexed compared with 9.3 for cisplatin alone arm ($p = 0.020$). For patients who received vitamin supplementation, the median survival was 13.3 versus 10 months ($p = 0.051$). Thus, the combination of pemetrexed and cisplatin was associated with a tolerable safety profile and superior efficacy compared with therapy with cisplatin alone. This is the first randomized trial to demonstrate a survival advantage for combination chemotherapy for patients with MPM. The study also documented improved therapeutic index with supplementation of vitamin B12, and folic acid for

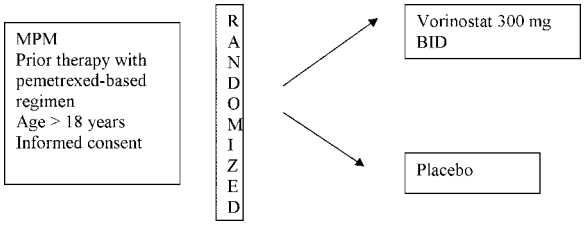

FIGURE 1. Schema of randomized phase III study (Vorinostat versus placebo).

patients during therapy with pemetrexed-cisplatin. The provocative results noted with the cisplatin-pemetrexed combination has heralded a new era for the treatment of MPM, which until then was devoid of an approved "standard of care." The regimen has been approved for the treatment of patients with advanced MPM by the Food and Drug Administration.

Pemetrexed can also be safely administered in combination with carboplatin for the treatment of advanced MPM. A phase II study evaluated the efficacy of this combination in patients with previously untreated MPM.[59] For the 102 patients included in the study, the response rate was approximately 18% and an additional 50% achieved disease stabilization. The median survival and progression-free survival (PFS) were 12.7 and 6.5 months, respectively. Therapy was tolerated well and both drugs were administered at nearly 100% of the planned dose intensity. Therefore, the carboplatin and pemetrexed combination can be considered as an alternative treatment options for patients who are not candidates for cisplatin-based therapy. A phase II study that evaluated the nonplatinum combination of pemetrexed and gemcitabine noted modest survival data that did not compare favorably with the platinum-pemetrexed regimen.[60] An ongoing randomized phase II study by the Eastern Cooperative Oncology Group compares the carboplatin-pemetrexed regimen to gemcitabine-pemetrexed in patients with previously untreated, advanced stage MPM.

RALTITREXED

Raltitrexed is a folate analog that exerts anticancer effect by inhibiting thymidilate synthase. A phase II study demonstrated a response rate of 21% for patients with advanced MPM with the administration of raltitrexed as monotherapy.[44] Based on this, a phase III study (Figure 1) was conducted to evaluate the therapeutic utility of raltitrexed in MPM (Table 3).[47] Advanced stage MPM patients were randomized to therapy with cisplatin alone or in combination with raltitrexed (3 mg/m^2 every 3 weeks). The response rate was 14% with cisplatin monotherapy compared with 24% with the combination. Overall survival, the primary end point of the study, was superior with cisplatin-raltitrexed (11.4 versus 8.8 months). The 1-year survival rate also favored the combination arm (46% versus 40%). The main adverse events associated with the combination were neutropenia and emesis. On the basis of these results, the combination of cisplatin-raltitrexed is another efficacious alternative for the treatment of patients with advanced MPM.

CHEMOTHERAPY VERSUS SUPPORTIVE CARE

Recently, the results of a randomized clinical trial that compared active symptom control (ASC) alone versus ASC in combination with chemotherapy were reported.[61] Either the combination of mitomycin, vinblastine and cisplatin (four cycles) or monotherapy with vinorelbine (weekly × 12) were administered. Endpoints included evaluation of survival and assessment of symptom improvement. The sample size was reduced during the course of the trial, because of slow accrual, thus, lowering the statistical power. There was a nonsignificant trend towards improved median survival with chemotherapy (8.5 versus 7.6 months). Symptom improvement occurred in all three patient groups, but the differences were not significant between them. Despite the apparent lack of benefit with chemotherapy, subset analysis revealed improved outcome for patients treated with vinorelbine in combination with ASC. Only 50 to 60% of the patients received the planned doses of chemotherapy. Though these results are disappointing, it should be noted that neither of the chemotherapy regimens used in the study were proven to be efficacious for patients with MPM. The low statistical power could be another contributory factor to the observed lack of efficacy enhancement with chemotherapy. Because the combination of cisplatin-pemetrexed confers survival advantage, its use in combination with ASC is the preferred treatment for patients with MPM.

MOLECULARLY TARGETED AGENTS IN THE TREATMENT OF MESOTHELIOMA

There are no standard treatment options for patients who experience disease progression with first-line chemotherapy. Currently, these patients are offered the option of

TABLE 3. Phase III Studies in MPM

Author	Regimen	Sample Size	Median Survival (m)	Response Rate
Vogelzang et al.[45]	Cisplatin	222	9.3	17%
	Cisplatin-Pemetrexed	226	12.1	41%
Van Meerbeeck et al.[47]	Cisplatin	124	8.8	14%
	Cisplatin-Raltitrexed	126	11.4	24%
Muers et al.[61]	ASC	136	7.6	Not reported
	ASC + MVP	137	7.8	
	ASC + Vinorelbine	136	9.4	

receiving experimental agents or therapy with a cytotoxic agents with supporting phase II data. For patients with symptomatic disease and rapidly declining performance status, the use of supportive care measures alone is appropriate in this setting. As a result, patients with relatively indolent disease, who are often treated with second-line therapy and beyond, tend to have better survival duration, sometimes even better than that seen with first-line therapy. This underscores the need for using novel trial designs such as randomized discontinuation method or by the use of a control arm with new agents that are being evaluated in the second-line therapy for mesothelioma. A number of new agents with unique mechanisms of action are being evaluated for the treatment of recurrent or refractory MPM.

EPIDERMAL GROWTH FACTOR RECEPTOR INHIBITORS

Several molecularly targeted therapeutic approached are currently under evaluation for the treatment of MPM. The epidermal growth factor receptor (EGFR) is frequently overexpressed in MPM. On the basis of this observation and preclinical data that suggested anticancer activity with gefitinib in mesothelioma cell lines, the CALGB group recently reported the results of a phase II trial that evaluated the role of gefitinib for the treatment of MPM.[62] No objective responses were noted and regimen was not deemed suitable for further evaluation. Erlotinib, another EGFR inhibitor, was also evaluated in a phase II study for patients with MPM.[63] No objective responses were seen despite a high rate of patients with EGFR expressing tumors (75%) in the study. Disease stabilization was noted in 15 of 33 patients with measurable disease.

ANTIANGIOGENIC AGENTS

Agents that inhibit the angiogenesis pathways are currently under investigation for the treatment of MPM. This is based on the observation of high levels of circulating vascular endothelial growth factor (VEGF) in patients with MPM. Furthermore, MPM tumors often tend to have high microvessel density, which has been linked with a poor outcome.[64] Bevacizumab, a monoclonal antibody against the VEGF, is approved for the treatment of colon and nonsquamous non-small cell lung cancer, in combination with chemotherapy. A randomized phase II study was conducted for patients with advanced MPM to evaluate whether the addition of bevacizumab results in enhancement of the efficacy of chemotherapy.[65] Patients were treated with the regimen of cisplatin and gemcitabine with or without bevacizumab. The treatment was tolerated well without any major toxicity. Nevertheless, there was no suggestion of improved outcome with the addition of bevacizumab. The median PFS, the primary end point was 6.9 and 6.0 months, respectively, with and without the addition of bevacizumab. Though the overall median survival was numerically superior for bevacizumab + chemotherapy (15.6 versus 14. 7 months), the difference was not statistically significant ($p = 0.91$). An exploratory subset analysis noted improved survival with bevacizumab-chemotherapy regimen in patients with low circulating levels of VEGF.

Phase II studies are also underway to evaluate small molecule inhibitors of the VEGF receptor tyrosine kinase. Sorafenib was evaluated as monotherapy for recurrent MPM in a phase II study by the CALGB.[66] Though treatment was tolerated well, the response rate of 4% did not meet the criteria for further evaluation of this agent as monotherapy in MPM. The study allowed patients with no prior therapy in addition to those who had progressed after one prior regimen. The median survival duration was 4.9 months in chemotherapy-naive patients and 14.9 months in those who had received prior therapy. This difference is probably a function of patient selection, as mentioned earlier. Vatalanib, another VEGF tyrosine kinase inhibitor has also been studied in this setting.[67] In a study of 47 patients, this agent was associated with an objective response in five patients and a median survival of 10 months. However, the study did not meet the prespecified end point of 3-month PFS rate to warrant further investigation. Other VEGF tyrosine kinase inhibitors that are currently under evaluation for the treatment of MPM include sunitinib, cediranib, vatalanib, and pazopanib. Because these agents have varying kinase inhibition profiles, it is hoped that they would be active agents for the treatment of MPM.

HISTONE DEACETYLASE INHIBITORS

Histone deacetylase (HDAC) inhibitors are novel anticancer agents that act by a variety of mechanisms. Histones are the core-proteins in the center of the DNA double helix. The histone proteins exist in either a nonacetylated transcriptionally inactive configuration or an acetylated state that is open to gene transcription. The dynamic equilibrium between the acetylated and nonaceylated forms is mediated by histone acetyltransferase and HDAC.[68] Agents that inhibit HDAC have recently demonstrated promising anticancer activity in early phase clinical trials. Vorinostat (Zolinza) is a small molecule inhibitor of HDAC that is approved by the FDA for the treatment of advanced, relapsed, or refractory cutaneous T cell lymphoma.[52,53] In addition to its inhibitory effect on HDAC, vorinostat also acetylates several key cell signaling proteins that play a role in regulating normal cell differentiation, apoptosis, and proliferation. Therefore, both histone and nonhistone protein-mediated effects of HDAC inhibitors are thought to be responsible for their anticancer effects.[54]

Initial studies of vorinostat have demonstrated objective responses in patients with MPM. In the initial phase I studies with the oral formulation of vorinostat, 13 patients with advanced MPM were included.[69] Twelve out of these patients had received prior systemic chemotherapy for MPM. Two objective partial responses were noted and four patients received ≥six cycles of therapy. The treatment regimen was tolerated well. Given the lack of proven options for salvage therapy for MPM, these promising results have prompted the initiation of a large randomized clinical trial to compare vorinostat to placebo. In this ongoing study, patients who received one or two prior regimens for advanced MPM are eligible. The primary end point is the determination of overall survival.

The mechanistic aspects of the efficacy noted with vorinostat in MPM are unclear. Because inhibitors of TS have

demonstrated activity in MPM, it is conceivable that repression of TS and cytidine triphosphate synthetase by HDAC inhibitors could play a role. Another mechanism may be the induction of apoptosis, which has been demonstrated with preclinical studies of sodium butyrate, a HDAC inhibitor, in mesothelioma cell lines.[56,57] HDAC inhibitors have also been shown to block angiogenic signaling by inhibiting VEGF-induced expression of VEGF receptors.[70] Furthermore, hypoxia-inducible factor-1 alpha, a key molecule that stimulates VEGF secretion, is regulated by acetylation mechanism.[59] It is hoped that ongoing studies with correlative science endpoints will shed more light in this front.

OTHER NOVEL AGENTS

A novel agent that has entered phase III evaluation in mesothelioma is ranpirnase, a cytotoxic amphibian ribonuclease. It induces apoptosis independently of p53 protein. The efficacy of ranpirnase was evaluated in a phase II study for patients with advanced MPM.[71] The study reported promising survival duration of 8.3 months. Importantly, objective responses were noted in 4 out of 81 patients with measurable disease. A large ongoing study ($N = 428$ patients) randomizes patients with MPM to therapy with doxorubicin in combination with or without ranpirnase. The study has completed accrual and the results are eagerly awaited. Other novel agents that have been evaluated in this setting include imatinib, an inhibitor of c-kit and bcr-abl tyrosine kinases. No objective responses were noted in a cohort of 25 patients with advanced MPM.[72]

Recent studies have documented that Src kinase, a nonreceptor tyrosine kinase is activated in tumors of patients with MPM.[73] Activation of this pathway has been linked with advanced stage and poor outcome in patients with MPM. Therefore, an ongoing phase II study is evaluating the role of dasatinib, an inhibitor of the Src kinase, for the treatment of patients with relapsed or refractory MPM.

Mesothelin is a glycosyl-phosphatidyl inositol-linked membrane protein of overexpressed in mesothelioma.[74] It seems to play an important role in cell adhesion by its interaction with MUC-1 (epithelial membrane antigen) 16. Morphotek antibody-009 is a mouse-human chimeric IgG1kappa monoclonal antibody with high affinity for human mesothelin. It has been shown to elicit cell-mediated immunity against cells bearing the mesothelin antigen. Based on this, clinical trials have been initiated to evaluate the utility of this agent in the treatment of malignancies that express mesothelin.

Vaccine approaches are also under investigation for the treatment of MPM. Wilm's tumor associated gene (WT)-1 is a transcription factor expressed in tissues of mesodermal origin during embryogenesis. Up-regulation of WT-1 has been linked with tumorigenesis of various malignancies including mesothelioma and is an attractive target for immunotherapy.[75] Therefore, WT-1 peptide epitopes that stimulate T-cell immunity are currently under evaluation for the treatment of mesothelioma. Preliminary results from ongoing studies have documented the safety of this vaccine.

CONCLUSIONS

MPM remains a difficult and growing problem. Surgical resection for patients with early stage MPM is considered standard therapy. Radiation has palliative benefit. For patients with advanced disease, combination chemotherapy with cisplatin and pemetrexed results in improvement in survival and quality of life, thus constituting the "standard of care." Molecularly targeted approaches are currently being studied for the treatment of MPM. Though the initial experience with inhibitors of the EGFR pathway and VEGF-pathway have been disappointing, the promising data noted with HDAC inhibitors have generated a renewed enthusiasm for evaluation of novel agents in this setting.

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