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Novel Therapies in Phase II and III Trials for Malignant Pleural Mesothelioma

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Abstract

Mesothelioma is a rare malignancy of the pleura with limited therapeutic options. Despite the desperate need to develop better treatment for this disease, the rarity of the tumor type creates formidable challenges in clinical research. Nonetheless, several novel agents are under investigation. Most efforts are directed toward improving standard first-line therapy with pemetrexed and cisplatin, or developing effective second-line treatments. Several classes of drugs are being explored, including those that impact DNA transcription, cell-cycle progression, angiogenesis, and immune tolerance. This article describes several ongoing or recently completed phase II and III trials using novel agents vorinostat, everolimus, CBP501, MORAb-009, NGR-hTNF, WT1 vaccine, bevacizumab, cediranib, and thalidomide.

Keywords

Mesothelioma; clinical trials

Background

Malignant pleural mesothelioma (MPM) is a rare malignancy of the pleura that is usually associated with asbestos exposure. Although distant metastases can occur, mesothelioma typically spreads and invades locally. Unfortunately, even with aggressive therapies, almost always recurs, and median overall survival is 6 to 18 months depending on the stage of disease at diagnosis.[1] Approximately 2000 to 3000 new cases are reported annually in the United States,[2] and the incidence continues to increase worldwide in industrialized nations, particularly in locations where asbestos continues to be used.[3]

A high proportion of patients with mesothelioma present with disease too advanced for surgical resection. For those patients, chemotherapy treatment with pemetrexed and cisplatin has been shown to improve median survival to 12 months.[4] However, attempts to move beyond this one treatment regimen are hampered by several factors. Because of the rarity of the disease, large randomized trials can take years to complete. This also results in a lack of interest from pharmaceutical companies and funding agencies to support studies in this

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orphan disease. Therefore, many questions remain unanswered and numerous needs remain unmet in this patient population, particularly including the identification of treatments that improve the efficacy of first-line therapy, and the establishment of second-line therapies. Fortunately, despite the many hurdles, several clinical trials are testing agents against a wide range of relevant targets (Table 1).

Inhibitors of Cellular Functions

Numerous small molecule inhibitors used to treat other solid tumors have failed to show activity in MPM. For example, despite overexpression of the epidermal growth factor receptor and the platelet-derived growth factor receptor in MPM, trials with gefitinib, erlotinib, and imatinib did not show activity in this disease.[5–8] Nonetheless, drugs that modulate other cellular functions, such as histone acetylation, the mammalian target of rapamycin (mTOR) pathway, and cell-cycle regulators, are being actively investigated.

Vorinostat

Histones are a family of proteins that function as the control and structural elements of chromatin. DNA transcription can only occur when chromatin is decondensed, which is regulated by a family of acetyltransferase and deacetylase proteins (HDACs).[9] HDACs inhibit gene transcription through removing lysine residues from histone tails and nonhistone proteins, which prevents chromatin relaxation. Overexpression and aberrant function of HDACs have been found in many cancers,[10,11] and many pharmacologic inhibitors of HDACs have been identified.[12,13] The most widely studied HDAC inhibitor is vorinostat, which is FDA-approved for the treatment of cutaneous T-cell lymphoma. As data have emerged identifying epigenetic regulation via histones as an important mechanism in the development of mesothelioma, HDAC inhibitors have become an appealing therapy to explore for this disease.[13]

The original phase I trial of oral vorinostat included 13 patients with MPM, and all but one had undergone prior chemotherapy.[14] Two patients had unconfirmed partial responses and were alive 27 and 21 months, respectively, after starting treatment. Six patients remained in the study for more than 4 months. Based on these promising results, a multi-center, randomized, placebo-controlled phase III study was undertaken of vorinostat in patients with progressive or relapsed MPM after chemotherapy with a pemetrexed-based regimen. Overall survival is the primary end point, with objective response, progression-free survival, pulmonary function, and quality of life as secondary outcomes. The trial completed accrual with 660 patients, and results should be forthcoming in the third quarter of 2011.

Everolimus

Loss of several tumor suppressor genes has been implicated in the development of malignant mesothelioma.[15] The neurofibromatosis type 2 (*NF2*) gene is absent in 50% to 60% of malignant mesotheliomas. *NF2* encodes Merlin, which mediates contact-dependent inhibition of cell proliferation in normal cells, primarily through inhibition of mTOR.[16] In knockout models of Merlin, mTOR activity becomes unregulated, and this leads to increased cell proliferation, which can be abrogated by mTOR inhibition. In mesothelioma cell lines,

Merlin loss activates mTOR complex 1 (mTORC1) signaling, and cells with *NF2* mutations are selectively sensitive to drugs targeting mTORC1.

These data provide the rationale for studying mTOR inhibitors, such as everolimus, in patients with mesothelioma. Everolimus is an oral derivative of rapamycin that is used as part of a multidrug immunosuppression regimen in solid organ transplantation, and has also been approved for the treatment of advanced renal cell carcinoma after sunitinib or sorafenib. SWOG is conducting a phase II trial of everolimus in patients with MPM who were previously treated with chemotherapy (ClinicalTrials.gov identifier: NCT00770120). The primary objective is to assess the 4-month progression-free survival in patients with unresectable MPM treated with everolimus.

CBP501

Although normal cells repair most DNA damage at the G1 checkpoint, cancer cells disrupt the G1 checkpoint and are therefore more dependent on the G2 checkpoint. Consequently, cancer cells might be susceptible to pharmacologic disruption of the G2 checkpoint.[17] CBP501 is a cell-cycle dysregulator that inhibits several kinases involved in cell-cycle arrest at G2.[18] These kinases are known to phosphorylate a serine on CDC25C, which prevents activation of the transition from G2 to M by CDC2/cyclin B. In vitro studies of CBP501 in combination with chemotherapy showed increases in the population of cancerous cells in G1 and enhanced cytotoxicity of cisplatin. Phase I trials of CBP501 alone and in combination with cisplatin have been completed.[19] The primary toxicity is an infusion-related urticarial rash, but no additional toxicities to those associated with the standard chemotherapy have been noted.

An open-label, international, randomized phase II trial is currently enrolling previously untreated patients with advanced MPM (ClinicalTrials.gov identifier: NCT00700336). Sixty-three patients will be randomized in a 2:1 fashion to either CBP501 plus pemetrexed/cisplatin or pemetrexed/cisplatin alone. This study will complete enrollment by the end of 2011.

Immunotherapy

Immunotherapy has been explored for the treatment of MPM based on the correlation between lymphocyte infiltration in mesothelioma tumors and better prognosis.[20] Additional studies have shown the existence of a specific humoral response to mesothelioma,[21,22] but immune tolerance often develops.[23] To overcome this immune tolerance, both passive monoclonal antibody and active vaccination immunotherapies are being investigated.

Anti-Mesothelin Antibodies

Mesothelin, a cytoplasmic membrane protein involved in cell adhesion, is uncommon in healthy tissues except for normal mesothelium. It is, however, overexpressed in several cancers, including mesothelioma, pancreatic cancer, ovary cancer, and non–small cell lung cancer, which makes it an attractive target for anticancer therapy.

MORAb-009 is a chimeric monoclonal antibody to human mesothelin. Preclinical data suggest that MORAb-009 blocks mesothelin-mediated cell adhesion and affects the antibody-dependent cell cytotoxicity of mesothelin-positive cell lines.[24] A phase I trial of MORAb-009 has been completed,[25] and an ongoing phase II multicenter, open-label, single-arm trial is now evaluating the efficacy and safety of MORAb-009 in combination with pemetrexed and cisplatin in patients with unresectable MPM who have not undergone prior systemic therapy (ClinicalTrials.gov identifier: NCT00738582). The primary end point is progression-free survival at 6 months, and secondary end points include overall response rate, disease recurrence, and overall survival.

SS1P is an immunotoxin-linked antibody against mesothelin. In a prior phase I single-agent trial conducted at the NCI, grade 3 toxicities included urticaria, vascular leak syndrome, and pleuritis.[26] Several heavily pretreated patients showed minor responses, and 2 experienced complete resolution of abdominal ascites: 1 from ovarian cancer and 1 from peritoneal mesothelioma. A phase I trial combining SS1P with pemetrexed and cisplatin showed the combination to be safe, with 5 of 7 patients with MPM showing response at the maximal tolerated dose.[27]

NGR-hTNF-α

Human tumor necrosis factor α (hTNF-α) has shown significant preclinical antitumor activity mediated through apoptosis of tumor endothelial cells via caspase activation but has proven too toxic for use in clinical trials.[28] To help favorably shift the dose– response curve, hTNF-α was fused to a cyclic tumor-homing peptide, NGR (asparagine-glycine-arginine), which selectively binds CD13 overexpressed on the endothelial cells of solid tumors.[29,30] A phase II trial of NGR-hTNF-α in previously treated patients with MPM showed a disease control rate of 50% and a median progression-free survival of 9.1 months among a small cohort who received weekly dosing.[28] Updated follow-up showed a 46% disease control rate, with a 2-year overall survival rate of 57% and a median progression-free survival of 9.1 months, among those who received weekly infusions.[31] Prompted by these encouraging results, a randomized double-blind phase III trial is underway of NGR-hTNF-α plus best investigator's choice (best supportive care alone or combined with single-agent chemotherapy) in patients with previously treated MPM (ClinicalTrials.gov identifier: NCT01098266). Notably, randomization is stratified by the receipt of concurrent chemotherapy. The primary end point of this study is overall survival, with planned enrollment of 390 patients.

WT1 Vaccine

The Wilms tumor suppressor gene, WT1, was initially identified in pediatric renal tumors but is also strongly expressed in many other malignancies, including mesothelioma. WT1 is abundant in mesothelioma (ranging from 72%–93%),[32] and immunohistochemical stains for WT1 are routinely used to confirm its diagnosis. Although WT1 is a nuclear protein, it is processed and presented on the cell surface, which makes it a viable immunotherapy target.

To overcome the poor immunogenicity of this tumor-associated self-antigen, synthetic analogue peptides were produced. Using computer prediction analysis, peptides predicted to

have high affinity for their target were tested in vitro for their ability to generate immune responses. Results showed that human T cells stimulated with the analog peptide can kill WT1+ mesothelioma cell lines.[33,34]

A pilot trial of a vaccine consisting of 4 WT1 peptides administered with adjuvant Montanide and sargramostim confirmed its safety and immunogenicity in patients with MPM.[35] The median survival of these patients was 14 months, which is encouraging for patients with previously treated MPM. One patient completed 12 vaccinations and remained progression-free 36 months later. To further explore the effects of the WT1 analog peptide vaccine, a randomized phase II trial is being conducted at Memorial Sloan-Kettering Cancer Center in patients with MPM who have completed multimodality therapy, with a primary end point of progression-free survival (ClinicalTrials.gov identifier: NCT01265433).

Angiogenesis

Mesothelioma cells secrete and express several angiogenic factors, including vascular endothelial growth factor (VEGF), VEGF receptor (VEGFR), platelet-derived growth factor (PDGF), and PDGF receptor (PDGFR).[36–38] VEGF is implicated in several aspects of cancer development and progression, which prompted the development of many effective agents to inhibit this pathway. Consequently, several antiangiogenic agents, particularly small molecule VEGFR tyrosine kinase inhibitors, including SU5416, vatalanib, sorafenib, and sunitinib, have been studied in mesothelioma and have shown low levels of activity.[39–42] Other inhibitors of angiogenesis continue to be explored in this disease.

Bevacizumab

Bevacizumab is a monoclonal antibody that binds to VEGF. In multiple tumor types, the addition of bevacizumab to chemotherapy has been shown to improve response rates, time to progression, and survival. Studies in MPM seek to show a similar benefit, although past results have not supported these findings. A randomized phase II trial in patients with advanced MPM examined the addition of the VEGF inhibitor bevacizumab to cisplatin and gemcitabine. This study did not show any improvement in response rate, progression-free survival, or overall survival.[43] In 2 single-arm phase II trials of bevacizumab plus pemetrexed and a platinum agent as first-line therapy, the median progression-free survival was 6.9 months and the median survival was 14 to 15 months.[44,45] A French randomized phase III trial is now investigating this combination (ClinicalTrials.gov identifier: NCT00651456). Preliminary data from the randomized phase II portion of this study met the criteria for continuation; the disease control rate at 6 months was 74% among those receiving bevacizumab compared with 43% in those not receiving bevacizumab.

Cediranib

Cediranib is an oral small molecule inhibitor of receptor tyrosine kinases that influence both the VEGF and PDGF pathways. A phase II trial of cediranib given after platinum-based chemotherapy showed a disease control rate of 42%.[46] Based on these encouraging results, SWOG in conducting a phase I/II trial of cediranib in combination with cisplatin and pemetrexed in chemotherapy-naïve patients with MPM (ClinicalTrials.gov identifier:

NCT01064648). The primary objective of the randomized phase II portion of the trial is to assess whether cisplatin and pemetrexed with cediranib improves progression-free survival compared with cisplatin and pemetrexed alone. Accrual is planned for 96 patients over 24 months and has 83% power to detect 66% improvement in median progression-free survival.

Thalidomide

Although thalidomide's use as a sedative was abandoned in the mid-20th century because of its teratogenic effects, more recently its use as an anticancer agent has been revisited. Although the exact mechanism has not been fully elucidated, thalidomide's putative target is angiogenesis. Given the abundance of angiogenic targets in mesothelioma, a phase I/II study of thalidomide was conducted, which identified a suitable dose and showed 27.5% disease stabilization for greater than 6 months.[47] However, a phase III trial of maintenance thalidomide versus observation in patients who completed platinum-based chemotherapy did not show any benefit in progression-free (16 vs. 15 weeks; $P = .83$) or overall survival (11 vs. 13 months; $P = .09$).[48]

Conclusions

Although significant progress has been made in the treatment of many malignancies, mesothelioma remains a therapeutic challenge, with disappointing results even when the most aggressive therapies are used. Given the lack of effective treatments, a substantial unmet need exists for improved first-line regimens and efficacious second-line treatments. As a result, many novel agents are currently in phase II and III clinical trials for the treatment of mesothelioma, and this article reviews some of the most promising drugs that span a wide variety of targets. Going forward, it will be important to pursue agents that are relevant based on the biology of this disease. Furthermore, it would be optimal to create a new research infrastructure to facilitate the study of novel therapies in MPM through maximizing the use of limited resources, both financial and patient population, while reducing redundant efforts.

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Table 1

Novel Agents in Clinical Trials

Drug	Line	Phase	Mechanism	Sponsor
Vorinostat	Secondor third	III	Histone deacetylase inhibitor	Merck & Co., Inc.
Everolimus	Secondor third	II	mTOR inhibitor	Southwest Oncology Group
CBP 501	First with pemetrexed and cisplatin	I/II	Cell-cycle regulator	CanBas
MORAb-009	First with pemetrexed and cisplatin	II	Monoclonal antibody to mesothelin	Morphotek Inc.
NGR015	Second	III	Caspase activation	MolMed
WT1 vaccine	Adjuvant	II	Peptide vaccine	Memorial Sloan-Kettering Cancer Center
Bevacizumab	First with pemetrexed and cisplatin	II/III	Monoclonal antibody to VEGF	Intergroupe Francophone de Cancérologie Thoracique
Cediranib	First with pemetrexed and cisplatin	I/II	VEGFR and PDGFR tyrosine kinase inhibitor	Southwest Oncology Group
Thalidomide	Maintenance	III	Anti-angiogenesis	Netherlands Cancer Institute

Abbreviations: mTOR, mammalian target of rapamycin; PDGFR, platelet-derived growth factor receptor; VEGF, vascular endothelial growth factor; VEGFR, vascular endothelial growth factor receptor.