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Current Issues in Malignant Pleural Mesothelioma Evaluation and Management

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ABSTRACT

Malignant pleural mesothelioma (MPM) is an uncommon disease most often associated with occupational asbestos exposure and is steadily increasing in worldwide incidence. Patients typically present at an older age, with advanced clinical stage and other medical comorbidities, making management quite challenging. Despite great efforts, the prognosis of MPM remains poor, especially at progression after initial treatment. Macroscopic complete resection of MPM can be achieved through extrapleural pneumonectomy (EPP) or extended (ie, radical) pleurectomy (e-P/D) in selected patients and can result in prolonged survival when incorporated into a multimodality approach. Given the morbidity associated with surgical resection of MPM, optimizing identification of appropriate patients is essential. Unfortunately, most patients are not candidates for EPP or e-P/D due to advanced stage, age, and/or medical comorbidity. Pemetrexed and platinum combination chemotherapy has become the cornerstone of therapy for patients with unresectable disease because the combination is associated with improved survival and quality of life in treated patients. However, MPM eventually becomes resistant to initial therapy, and benefit to further lines of therapy has not been substantiated in randomized clinical trials. Translational research has provided exciting insights into tumorigenesis, biomarkers, and immune response in MPM, leading to the development of multiple novel therapeutic agents that are currently in clinical trials. These advances hold the promise of a new era in the treatment of MPM and suggest that this disease will not be left behind in the war on cancer. ***The Oncologist*** 2014;19:975–984

Implications for Practice: Although uncommon, malignant pleural mesothelioma (MPM) is being diagnosed at an increasing rate worldwide due to continued workplace exposure in developing countries to asbestos and other potentially carcinogenic inhaled silicates. This article emphasizes the need for multidisciplinary evaluation at diagnosis to identify appropriate candidates for multimodality therapy and to optimize survival outcomes for this deadly disease. A growing body of data suggests that lung-sparing extended pleurectomy is the option of choice for most patients who are surgical candidates. Insights into altered molecular pathways and the immunology of MPM have led to clinical trials of novel drugs.

INTRODUCTION

Malignant pleural mesothelioma (MPM) is a highly lethal disease with 5-year overall survival (OS) of less than 10%, which has not changed for the past four decades [1]. Treatment-related mortality and morbidity continue to pose unique challenges. In this paper, we review the current epidemiology, diagnosis, and treatment of MPM, with a focus on multimodality therapy and novel agents.

EPIDEMIOLOGY

The annual incidence of MPM in the United States is estimated to be 1 in every 100,000, with approximately 3,000 new cases per year [1]. It is more common in men, and the majority of patients are over the age of 65 years.

The incidence of MPM in the U.S. peaked around the turn of this century and has since slowly started to decline, mainly in male patients [1]. Worldwide, however, MPM rates are still increasing. In developed countries, such as the U.K. and Australia, the peak incidence is expected to occur before 2030 [2]. In contrast, the incidence of mesothelioma is predicted to increase dramatically in developing countries where asbestos is still used in the workplace [3, 4]. Furthermore, the burden from the high mortality rate of mesothelioma is heavy. The mortality rate in the U.K., for example, has risen rapidly since 1968. Between 1968 and 2050 it is expected that there will have been approximately 91,000 deaths from mesothelioma in U.K., with 61,000 occurring after 2007 [4].

Occupational exposure to asbestos is the single most important risk factor associated with MPM. Asbestos is used in cement, ceiling and pool tiles, and automobile brake linings and in shipbuilding. The lifetime risk of developing MPM

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among asbestos workers was thought to be as high as 10% [5]. Family members of asbestos workers also have increased risk from second-hand exposure. There is a long latency (at least 20–30 years) from the time of asbestos exposure to the development of mesothelioma [6], and the two events appear to have a dose-response association [7]. Nonoccupational exposure to asbestos (e.g., in areas with asbestos-rich soil or inhalation of other fibrous silicates) can also contribute to an increased risk of MPM [8–10].

Ionizing radiation (therapeutic or nontherapeutic) to the upper body may be a risk factor for the subsequent development of MPM, again, with a long latent period [11–13]. Oncogenic viral infections, such as Simian virus 40 infections, have been implicated in the etiology of MPM [14, 15], although a clear relationship has yet to be established [16, 17].

Inactivation of the nuclear deubiquitinase BRCA1-associated protein 1 (BAP1), an important regulator of transcription factors related to tumorigenesis, has been associated with MPM [18, 19]. Germline mutations in *BAP1* were identified in two families with high incidence of MPM [20], and *BAP1* inactivation through somatic mutations was detected in 23% of MPM tumor tissues [21]. These emerging data suggest individuals with loss of BAP1 may have higher risk of developing MPM, especially after asbestos exposure; close monitoring and early intervention might be warranted, although genetic screening strategies have yet to be identified.

Diagnosis and Staging

Pulmonary symptoms (e.g., chest pain, dyspnea, cough) with unilateral large-volume pleural effusion in a patient with history of asbestos exposure should raise the suspicion of MPM; however, pleural fluid cytology from thoracentesis is often nondiagnostic, even after repeated attempts. More invasive procedures, such as core needle biopsy or video-assisted thoracic surgery, have higher diagnostic yields and are frequently needed [22].

There are three major histologic subtypes of MPM: epithelioid, sarcomatoid, and mixed-type (biphasic). The epithelioid subtype is associated with the best outcomes, whereas the sarcomatoid subtype typically has a poor prognosis [23]. Further histologic features may provide additional prognostic value. It was suggested, for example, that the pleomorphic subtype predicts aggressive behavior in epithelioid MPM with no survival difference from biphasic or sarcomatoid MPM [24], whereas a high degree of chronic inflammation in stroma is associated with improved survival in epithelioid MPM [25]. On immunohistochemical (IHC) staining, MPM is often positive for pan-cytokeratin, calretinin, cytokeratin 5/6, and Wilms' tumor 1 (WT1; nuclear staining) but negative for carcinoembyonic antigen or thyroid transcription factor-1 [26]. To date, there has been no single IHC marker identified with both high sensitivity and specificity for screening or diagnosis. Soluble mesothelin-related proteins might be useful in the diagnosis, treatment, and monitoring of MPM, although they have not been proven to be prognostic [27–29]. Recent studies suggested high sensitivity and specificity of fibulin-3 (plasma and effusion levels) in MPM diagnosis, but further validation is needed [30].

The most widely used staging system for MPM is the TNM system adopted by the American Joint Committee on Cancer (AJCC). Clinical staging of mesothelioma is often based on radiographic findings. Compared with traditional computed tomography (CT) scanning, positron emission tomography/CT (PET/CT) imaging appears to be more accurate in preoperative assessment of potentially resectable tumors [31], and higher standardized uptake value (>4) appears to be a poor risk factor [32]. Tumor upstaging through detection of T4 disease or nodal/distant metastases was frequent with PET/CT compared with CT alone, avoiding surgery in up to 30%–40% of MPM patients felt to have potentially resectable tumors [33, 34]. Although useful, the current AJCC system is inadequate to accurately define surgical candidacy, and it provides no clear prognostic insights [35]. The International Association for the Study of Lung Cancer (IASLC) and the International Mesothelioma Interest Group have created an MPM patient database and are incorporating this information as the basis for the planned 8th edition of the TNM system, expected in late 2015 [36].

Current Surgical Management

The role of surgery in the management of MPM remains controversial [37]. Four therapeutic surgical procedures have been defined: extrapleural pneumonectomy (EPP), extended pleurectomy/decortication (e-P/D) or radical P/D, P/D, and partial pleurectomy (Table 1).

To evaluate the effectiveness of EPP to extend quality-adjusted survival within multimodality therapy, the Mesothelioma and Radical Surgery (MARS) trial group first performed a phase II feasibility study [38]. A total of 112 eligible patients recruited from 11 collaborating centers in the U.K. entered the first registration to receive platinum-based chemotherapy. Fifty patients (45%) were eventually randomized to EPP (24 of 50) or best nonsurgical care (26 of 50). A total of 67% (16 of 24) in the surgery arm completed EPP satisfactorily [39]. Median survival (after induction chemotherapy) was 14.4 months for the EPP group and 19.5 months for the non-EPP group. Median quality-of-life scores were lower in the EPP group, although not statistically significant [39]. The sample size was insufficient to analyze outcome as the primary endpoint, but the results have prompted debate that EPP offers no survival benefit and possibly harms patients within the multimodality treatment setting.

The morbidity associated with EPP has led to the development of alternative lung-sparing procedures such as P/D and e-P/D. In a systemic review of 11 retrospective studies, Zahid et al. concluded that these procedures may lead to superior survival rates but at the cost of higher morbidity rates with palliative treatment [40]. Radical P/D achieved a higher median survival than best supportive care (14.5 versus 4.5 months) and nonradical decortication (15.3 versus 7.1 months, $p < .001$) but had a complication rate of 30% and an operative mortality rate of 9.1% [40]. In another systemic review of 1,270 patients, Teh et al. reported a 1-year postoperative survival rate of 51%, but it dropped to 9% at 5 years [41].

To date, there are no randomized comparisons of these two surgical approaches (Table 2). The choice of procedure can be influenced by multiple factors, including patient age and comorbidity, clinical stage, patient wishes, and expertise at specific surgical centers. Based on a Web-based survey from 62 mesothelioma surgeons at 39 centers in 14 countries [42], most surgeons (88%) agreed that the goal of cytoreductive surgery should be macroscopic complete resection of tumor,

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Table 1. International Association for the Study of Lung Cancer surgical definitions

Surgical term	Definition
EPP	En bloc resection of the parietal and visceral pleura with the ipsilateral lung, pericardium, and diaphragm; in cases in which the pericardium or the diaphragm is not involved by tumor, these structures may be left intact
e-P/D (radical)	Parietal and visceral pleurectomy to remove all gross tumor with resection of the diaphragm and/or the pericardium
P/D	Parietal and visceral pleurectomy to remove all gross tumor without diaphragm or pericardial resection
Partial pleurectomy	Partial removal of parietal and/or visceral pleura for diagnostic or palliative purposes but leaving gross tumor behind

Abbreviations: EPP, extrapleural pleuropneumonectomy; e-P/D, extended pleurectomy/decortication; P/D, pleurectomy/decortication.

which could most often be achieved by EPP (90%) or e-P/D (68%) but less so by P/D (23%).

In an extensive retrospective case series including 663 consecutive patients undergoing EPP or P/D at three U.S. mesothelioma surgical centers, Flores et al. reported better median survival for P/D versus EPP (16 versus 12 months) [43]. This was statistically significant ($p < .001$) after controlling for sex, histology, stage, and receipt of multimodality therapy. Compared with EPP, P/D was associated with lower operative mortality (3% versus 7%) and lower distant recurrence rate (35% versus 66%) but not local recurrence rate (65% versus 33%) [43]. The IASLC also analyzed its database of 3,101 patients from 15 centers on 4 continents and showed a survival benefit of EPP only for stage I patients (40 versus 23 months) [36]; however, this analysis could be subject to selection bias.

Lang-Lazdunski et al. compared two trimodality regimens involving EPP or e-P/D in a prospective series involving 36 patients [44]. Compared with EPP, all patients in the e-P/D group were able to complete trimodality therapy (100% versus 68%) and with significantly better median survival (23 versus 12.8 months) and 5-year survival (30.1% versus 9%) [44].

Two randomized trials are set to open soon: the MARS-2 trial, to compare e-P/D with platinum/pemetrexed chemotherapy versus chemotherapy alone, and a European Organization for Research and Treatment of Cancer (EORTC) trial, to compare e-P/D either preceded or followed by chemotherapy in early stage MPM [37]. These will hopefully clarify the role of e-P/D as part of a multimodality treatment approach.

Multimodality Therapy

At diagnosis, only a minority of MPM patients are candidates for definitive surgery. These patients have significantly better outcomes when managed with a multimodal approach rather than by surgery alone, and this finding has been confirmed in both retrospective and prospective studies [36, 45–47]. Consequently, an upfront multidisciplinary evaluation is essential.

At diagnosis, only a minority of MPM patients are candidates for definitive surgery. These patients have significantly better outcomes when managed with a multimodal approach rather than by surgery alone, and this finding has been confirmed in both retrospective and prospective studies.

Radiation therapy is conventionally delivered after surgery for local control and is conventionally performed after EPP. In a phase II trial conducted by Rusch et al. [48], adjuvant radiation following EPP at a median dose of 54 Gy was well tolerated and was associated with prolonged survival for early stage (I/II) tumors (median survival: 33.8 months). To further improve local control and to minimize toxicity, Rice et al. explored the use of intensity-modulated radiation therapy (IMRT) after EPP without routine chemotherapy [49]. Median OS and 3-year survival was 14.2 months and 20% ($n = 63$), and further improvement in survival was associated with early stage (node-negative) and epithelioid histology. Only three patients had recurrence within the irradiated field, but distant metastases (54%) remained significant, indicating the need for combined systemic therapy [49]. Cho and colleagues recently published their phase I/II experience with neoadjuvant IMRT [50]. Twenty-five eligible patients (18% of a total of 138 patients screened) all completed IMRT (25 Gy to the entire ipsilateral hemithorax with concomitant 5-Gy boost to areas at risk) within 1 week prior to EPP. Adjuvant chemotherapy was offered to ypN2 patients (5 of 13 of these patients actually received chemotherapy). No perioperative mortality was observed, although 13 patients (52%) developed grade ≥ 3 surgical complications. Cumulative 3-year survival reached 84% in epithelial subtypes compared with 13% in biphasic subtypes ($p = .0002$), suggesting this novel approach may be preferred for selected patient subgroups. Larger numbers of patients and longer follow-up are also necessary.

Adjuvant chemotherapy and intraoperative therapies also lead to improved survival after EPP or e-P/D. In a retrospective analysis, adjuvant systemic chemotherapy significantly improved survival compared with surgery alone (35 versus 13 months) [51]. Hyperthermic intraoperative intracavitary cisplatin perfusion immediately after EPP can be performed with acceptable morbidity and mortality [52]. Sugarbaker et al. investigated the addition of this approach among patients with favorable prognostic factors (i.e., epithelial histology, low tumor burden, female sex, or male with normal hemoglobin) [53]. Of the 103 identified patients, 72 received hyperthermic intraoperative cisplatin chemotherapy. This group exhibited a significantly longer interval to recurrence (27.1 vs 12.8 months) and OS (35.3 vs 22.8 months) compared with patients without treatment. The benefits were particularly evident among the subgroups of patients who had not received hemithoracic radiotherapy and who had pathologic stage N1 or N2 disease.

Friedberg et al. evaluated intraoperative photodynamic therapy (PDT) in patients who underwent macroscopic complete resection (14 with modified EPP, 14 with e-P/D) [54]. The pleurectomy plus PDT group had significantly better

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Table 2. Multimodality data comparing EPP and P/D

Therapy	*n*	OS (months)	2-Year OS (%)	5-Year OS (%)
Flores et al. [43] (retrospective)			—	—
EPP	385	12		
P/D	278	16		
Rusch et al. [36] (retrospective)			—	—
EPP	1,190	40/23/16/12[a]		
P/D	299	23/20/19/15[a]		
Lang-Lazdunski, et al. [44] (prospective)				
Induction chemotherapy followed by EPP then hemithoracic radiation (54 Gy)	22	12.8	18	9
e-P/D plus hyperthermic intraoperative povidone-iodine followed by adjuvant chemotherapy and radiation to chest tube/thoracotomy sites only	54	23	49	30

[a]Listed by best TNM stage I/II/III/IV.
Abbreviations: —, not available; EPP, extrapleural pleuropneumonectomy; e-P/D, extended pleurectomy/decortication; OS, overall survival; P/D, pleurectomy/decortication.

survival at a median follow-up of 2.1 years (median OS not yet reached versus 8.4 months), which was also superior to previously reported results for e-PD alone. The authors extended their cohort to include 38 patients treated with e-PD plus PDT, most with stage III/IV disease and epithelial histology, and 35 patients received chemotherapy [55]. At a median follow-up of 34.4 months, the median OS and progression-free survival (PFS) were 31.7 and 9.6 months, respectively. In another prospective study, Lang-Lazdunski et al. assessed e-P/D and hyperthermic pleural lavage with povidone-iodine followed by prophylactic radiation (to thoracotomy and chest tube sites) and adjuvant chemotherapy in comparison to neoadjuvant chemotherapy followed by EPP and adjuvant radiation [44]. Survival was significantly better in the e-P/D group compared with EPP (23 versus 12.8 months). Although inconclusive, this result suggested that povidone-iodine lavage is safe and may be an effective intraoperative adjunct to pleurectomy.

Systemic Therapy

Despite these varied surgical approaches and controversies, the majority of MPM patients present with unresectable disease or are deemed inoperable due to age or medical comorbidities and are primarily treated with systemic therapies with the goals of disease palliation and survival prolongation [56].

Cytotoxic Therapy

Meta-analyses have shown that most single-agent chemotherapies exhibit low activity, with the exception of cisplatin [57, 58]. Response rates are higher with combination therapy compared with single agents, and platinum-based regimens are superior to non-platinum-based regimens [56].

Vogelzang et al. were the first to test the efficacy of cisplatin plus pemetrexed in a phase III clinical trial (Evaluation of Mesothelioma in a Phase III Trial of Pemetrexed With Cisplatin [EMPHACIS]) [59]. A total of 456 patients were randomized to receive either pemetrexed plus cisplatin or cisplatin alone. Compared with single-agent cisplatin, patients in the combination chemotherapy arm had improved response rate (RR; 41.3% versus 16.7%, $p < .0001$), time to progression (5.7 versus 3.9 months, $p = .001$), and OS (12.1 versus 9.3 months, $p = .020$). After 117 patients had enrolled, folic acid and vitamin B12 were added, resulting in a significant reduction in toxicities in the pemetrexed plus cisplatin arm without adversely affecting survival. The EORTC conducted a similar phase III trial comparing the combination of raltitrexed plus cisplatin with cisplatin alone and confirmed that combination therapy is superior [60]. Consequently, the cisplatin-antifolate combination is currently considered standard of care as first-line treatment.

Chemotherapy beyond first-line treatment has been less well studied, and the optimal regimen is not known [61]. Poststudy chemotherapy (PSC; most commonly single agent gemcitabine or vinorelbine) in the EMPHACIS trial was associated with prolonged survival; but it was not clear whether this was associated with PSC or whether patients who had prolonged survival tended to receive more chemotherapy [62]. A multicenter phase III study compared second-line pemetrexed plus best supportive care (BSC) and BSC alone in pemetrexed-naïve patients with relapsed MPM [63]. Second-line pemetrexed significantly increased median PFS, time to progression, and time to treatment failure but provided no OS benefit (8.4 versus 9.7 months); however, 52% of patients in the BSC arm received chemotherapy at time of progression. Cancer and Leukemia Group B is conducting a randomized phase II trial (CALGB 30901) of pemetrexed versus observation for MPM patients without progression after first-line pemetrexed plus platinum chemotherapy and hopefully will clarify the role of maintenance pemetrexed. Table 3 summarizes the current evidence for second-line (and beyond) chemotherapy [64–68].

Targeted Therapy

The need for more effective therapies for MPM has prompted basic research to identify novel therapeutic targets (Table 4).

Epigenetic regulation of tumor suppressor genes has emerged as an important mechanism that leads to tumorigenesis. The histone deacetylase family proteins (HDACs) inhibit DNA transcription through histone modifications, and its overexpression and/or aberrant function have been found in many cancers, including mesothelioma [69, 70]. Vorinostat is one of the best-studied HDAC inhibitors and currently

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Table 3. Activity of second-line regimens after pemetrexed-based chemotherapy

Study	Agents	*n*	RR (%)	PFS (months)	OS (months)
Ceresoli et al. [68]	Pemetrexed ± platinum	31	19	3.8	10.5
Xanthopoulos et al. [66]	Oxaliplatin ± gemcitabine	29	6.9	2.2	5.7
Zucali et al. [65]	Gemcitabine + vinorelbine	30	10	2.8	10.9
Toyokawa et al. [67]	Gemcitabine + vinorelbine	17	18	6.0	11.2
Zucali et al. [64]	Vinorelbine	59	15.2	2.3	6.2

Abbreviations: OS, overall survival; PFS, progression-free survival; RR, response rate.

Table 4. Targets of interest and corresponding agents in mesothelioma

Target	Agent
Angiogenesis (VEGF, VEGFR, PDGFR, FGFR)	Bevacizumab, vatalanib, cediranib, nintedanib
NF2/merlin/FAK	Defactinib (VS-6063)
PI3K/mTOR	GDC-0980, VS-5584, LY3023414
Mesothelin	Amatuximab, SS1P, CRS-207
WT1	WT1 vaccine
CTLA4	tremelimumab

Abbreviations: FAK, focal adhesion kinase; FGFR, fibroblast growth factor receptor; merlin, moesin-ezrin-radixin-like protein; mTOR, mammalian target of rapamycin; NF2, neurofibromatosis type-2; PDGF, platelet-derived growth factor; PDGFR, PDGF receptor; PI3K, phosphatidylinositol 3-kinase; VEGF, vascular endothelial growth factor; VEGFR, VEGF receptor.

is approved by the U.S. Food and Drug Administration for cutaneous T-cell lymphoma treatment. The original phase I trial of vorinostat included 13 patients with MPM, and 2 of them had a partial response (15.4%) [71]. This led to a multicenter phase III study (VANTAGE 014) of vorinostat in patients who progressed after first-line pemetrexed-based chemotherapy. Despite the huge collaborative efforts, this largest-ever randomized trial in mesothelioma (660 patients) failed to show a benefit in OS (30.7 versus 27.1 weeks, $p = .858$) and only a marginal improvement in PFS (6.3 versus 6.1 weeks, $p < .001$) [72].

Mesothelioma cells secrete and express several angiogenic factors such as vascular endothelial growth factor (VEGF) and VEGF receptor (VEGFR), platelet-derived growth factor (PDGF) and PDGF receptor (PDGFR), and fibroblast growth factor receptor (FGFR) [73]. Bevacizumab, an anti-VEGF monoclonal antibody, did not significantly improve either PFS or OS in patients with advanced MPM when added to first-line gemcitabine-cisplatin chemotherapy [74]. Another phase II trial evaluated the addition of bevacizumab to first-line pemetrexed and cisplatin but failed to achieve its primary endpoint (33% improvement in PFS at 6 months compared with historical controls) [75]. Interim analysis from a French multicenter randomized phase II/III trial of pemetrexed and cisplatin with or without bevacizumab (MAPS) was recently reported [76]. Compared with chemotherapy alone, patients in the bevacizumab arm had a RR of 14% and a better disease control (73.5% versus 43.2%; $p = .01$) at 6 months. This trial will hopefully complete recruitment soon [77], and its final results are expected to clarify the role (if any) of bevacizumab in MPM treatment.

Nintedanib (BIBF 1120; Boehringer Ingelheim GmbH, Ingelheim, Germany, http://www.boehringer-ingelheim.com) is a potent oral triple angiokinase inhibitor that targets all three major angiogenic pathways [78]. In phase I/II clinical trials, nintedanib showed an acceptable safety profile and antitumor activities [79]. In the phase III LUME-Lung 1 study for patients with non-small cell lung cancer, second-line nintedanib plus docetaxel significantly improved PFS compared with docetaxel alone (3.4 versus 2.7 months; $p = .0019$) and improved OS in patients with adenocarcinoma histology (12.6 versus 10.3 months; $p = .0359$) [80]. An ongoing randomized multicenter phase II trial will evaluate nintedanib in combination with pemetrexed and cisplatin followed by maintenance nintedanib compared with chemotherapy alone in patients with unresectable MPM. SWOG is also studying the addition of the oral anti-VEGFR tyrosine kinase inhibitor cediranib versus placebo to pemetrexed-cisplatin in a randomized phase II trial.

Loss of the tumor suppressor protein moesin-ezrin-radixin-like protein (merlin) causes activation of multiple mitogenic signaling pathways, including the mammalian target of rapamycin (mTOR) and focal adhesion kinase (FAK) pathways [81]. About 40% of MPM patients carry inactivating mutations in the neurofibromin 2 (*NF2*) gene, which encodes for merlin [82, 83], and overexpression of FAK has been implicated in increased invasiveness of mesothelioma cell lines [84]. A recently reported phase I study of GSK2256098 (an oral FAK inhibitor; GlaxoSmithKline, Brentford, U.K., http://www.gsk.com) that included 23 patients with recurrent MPM suggested that merlin loss may result in improved PFS response to FAK inhibition [85]. Defactinib (VS-6063; Verastem, Cambridge, MA, http://www.verastem.com) is a highly potent, selective FAK inhibitor. A phase II randomized multicenter study of defactinib maintenance in MPM patients who have not progressed after first-line pemetrexed-platinum chemotherapy is actively recruiting.

The phosphatidylinositol 3-kinase (PI3K), AKT, and mTOR (PI3K/AKT/mTOR) pathway is one of the key regulators in cell survival, proliferation, and apoptosis [86]. Aberrant signaling cascade has been demonstrated in several cancer types, including mesothelioma [87, 88]. Because merlin is a negative regulator of the mTOR pathway, mTOR and merlin loss has become a target of interest in MPM [89]. The mTOR inhibitor rapamycin showed a much enhanced growth-inhibitory effect on merlin-negative mesothelioma cells compared with merlin-positive cells [90]. A SWOG phase II study of post-front-line mTOR inhibitor everolimus (RAD001) failed to show activity in unselected patients [91]. GDC-0980 (Genentech, South San Francisco, CA, http://www.gene.com) is a potent, selective oral PI3K/mTOR dual inhibitor that has demonstrated broad activity in various xenograft cancer models [92]. In a recently reported phase I study by Dolly et al., this drug showed noticeable antitumor activity in MPM patients at a generally well-tolerated dose [93]. Two additional early stage studies on dual PI3K/mTOR inhibitors LY3023414 (Eli Lilly and Company, Indianapolis, IN, http://www.lilly.com) and

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Table 5. Ongoing randomized trials of targeted agents and immunotherapies in mesothelioma

Trial	Phase	Arms	Setting
NCT00651456	II/III	Pemetrexed/cisplatin with or without bevacizumab	Front line
NCT01907100	II	Nintedanib (BIBF 1120) or placebo in combination with pemetrexed/cisplatin followed by nintedanib vs. placebo alone	Front line
NCT01064648	I/II	Cediranib vs. placebo plus pemetrexed/cisplatin followed by cediranib or placebo alone	Front line
NCT01870609	II	Defactinib (VS-6063) vs. placebo after first-line chemotherapy (pemetrexed/platinum)	Maintenance
NCT01265433 NCT01890980	II	WT1 vaccine plus montanide plus GM-CSF vs. montanide plus GM-CSF	Adjuvant
NCT01843374	II	Tremelimumab vs. placebo	Second or third line

Abbreviation: GM-CSF, granulocyte-macrophage colony stimulating factor.

VS-5584 (Verastem) are currently recruiting patients with advanced cancers, including MPM.

Immunotherapy

The immune system plays a fundamental role in tumor surveillance and tumor growth control. Although highly infiltrated by a population of immune cells, mesothelioma appears to enjoy an "immune tolerance" state [94] . Decrease in cytotoxic T cells and natural killer lymphocytes and antigen-presenting cells, increase in regulatory T cells, and production of immunoregulatory cytokines may all contribute to the suppression of immune response [95, 96]. Consequently, reconstitution of the immune system to target tumor cells has become an attractive approach and one of the most active areas in mesothelioma research [97].

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Mesothelin is a cell-surface glycoprotein widely expressed in normal and malignant mesothelial cells and in other solid tumors [98]. It may be a useful biomarker and an important target for mesothelin-expressing tumors [99] and may promote tumor invasion and matrix metalloproteinase 9 expression in MPM [100]. Amatuximab (MORAb-009; Morphotek, Exton, PA, http://www.morphotek.com), a high-affinity monoclonal antibody toward mesothelin, has been evaluated in a phase I trial [101]. In 24 previously treated patients (including 13 with MPM), amatuximab was well tolerated, and 11 patients had stable disease after receiving at least one cycle. In a single-arm phase II study of amatuximab plus pemetrexed and cisplatin, Hassan et al. reported a partial RR of 39% ($n = 30$), and 51% ($n = 39$) had stable disease [102]. The same group has also investigated SS1P, a recombinant immunotoxin consisting of an antimesothelin antibody linked to a *Pseudomonas* exotoxin [103]. In a phase I trial, SS1P was well tolerated and showed activity in heavily pretreated patients with mesothelin-expressing cancers [104]. In a recently published phase II study, major antitumor response was observed in 3 of 10 patients with advanced chemorefractory mesothelioma when SS1P was given together with immunosuppression [105]. CRS-207 (Aduro BioTech, Berkeley, CA, http://www.adurobiotech.com) is a live-attenuated *Listeria* monocytogene vaccine designed to express mesothelin that was shown to be safe and to produce mesothelin-specific T-cell responses in a phase I trial that included five patients with MPM [106]. A phase IB trial of CRS-207 in combination with pemetrexed and cisplatin as front-line therapy is currently accruing MPM patients (ClinicalTrials.gov identifier NCT01675765).

WT1 protein is an oncogenic transcription factor commonly overexpressed in MPM. Processed WT1 peptides can be presented to the immune system, making it an attractive target for T-cell-based immunotherapy [107]. Krug et al. designed a WT1 vaccine and found it to be safe and effective in a pilot study [108]. The group is currently testing the vaccine in a randomized phase II trial in MPM patients with minimal disease burden after multimodality therapy [109]. Dao et al. engineered a fully human "T cell receptor–like" monoclonal antibody, ESK1 [110]. They found that ESK1 bound to several cancer cell lines (including mesothelioma) and primary leukemia cells with high avidity and nearly cleared all leukemia in two mouse models without toxicity. These exciting preclinical data have positioned ESK1 to be tested further in clinical trials.

In normal epithelial cells, transforming growth factor β (TGF-β) is a potent growth inhibitor and promoter of cellular differentiation [111]. However, tumor cells are often insensitive to this cytokine and can "utilize" TGF-β to promote tumor angiogenesis and host immunosuppression [112]. Significant levels of TGF-β are produced in MPM cells lines and in primary MPM tissues and pleural effusions [113, 114]. GC1008 (fresolimumab; Genzyme, Cambridge, MA, http://www.genzyme.com) is a human monoclonal antibody capable of neutralizing all mammalian isoforms of TGF-β with high affinity [115]. The first phase II trial of GC1008 in pretreated progressive MPM was terminated, unfortunately, after only 13 enrollments when the manufacturer discontinued development of the antibody for oncology indications [116]. Although partial or complete radiographic responses were not observed, 3 patients showed stable disease at 3 months. Serum from 5 patients showed new or enhanced levels of antitumor antibodies, and these patients had increased median OS compared with those who did not show new or enhanced antitumor antibody levels (15 versus 7.5 months; $p < .03$).

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Sterman et al. evaluated locally administered immunotherapy using two intrapleural doses of an adenoviral vector encoding human interferon-α (Ad.IFN-α2b), and five of nine patients showed evidence of disease stability or tumor regression in the pilot study [117]. The investigators then conducted a phase I/II trial involving repeated intrapleural "vaccination" with Ad.IFN-α2b concomitant with high-dose cyclooxygenase-2 inhibitor celecoxib, followed by standard first-line (pemetrexed-based) or second-line (gemcitabine-based) chemotherapy [118]. The overall RR was 31%, and the disease control rate was 78%. Patients who received first-line chemotherapy ($n = 14$) had median survival of 10.5 months, whereas second-line patients ($n = 21$) had median survival of 15.0 months. Randomized multicenter trials are awaited to confirm these promising results.

The antitumor activity of T cells can be inhibited by negative regulatory "checkpoint" proteins on the cell surface, such as cytotoxic T-lymphocyte-associated protein 4 (CTLA4) and programmed cell death 1 (PD1) [119]. Preclinical studies have demonstrated that CTLA4 blockage could augment endogenous responses to tumor cells, leading to tumor cell death [120]. In a recently published single-arm phase II study, Calabrò et al. evaluated tremelimumab (MedImmune, Gaithersburg, MD, https://www.medimmune.com), a human IgG2 monoclonal antibody to CTLA4, in patients with chemotherapy-resistant MPM [121]. Although the study did not reach its primary endpoint of a 17% target RR, the disease control rate was 31% (9 of 29 patients). The median PFS and OS were 6.2 and 10.7 months, respectively. A larger multicenter randomized phase II trial comparing tremelimumab to placebo in the second- or third-line setting is currently recruiting. Trials of PD1 and ligand PD-L1 monoclonal antibodies are awaited.

Conclusion

Despite the advancements in surgical approaches, radiation techniques, and modern chemotherapeutics, MPM remains a highly lethal disease that is rarely cured. Only a small percentage of fit patients with good prognostic factors may benefit from multimodality therapy, underscoring the importance of surgical candidate selection. MPM inevitably progresses after standard antifolate-platinum chemotherapy and is resistant to other cytotoxic agents; no trials in the second- or third-line setting have shown a survival benefit. Clinical trial accruals of MPM have been hampered by the rarity of the disease; therefore, international collaborations are essential. Basic researchers have identified new biomarkers, explored novel antitumor mechanisms, and successfully translated several findings into exciting targeted agents that are actively being tested in the clinic (Table 5). We remain confident that, in the near future, effective therapies for MPM will result from these investigations and give patients realistic hope for meaningful prolongation of survival with this disease.

Author Contributions

Conception/Design: Jing Ai, James P. Stevenson
Collection and/or assembly of data: Jing Ai, James P. Stevenson
Data analysis and interpretation: Jing Ai, James P. Stevenson
Manuscript writing: Jing Ai, James P. Stevenson
Final approval of manuscript: Jing Ai, James P. Stevenson

Disclosures

James P. Stevenson: Verastem, Boehringer Ingelheim, Medimmune (RF). The other author indicated no financial relationships.
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For Further Reading:
Kyle W. Robinson, Alan B. Sandler. The Role of MET Receptor Tyrosine Kinase in Non-Small Cell Lung Cancer and Clinical Development of Targeted Anti-MET Agents. ***The Oncologist*** 2013;18:115–122.

Implications for Practice:
Identification of the role of the HGF–MET pathway in cancer, and specifically in non-small cell lung cancer (NSCLC) has led to the development of pharmaceutical agents targeting this pathway. In particular, MET's role in secondary resistance to EGFR-directed therapies has led to the investigation of combining MET-directed agents with erlotinib in patients with metastatic NSCLC. This article reviews the early development of MET-directed therapies as well as currently ongoing Phase III studies. We await the results of these studies, which will determine whether targeting MET in combination with EGFR is a valid clinical option in patients whose cancers progress following treatment with EGFR inhibitors.