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REVIEW ARTICLE

Malignant Pleural Mesothelioma

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ABSTRACT

Malignant pleural mesothelioma (MPM) is a deadly disease that occurs in 2,000 to 3,000 people each year in the United States. Although MPM is an extremely difficult disease to treat, with the median overall survival ranging between 9 and 17 months regardless of stage, there has been significant progress over the last few years that has reshaped the clinical landscape. This article will provide a comprehensive discussion of the latest developments in the treatment of MPM. We will provide an update of the major clinical trials that impact mesothelioma treatment in the resectable and unresectable settings, discuss the impact of novel therapeutics, and provide perspective on where the clinical research in mesothelioma is moving. In addition, there are controversial issues, such as the role of extrapleural pneumonectomy, adjuvant radiotherapy, and use of intensity-modulated radiotherapy versus hemithoracic therapy that will also be addressed in this manuscript.

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INTRODUCTION

Malignant pleural mesothelioma (MPM) is a deadly disease that occurs in 2,000 to 3,000 people each year in the United States. After the 1970s bans on asbestos were initiated, it was believed that the United States incidence of MPM would peak in 2004.[1,2] However, MPM remains a serious problem as the worldwide incidence of the disease continues to increase; in Western Europe, more than 5,000 new cases per year are estimated to occur, with more than a quarter of a million deaths expected to occur over the next 40 years.[3-5] In Japan, the peak incidence is predicted in 2025, and 103,000 deaths are anticipated over the next 40 years.[5]

MPM occurs predominantly in men (ratio of men to women, 5:1), and risk increases with age (median age at diagnosis is 72 years in the United States; range, 45 to 85 years).[6,7] There are three main histologic subtypes of mesothelioma: epithelioid, biphasic, and sarcomatoid. Epithelioid tumors are most common and have a better prognosis than biphasic and sarcomatoid tumors. The major risk factor for MPM is occupational exposure to asbestos,[8] often with development of the disease between 20 and 60 years later.[9] Less frequently, prior radiation exposure and simian virus 40 have been suggested as causative agents in MPM.[5,10-13] Familial forms of MPM with autosomal dominant inheritance have been reported in the Cappadocia region of Turkey (Tuzkoy, Karain, and Sarihidir).[8,10,14]

Currently, there are no approved screening modalities for the early detection of mesothelioma. However, two serum markers have recently been developed, serum mesothelin-related peptide and osteopontin. Serum mesothelin-related peptide, which is elevated in patients with epithelioid and biphasic MPM, may be predictive of disease recurrence after surgical resection.[15,16] Osteopontin, a glycoprotein that binds integrin and CD44 receptors, may distinguish patients with MPM from those who have benign pleural changes resulting from asbestos exposure.[17,18]

MPM is an extremely difficult disease to treat, with the median overall survival ranging between 9 and 17 months, regardless of stage. Part of the difficulty in making progress in this disease type has been that there are few randomized controlled studies as a result of the small numbers of patients, problematic response measurements, variable staging of the disease between the trials (surgical staging *v* radiographic staging), and histologic heterogeneity in the patients enrolled onto trials. However, despite these limitations, there have been developments over the last few years that may ultimately reshape the clinical landscape.[19-21] This article will provide a comprehensive discussion of the latest progress in the treatment of MPM.

RESECTABLE DISEASE

Surgery

Surgical techniques used in treating patients with MPM include diagnostic video-assisted thoracoscopy, palliative pleurectomy/decortication (P/D),

and extrapleural pneumonectomy (EPP). P/D consists of an open thoracotomy; removal of the parietal pleura, pleura over the mediastinum, pericardium, and diaphragm; and stripping of the visceral pleura for decortication. An EPP includes en bloc removal of tissues in the hemithorax, including the parietal and visceral pleura, involved lung, mediastinal lymph nodes, diaphragm, and pericardium. In most cancer centers, patients with significant cardiac comorbidities, sarcomatoid histology, mediastinal lymph nodes, and poor performance status are not considered candidates for EPP because they usually have a worse prognosis.[22,23]

Patients who receive P/D alone often experience local recurrence as the first site of disease recurrence and, less frequently, distant recurrence; the local and distant recurrence rates are 64% to 72% and 10% to 36%, respectively. This is in contrast to EPP alone, for which the distant recurrence rate is higher than that of local recurrence (41% to 44% *v* 31% to 65%).[22-24] Although EPP may alter the pattern of recurrence with less locoregional recurrence, it remains a surgical procedure that is associated with high morbidity, and its contribution toward overall survival benefit remains unclear. The 30-day operative mortality rate for EPP in experienced centers ranges between 3.4% and 18%, and the 2-year survival rate is 10% to 37%.[21,25-28]

The choice of surgical resection technique at this time is controversial. Previously, it was assumed that EPP was the only treatment modality that could ensure long-term survival for patients with MPM because it macroscopically removed all gross disease. However, a complete R0 resection is theoretically impossible, because neither EPP nor P/D will eliminate residual microscopic disease. It is therefore difficult to identify the role of EPP in MPM, because there are no definitive results available yet from randomized trials. At present, there is one ongoing phase III trial called the Mesothelioma and Radical Surgery trial that randomly assigns patients with MPM to either receive an EPP or a surgical debulking that is not an EPP.[29] Patients in both arms of the trial may receive induction chemotherapy and or adjuvant radiotherapy, because it is believed that trimodality treatment can improve survival and locoregional control.[20,30,31] Once this trial is completed, the role of EPP in MPM may be better defined.

Recently, from a large retrospective analysis (n = 663) comparing EPP with P/D, Flores et al[30] reported that P/D in combination with various multimodality therapies may also provide long-term survival benefit. This analysis showed that women; patients with earlier stage disease, epithelioid histology, treatment with multimodality therapy; and those who underwent P/D had better survival outcomes.[30] After eliminating the operative deaths, multivariate analysis showed that EPP led to worse survival than P/D (hazard ratio [HR] = 1.4; $P < .001$). Also, the choice of surgery did not affect survival outcomes for patients with either early-stage (I and II) or higher-stage (III and IV) disease. It therefore remains unclear which surgical resection may benefit a particular patient, and prospective randomized trials are needed to define this issue.

Adjuvant Radiation Therapy

In MPM, radiotherapy can be delivered either prophylactically to prevent tumor seeding at a surgically instrumented incision site (ie, chest tube sites) or for definitive intent to the entire hemithorax after surgical resection with EPP. Three small randomized studies compared prophylactic radiation with no radiation at chest tube drain or pleural biopsy sites.[32-34] Two trials report no benefit; whereas one did; it therefore remains controversial whether prophylactic radiotherapy is warranted.

In the definitive setting, adjuvant hemithoracic radiotherapy (54 Gy) added to EPP improves local control, with a 13% risk of local recurrence and 64% incidence of distant metastasis.[31] To date, the only treatment modality that decreases the risk of local recurrence after surgical resection is radiotherapy.[31] High-dose radiotherapy (54 Gy) with sequential chemotherapy was reported to improve locoregional control over moderate-dose radiotherapy (30 Gy to hemithorax, 40 Gy to mediastinum, and boost to 54 Gy in positive margins or nodes).[35] However, this result (n = 39) was not statistically significant, and the dose of radiotherapy did not predict for survival.

Alternative radiotherapy techniques, such as intensity-modulated radiation therapy, have early reports demonstrating a 95% chance of disease control in the irradiated field and a locoregional control rate of 87%.[21,36] However, intensity-modulated radiation therapy is not the standard of care, as there have been reports of high toxicity and morbidity (ie, fatal pneumonitis) associated with its use.[37]

Chemotherapy

In patients with resectable MPM, chemotherapy can be given in the neoadjuvant or adjuvant settings, concurrent with radiation. Table 1 lists the major neoadjuvant clinical trials.

Neoadjuvant chemotherapy. Owing to the small number of MPM candidates for EPP, few neoadjuvant trials have been successful. All neoadjuvant regimens studied to date include platinum doublets in single-arm trials, with the median survival ranging between 19 and 25 months (Table 1).[20,38-41] The largest of these prospective trials (n = 75) administered platinum and pemetrexed and reported preliminary results of a median time to progression of 13.1 months,

Table 1. Induction Chemotherapy Trials for Resectable MPM

First Author	No. of Patients	% Epithelioid	pN2 (%)	Regimen	No. of Cycles	Response Rate (%)	% EPP	Completed Adjuvant XRT (%)	Median PFS (months)	Median OS (months)
Weder[38]	19	74	0	Cisplatin plus gemcitabine	3	32	84	68	16.5	23
Flores[39]	19	74	37	Cisplatin plus gemcitabine	4	26	42	42	NR	19
Weder[40]	61	69	23	Cisplatin plus gemcitabine	3	NR	61	59	13.5	19.8
Rea[41]	21	95	24	Carboplatin plus gemcitabine	4	33	81	71	NR	25.5
Krug[20]	75	80	45	Cisplatin plus pemetrexed	4	29.3	67	56	13.1	16.6

Abbreviations: MPM, malignant pleural mesothelioma; pN2, pathologic N2 disease; EPP, extrapleural pneumonectomy; XRT, radiation therapy; PFS, progression-free survival; OS, overall survival; NR, not reported.

overall survival of 16.6 months, and 1-year overall survival rate of 67%.[20] The response rate to induction chemotherapy was 29%, with 67% of the patients (n = 50) undergoing EPP and only 56% proceeding to adjuvant radiotherapy. The subgroup analysis indicated that patients with a complete or partial response to neoadjuvant chemotherapy had a trend toward prolonged overall survival (29.1 *v* 13.9 months; $P = .076$). Because the efficacy of neoadjuvant chemotherapy remains unproven, a neoadjuvant trial at The University of Texas M. D. Anderson Cancer Center (Houston, TX) using dasatinib is currently underway and will provide maintenance dasatinib after surgery, adjuvant radiation, and adjuvant chemotherapy in patients with MPM with a response to induction therapy.

Adjuvant chemoradiotherapy. Adjuvant chemoradiotherapy is difficult to administer after EPP because of associated toxicities, and as such, there are few trials available to review. One of the largest series evaluated 183 patients who received EPP followed by carboplatin and paclitaxel for two cycles, then thoracic radiation therapy (50-Gy dose) with concurrent paclitaxel weekly, and then carboplatin and paclitaxel for two cycles.[27,42] For the 176 patients who survived the EPP, the 2-year-survival rate was 38%, the 5-year-survival rate was 15%, and the median overall survival was 19 months.[42] Patients with epithelioid histology, negative resection margins, and no extrapleural lymph node metastasis had the best prognosis, with a median overall survival of 51 months ($P = .013$).[42] This series has since been updated to include 496 patients. The 418 patients who received EPP had a median overall survival of 18.9 months and a 5-year overall survival rate of 13.9%.[25,43]

UNRESECTABLE DISEASE

Chemotherapy

Historically, assessing clinical benefit in patients with unresectable MPM has been challenging. As guidelines, there are favorable clinical prognostic features, which include epithelioid histology, female sex, and no nodal metastasis; whereas patients with sarcomatoid histology, poor performance status, and elevated hematologic parameters have a worse prognosis.[44,45] However, treatment response assessments are limited by the complexity of measuring the asymmetric tumor rind. A system called the modified Response Evaluation Criteria in Solid Tumors can be reliably used to assess tumor response[46,47]; however, these measurements do not always predict survival.[48] The European Organisation for Research and Treatment of Cancer (EORTC) has therefore proposed that progression-free survival rates at 3, 4, 5, and 6 months be used as the primary end points in phase II trials to reflect the potential survival benefit of cytostatic agents.[49]

Before 2003, few chemotherapy agents had response rates higher than 20%.[50] Ellis et al[51] reviewed 119 trials (eight randomized, 111 noncomparative) and reported that combination chemotherapy had higher response rates than single agents. Platinum-containing regimens had higher response rates compared with non–platinum-containing regimens, with cisplatin yielding better outcomes than carboplatin. Platinum agents combined with anthracyclines (32.4%), gemcitabine, or irinotecan (26.1%) had the highest response rates. When platinum agents were combined with immunomodulator effectors, such as interleukin or interferon, the response rate was 12%.[51] These data do have limitations, as most MPM trials are single-arm phase II studies, owing to the small number of available patients.

Front-Line Chemotherapy

As MPM is more chemotherapy resistant than other tumor types, the Medical Research Council conducted a randomized phase III trial comparing active supportive care with two different chemotherapy regimens (mitomycin, vinblastine, and cisplatin or weekly vinorelbine) and reported that chemotherapy did not significantly improve survival over active supportive care.[52] However, when analyzing the results from the single-agent vinorelbine arm, there was a trend toward survival that did not reach statistical significance, likely because the study was underpowered to determine this survival difference between the individual arms. Patients who received vinorelbine had a median progression-free survival of 6.2 months (HR = 0.82; $P = .114$) and median overall survival of 9.5 months (HR = 0.8; $P = .08$).[52] This suggests that certain chemotherapy agents do improve survival for patients with MPM. In addition, subsequent randomized trials using newer agents such as pemetrexed and raltitrexed combined with platinum agents confirm the survival benefit over cisplatin alone.[19,53] Table 2 lists the response rates to selected chemotherapy agents and regimens.

Platinum and antifolates. The combination of cisplatin (75 mg/m^2) and pemetrexed (500 mg/m^2) given every 3 weeks was established as a standard-of-care front-line regimen after the largest phase III trial conducted in patients (n = 456) with chemotherapy-naïve MPM demonstrated a survival improvement over cisplatin alone.[19] The combination regimen had a 41.3% response rate, median time to progression of 5.7 months, and median overall survival of 12.1 months. Patient quality of life also improved rapidly—within the first three cycles of treatment—with statistically significant improvements often seen by week 15.[58] This regimen is now the benchmark against which other front-line regimens are evaluated.

Other antifolates have been investigated, but they are less commonly used then pemetrexed. The EORTC reported that raltitrexed (3 mg/m^2) combined with cisplatin (80 mg/m^2) improved the overall response rate compared with cisplatin alone (24% *v* 14%; $P = .06$), with no reported difference in quality of life.[53] However, although the response rate was not statistically significant, the median overall survival in patients receiving raltitrexed plus cisplatin was increased to 11.4 months, and the 1-year survival rate was increased to 46% (HR = 0.76; $P = .048$).[53]

Other combination and maintenance regimens under investigation have substituted carboplatin for cisplatin. Carboplatin plus pemetrexed yields response rates of 6% to 22%, median time to progression of 6.5 to 7 months, and median overall survival of 9.3 to 12.7 months.[56,57,59,60] The International Extended Access Program[61] trial conducted in 1,704 patients with chemotherapy-naïve or pretreated MPM found that cisplatin plus pemetrexed and carboplatin plus pemetrexed had similar response rates (26.3% and 21.7%), time to progression (7 months and 6.9 months), and 1-year overall survival rates (63.1% and 64%). In the International Extended Access Program, single-agent pemetrexed achieves response rates of 10.5% and 12.1% for chemotherapy-naïve and pretreated patients with MPM, respectively.[62]

The concept of maintenance or continued therapy after front-line treatment remains investigational. One small study has shown the feasibility of maintenance pemetrexed and demonstrated that responses could occur even after six cycles of treatment.[63] However, the role of maintenance therapy requires additional examination in larger prospective trials before being implemented as

Table 2. Response Rate of Selected Chemotherapy Agents in MPM From Phase II/III Trials and the International Expanded Access Program*

Chemotherapy Agents	No. of Trials	No. of Patients	Response Rate (%)	Median PFS (months)	Median OS (months)
Single agent					
Cisplatin	5	108	20	NR (5 trials NR)	5-11 (1 trial NR)
Cisplatin†	2	346	15.7	3.9-4	8.8-9.3
Carboplatin	3	89	10.1	2.8 (2 trials NR)	7.1-8 (1 trial NR)
Pemetrexed					
Chemotherapy-naïve	1‡	319	10.5	6	14.1
Pretreated	1‡	493	12.1	4.9	NR
Pretreated	2	214	13.1	3.6 (1 trial NR)	4.1-8.4
Vinflunine	1	67	13.8	3.2	10.8
Vinorelbine					
Chemotherapy-naïve	2	165	18.8	6.2 (1 trial NR)	9.5-10.6
Pretreated	1	63	16	NR	9.6
Antimetabolites	8	319	9.0	1.5-5.2 (4 trials NR)	4.9-11 (1 trial NR)
Gemcitabine	3	72	6.7	1.7 (2 trials NR)	4.7-8 (1 trial NR)
Anthracyclines or mitoxantrone	10	319	6.1	5 (8 trials NR)	4.5-17 (2 trials NR)
Taxanes	4	111	5.1	2.2-3.5 (1 trial NR)	4-12.4
Topoisomerase inhibitors	4	117	4.9	2.3 (3 trials NR)	7.3-17
Alkylating agents	7	194	4.6	2.5 (7 trials NR)	6.5-10 (1 trial NR)
Other	12	376	4.0	2.1-3.4 (6 trials NR)	5-13.2 (4 trials NR)
Combination therapies					
Cisplatin plus pemetrexed	1	226	41	5.7	12.1
Cisplatin plus pemetrexed	1‡	843	26.3	7	NR (1-year OS 63.1%)
Carboplatin plus pemetrexed	1‡	861	21.7	6.9	NR (1-year OS 64%)
Carboplatin plus pemetrexed	2§	178	21.3	6.5-8	12.7-14
Cisplatin plus raltitrexed	1	126	24	5.3	11.4
Cisplatin plus gemcitabine	5	184	25	6-8	9.6-13
Carboplatin plus gemcitabine	2	70	24.3	10 (1 trial NR)	10.8-16.5
Cisplatin plus vinorelbine	1	54	29.6	7.2	16.8
Platinum-based	19	790	24.9	2.7-10 (9 trials NR)	6-19.2 (3 trials NR)
Cisplatin plus anthracycline	6	151	28.5	4.8 (5 trials NR)	8.8-15 (1 trial NR)
Cisplatin, nonanthracycline	20	547	23.2	2.7-12 (5 trials NR)	6.4-19.2 (3 trials NR)
Cisplatin, mitomycin, vinblastine	2	176	13	5.1 (1 trial NR)	6-7.8
Anthracycline, nonplatinum	8	213	11.3	2.3-6.3 (6 trials NR)	5.7-11 (1 trial NR)
Nonplatinum, nonanthracycline	5	172	15.7	4.3-7 (2 trials NR)	8-13.5 (1 trial NR)

Abbreviations: MPM, malignant pleural mesothelioma; PFS, progression-free survival; OS, overall survival; NR, not reported.
*Data were originally published in Berghmans et al[54] and adapted from Fennell et al.[55]
†Data from the cisplatin control arms in the phase III trials of Vogelzang et al[19] and van Meerbeeck et al.[53]
‡International Expanded Access Program.
§Phase II trials of Ceresoli et al[56] and Castagneto et al.[57]

common practice. The Cancer and Leukemia Group B (CALGB) is planning a randomized trial to study maintenance therapy.

Additional front-line chemotherapy agents. Gemcitabine as a single agent has response rates between 0% and 31%[64]; combining gemcitabine with cisplatin leads to response rates between 12% and 48% and median overall survival times of 9.4 to 13 months.[65-69] The efficacy of a carboplatin plus gemcitabine regimen has also been reported, with a 1-year survival rate of 53% and time to progression of 40 weeks.[70] Lee et al[71] recently presented a retrospective Canadian series comparing platinum plus gemcitabine (n = 38) with platinum plus pemetrexed (n = 34) and reported no difference in overall survival. An ongoing Eastern Cooperative Oncology Group trial in patients with good performance status is comparing carboplatin plus pemetrexed to gemcitabine plus pemetrexed. Janne et al[72] recently reported a phase II trial in chemotherapy-naïve patients with MPM using two different schedules of pemetrexed and gemcitabine and reported a 17% to 26% response rate, and median survival of 8.08 to 10.12 months.

Previously, vinorelbine was the only vinca alkaloid that had single-agent activity in MPM, with response rates of 24% and median overall survival of 10.6 months.[73] In one front-line trial (n = 54), cisplatin added to vinorelbine improved the response rate to 29.6%, median time to progression to 7.2 months, and overall survival to 16.8 months.[74] However, the newest vinca alkaloid vinflunine, has shown similar efficacy in chemotherapy-naïve patients. Vinflunine (320 mg/m^2) was given intravenously every 3 weeks to 67 patients with MPM, with a 13.8% response rate, a median progression-free survival of 3.2 months, and a median overall survival of 10.8 months.[75]

The Japanese have conducted several irinotecan-based clinical trials for patients with unresectable MPM. One pilot trial studied a triplet regimen of irinotecan and cisplatin followed by doxorubicin;

the overall response rate was 36%.[76] A phase II trial used methotrexate, irinotecan, and doxorubicin; a 21% partial response rate was reported, and the rate in the chemotherapy-naïve patients was 24%.[77] Although these triplet regimens showed tolerability and efficacy, irinotecan has not been developed for MPM in the United States. In the only US trial of irinotecan for MPM, CALGB studied single-agent irinotecan (125 mg/m^2 weekly for 4 of 6 weeks) in chemotherapy-naïve patients; the regimen had a 0% response rate and substantial toxicity.[78] It is therefore likely that irinotecan-based regimens will remain geographically sponsored.

Second-Line Chemotherapy

At this time, there is no widely approved salvage regimen used for MPM. However, there is growing evidence that if pemetrexed is not given in the front-line setting, it should be administered in the salvage setting, either alone or in combination with platinum agents.[79,80] Jassem et al[81] conducted a phase III trial comparing second-line pemetrexed with best supportive care and reported that pemetrexed improved tumor response and progression-free survival but did not improve overall survival for unselected patients. The subgroup analysis demonstrated that patients who had responded to front-line chemotherapy had a trend toward longer overall survival with second-line pemetrexed. Gemcitabine plus vinorelbine was also found to have some efficacy as a salvage regimen in 28 patients who had failed to respond to pemetrexed-based chemotherapy.[82] The response rate was 7.4%, with stabilization of disease in an additional 37% of patients and a median time to progression of 2.8 months. Single-agent vinorelbine has also been evaluated in a phase II trial (n = 63), with a reported response rate of 16% and overall survival of 9.6 months.[83]

Biologic Therapy

Novel biologic therapies that have been successful against other solid tumors have also begun to be studied in MPM. To date, despite preclinical data demonstrating overexpression of epidermal growth factor receptor and platelet-derived growth factor receptor (PDGFR) on MPM tumor cells, clinical trials have shown no significant benefit from using single-agent inhibitors of the epidermal growth factor receptor (gefitinib or erlotinib)[84,85] or of the PDGFR (imatinib mesylate).[86-88] However, many new targets and biologic agents may have potential in the treatment of this disease (Table 3).

Antiangiogenic agents. Angiogenic inhibition with the monoclonal antibody bevacizumab provides a survival benefit in colorectal carcinoma and non–small-cell lung cancer. Patients with MPM have high levels of plasma vascular endothelial growth factor (VEGF), and as in lung cancer, higher levels of serum VEGF are correlated with a worse prognosis.[101] However, a front-line phase II randomized trial (n = 115) using cisplatin and gemcitabine with or without bevacizumab did not show an improvement in response rate nor survival with the addition of bevacizumab.[89] A subgroup analysis noted that higher baseline plasma VEGF levels were correlated with a shorter progression-free and overall survival ($P = .02$; $P = .0066$) and that patients with VEGF levels less than the median had longer progression-free and overall survival when treated with bevacizumab. This suggests that antiangiogenic therapy could benefit some patients with MPM; and several ongoing MPM studies with bevacizumab may further define which patients should receive antiangiogenic treatment. One such trial is a front-line study of cisplatin, pemetrexed, and bevacizumab. In the salvage setting, a small bevacizumab plus erlotinib trial (n = 24) recently reported no radiographic responses, with

Table 3. Novel Therapeutic Agents

Target	Agent	Trial Phase	No. of Patients	RR (%)	Median PFS (months)	Median OS (months)
EGFR	Gefitinib 500 mg[84]	II	43	4	2.6	6.8
	Erlotinib[85]	II	63	0	2	10
PDGFR, c-Kit	Imatinib mesylate 800 mg[88]	II	29	0	NR*	NR
	Imatinib mesylate 400-800 mg[86]	II	25	0	2.1	13.3
VEGF	Cisplatin/gemcitabine/bevacizumab[89] versus cisplatin/gemcitabine	II	115	25 *v* 22; $P = .88$	6.9 *v* 6.0; 15.6 *v* 14.7; $P = .91$	
Flk-1/KDR	Semaxinib[90,91]	II	23	11	NR	12.3
VEGF, TNF-α bFGF	Thalidomide 200-400 mg[92,93]	II	40	27.5 (stable disease at 6 months)†		7.6
VEGFR-1, -2, -3 PDGFR, c-Kit	Vatalanib[94]	II	47	11	4.1	10
VEGFR-2 PDGFRb, Raf	Sorafenib[95]	II	51	4.4	3.7	10.7
VEGFR-1, -2, -3, PDGFR	Sunitinib[96]	II	22	15	3.5	5.9
RET, c-Kit, Flt-3tRNA	Ranpirnase[97]	II	105	5	3.4	6
tRNA	Ranpirnase versus doxorubicin[98,99]	III	154	NR	NR	8.4 *v* 8.2; P = NS
Histone deacetylase	Vorinostat[100] 300-400 mg BID × 3 d/wk	I	10‡	20	NR	NR

Abbreviations: RR, response rate; PFS, progression-free survival; OS, overall survival; EGFR, epidermal growth factor receptor; PDGFR, platelet-derived growth factor receptor; NR, not reported; VEGF, vascular endothelial growth factor; TNF-α, tumor necrosis factor α; VEGFR, vascular endothelial growth factor receptor; NS, not significant; BID, twice per day.

*Four patients had stable disease ≥ 3 months.

†The primary end point on this trial was the rate of disease stabilization at 6 months.

‡Thirteen patients were enrolled; intent-to-treat population yielded a 15% response rate.

a median time to progression of 2.2 months and median overall survival of 5.8 months.[102]

It is possible that VEGF receptor (VEGFR) tyrosine kinase inhibitors or concomitant inhibition of other tumor or angiogenesis targets will be needed to achieve the greatest antitumor effect for MPM. Several oral multikinase inhibitors that include VEGF/VEGFR pathway inhibition have been investigated in MPM. SU5416, or semaxanib (also targeting Flk-1/KDR), and thalidomide have been reported to produce clinical activity.[90-92] Thalidomide as a single agent has been reported to achieve disease stabilization in 25% of patients for more than 6 months[93] and is under investigation in an international trial, with patients with MPM receiving four cycles of platinum plus pemetrexed followed by thalidomide or best supportive care. In one phase II trial, vatalanib (targeting VEGFR-1, -2,and -3; PDGFR; and c-Kit) had an 11% response rate, a 66% stable-disease rate, median progression-free survival of 4.1 months, and median overall survival of 10 months.[94] Sunitinib (targeting VEGFR, PDGFR, c-Kit, and Flt-3) has been evaluated in a phase II single-arm trial in patients who had experienced treatment failure with one platinum plus pemetrexed regimen.[96] Of 22 assessable patients, there was a 15% partial response rate and 55% stable disease rate by modified Response Evaluation Criteria in Solid Tumors. In patients without a talc pleurodesis, 10 were evaluated by [^{18}F]fluorodeoxyglucose positron emission tomography and a 30% metabolic response (defined as a decrease in standardized uptake value levels) was seen. The median overall survival was 5.9 months, and median time to progression was 3.5 months. There was one treatment-related death attributed to pulmonary infiltrates and respiratory failure. A phase II trial (CALGB 30307) using sorafenib (targeting VEGFR-2, PDGFR, and Raf) at 400 mg twice daily for MPM that was chemotherapy-naïve or previously treated with pemetrexed found grade 3 to 4 adverse effects that included fatigue in 25% of patients and hand-foot syndrome in 13%.[95,103] The overall response rate was only 4.4%, with a 38.8% disease-stabilization rate, median failure-free survival of 4.1 months, and median overall survival of 10.4 months. Chemotherapy-naïve patients had worse survival outcomes than the previously treated patients.

Other ongoing antiangiogenic agents in clinical trials include AZD2171 (targeting KDR, Flt-1 and -4, and PDGFR) in pretreated patients (Southwest Oncology Group) and cisplatin, pemetrexed, and AZD2171 (Southwest Oncology Group) in chemotherapy-naïve patients; sunitinib (targeting VEGFR, PDGFR-β, c-Kit, and Flt-3) in both front-line and salvage therapy settings (National Cancer Institute of Canada); and pazopanib, or GW786034 (targeting VEGFR-1, -2, and -3 and PDGFR) by the North Central Cancer Treatment Group. Although imatinib mesylate (targeting PDGFR-β, c-Kit, and BCR-Abl) as a single agent did not demonstrate activity in MPM, combination regimens with cisplatin plus pemetrexed in chemotherapy-naïve patients (M. D. Anderson Cancer Center) and with gemcitabine in pretreated patients (Gruppo Italiano Mesotelioma) are underway.[104,105]

Ribonuclease inhibitors. Ranpirnase specifically targets tumor cell tRNA and inhibits protein synthesis, resulting in cell cycle arrest at the G_1 phase. The adverse effect profile includes hypersensitivity, renal toxicity (proteinuria, azotemia), fatigue, and peripheral edema. Single-agent ranpirnase in a phase II MPM trial resulted in a 5% response rate, a 43% stable disease rate, and a median overall survival of 6 months.[97] A phase III trial (n = 105) compared ranpirnase (480 μg/m^2 weekly) with doxorubicin (60 mg/m^2 every 3 weeks) and showed no difference in overall survival in the intent-to-treat analysis. However, patients with CALGB prognostic groups 1 to 4 and EORTC risk criteria had a 2-month survival benefit when treated with ranpirnase over doxorubicin.[98,99,106,107] A large international phase III trial (P30-302) comparing doxorubicin with the combination of doxorubicin and ranpirnase is ongoing (Table 3).

Histone deacetylase inhibitors. Histone acetylation regulates gene expression by allowing transcription factor access to genomic DNA. Deacetylation of histones leads to cell cycle progression and unchecked growth. Histone deacetylase inhibitors (HDACIs) are agents that prevent deacetylation and reinstate control over the cell cycle. Preclinical studies have shown that HDACIs inhibit cell cycle progression and/or induce tumor apoptosis. However, the exact antitumor mechanism of HDACIs is unknown, although caspase and bcl-xL may be involved.[108,109] It is also believed that the antitumor effect of HDACIs may result from targeting nonhistone proteins, such as α-tubulin, p53, heat shock protein 90, and Ku70.[110]

Suberoylanilide hydroxamic acid (SAHA), or vorinostat, an oral HDACI, was studied in an early phase I trial that included 13 patients with mesothelioma (12 patients were previously treated). Single-agent SAHA given at 300 mg or 400 mg twice daily for 3 consecutive days per week yielded two partial responses in this small number of patients.[100] The main toxicities were fatigue, anorexia, dehydration, nausea/vomiting, and diarrhea. An ongoing randomized, placebo-controlled, phase III trial of SAHA plans to accrue 660 patients with MPM for whom one or two prior therapies have failed (Table 3). Belinostat, also called PDX101, is an additional HDACI under investigation. It is a reversible hydroxamic acid, as is vorinostat.

Proteasome inhibitors. Proteasome complexes process ubiquitinated proteins and facilitate protein degradation. When proteasome activity is inhibited, nuclear factor-κB production is also inhibited, and tumor cells undergo apoptosis. Preclinical studies in cell lines and murine xenograft models showed antitumor activity against MPM,[111,112] and two European trials are underway using single-agent bortezomib (All Ireland Cooperative Oncology Research Group/Gruppo Italiano Mesotelioma) and the combination of cisplatin and bortezomib (EORTC).[111]

Gene therapy. Early work with gene therapy used adenovirus vectors containing the herpesvirus thymidine kinase (Ad-HSVtk) suicide gene administered intrapleurally followed by intravenous ganciclovir.[113,114] The premise for this work was to transduce viral thymidine kinase into the cancer cells and then administer the antiviral agent ganciclovir to selectively kill the tumor cells. Ganciclovir is metabolized to cytotoxic ganciclovir triphosphates by the thymidine kinase gene, which can potentially diffuse through the tumor and kill cells that are expressing the transgene.[114] In addition to the direct anticancer effect, it was also presumed that an adenoviral-induced inflammatory response would stimulate the host immune system to attack the cancer cells.[115] A phase I trial was therefore conducted using intrapleural Ad-HSVtk followed by 2 weeks of ganciclovir in 21 previously untreated patients with MPM.[116] This trial demonstrated feasibility, with 11 of 20 assessable patients having transfer of the *HSVtk* gene into superficial tumor layers and two patients reporting long-term survival over 6.5 years.[117] Analysis of these data suggested that the antitumor effect was more likely related to the immune modulatory effect from the Ad-HSVtk and ganciclovir rather than the direct anticancer effect for which it was originally designed. Therefore, a clinical trial using an adenoviral vector containing an immune stimulant interferon beta (IFN-β) was undertaken. This phase I trial injected adenoviral human

interferon beta intrapleurally into 10 patients (seven had mesothelioma) and demonstrated successful gene transfer in seven patients. Three of the seven patients with mesothelioma had disease stability at 60 days.[115] The main toxicities seen in the trial were transient hypoxia and reversible liver function value elevations.[115] Further studies using the strategy of gene therapy and immune modulation are ongoing.

Other targets and agents. In patients with MPM, activated Src kinase may be a potential therapeutic target as studies of archival tumor tissue show that overexpression of activated Src kinase protein (phosphorylated Src Y^{419}) is correlated with more advanced MPM disease and that preclinical studies with dasatinib, a multitargeted Src tyrosine kinase inhibitor, can lead to MPM cell cycle arrest, apoptosis, and impair the ability of the tumor cell to migrate and invade.[118] Dasatinib is currently under investigation in clinical trials for the neoadjuvant setting (M. D. Anderson) and also as a second-line agent through a phase II trial sponsored by CALGB. Three antimesothelin agents are currently in clinical trials for mesothelioma: SS1P (an immunotoxin), Morab009 (an antimesothelin monoclonal antibody) and CRS-207(a *Listeria monocytogene* mesothelin vaccine).[119,120] Both SS1P and Morab009 have completed single-agent trials and are now being investigated in phase I/II trials in combination with cisplatin and pemetrexed; CRS-207 is being evaluated as a single agent in phase I trials. Potential future targets for MPM therapy include the insulin-growth factor pathway, MEK pathway, and the PI3K/AKT pathways.[121-123] Vaccines are also under investigation; the Memorial Sloan-Kettering Cancer Center recently reported results from a pilot trial of a Wilms' tumor 1 peptide vaccine, which demonstrated some activity against MPM.[124] An adjuvant clinical trial using the Wilms' tumor 1 vaccine is currently under development.

In conclusion, at this time, surgical resection and adjuvant radiation therapy remain the mainstay of treatment for patients with resectable MPM. There is substantial evidence that systemic treatment is also necessary, as improvements in local control have been accompanied by increased rates of distant metastasis. Unfortunately, the optimal multimodality management of these patients remains unclear. Therefore, the use of systemic chemotherapy (neoadjuvant, intrapleural, and adjuvant) remains experimental, and it is encouraged that systemic treatment be administered in the setting of clinical trials.

For the patient with unresectable MPM, the antifolates or gemcitabine, given in combination with a platinum agent, have made the greatest clinical impact to date. Further progress is needed, however, and enrollment of patients with MPM onto clinical trials of novel therapeutic agents should be a priority. In addition to identifying new therapeutic targets, key issues that deserve further investigation include understanding the role of immune modulation, determining whether maintenance therapy should be used after front-line chemotherapy, distinguishing the genomic profiles between the histologic subtypes to ascertain whether they should be treated differently, identifying more accurate means of measuring clinical response, and validating surrogate blood-based markers for response. New strategies and target pathways under investigation will hopefully provide better therapeutic options for patients with MPM in the future.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

The author(s) indicated no potential conflicts of interest.

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