Review Article

Current Therapies for Malignant Mesothelioma

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Abstract

Malignant mesothelioma (MM) is a deadly cancer caused by asbestos exposure that is increasing worldwide. Early diagnosis for this cancer is very difficult and MM is mostly resistant to conventional therapies. A host of factors may be responsible for development of MM and imparting drug resistance to this cancer. Understanding these processes will be important in designing therapeutic approaches for MM. Some of the conventional as well as current approaches for MM therapy are discussed in this review.

Introduction

Malignant mesothelioma (MM) is caused by asbestos-exposure to mesothelial cells of pleural or peritoneal cavity. Asbestos exposure is the contributory factor for MM for more than 80% of reported cases. Other less popular causes for MM include viruses, radiation, chemicals and familial susceptibility. The origin cell for MM is mesothelial cell, which is functionally diverse flat and thin cell and provides a protective layer to internal organs. Asbestos fibers once inhaled can make their way to lung pleura by unknown mechanisms to affect mesothelium layer of pleura and cause MM. As asbestos fibers cannot be metabolized they do not act like most chemical carcinogens. How asbestos fibers promote MM development may involve many mechanisms, however, the most accepted one is the induction of inflammation and signaling pathways important in transformation by reactive oxygen species (ROS) generated by asbestos fibers. Latency period for development of MM is from 10-50 years after asbestos exposure. MM is normally diagnosed at a late stage and has a poor prognosis with a median survival of 9-13 months. The annual incidence rate of MM in United States is plateaued to ~3000 cases/year, however, it is still increasing in many parts of the world. MM is mostly unresponsive to currently available treatment options and therefore there is an emergent need to develop effective therapeutic options to treat this deadly cancer. In the present review we compiled the information available in literature related to current therapies available for MM treatment.

Conventional Therapies for Malignant Mesothelioma

Surgery

Currently the only potentially curative treatment available for MPM is surgical resection of the tumor. Majority of patients who are diagnosed with MPM are unfortunately unable to undergo surgical resections due to the advanced spread of the disease; in these cases, palliative surgery may be employed to relieve or prevent the symptoms. In pleural MM, multiple tumor migratory factors promote the development of intracavitary tumors rather than distal metastasis, as seen in other cancers [1]. Therefore, in patients who are candidates for surgery, surgical or cytoreductive procedures such as extrapleural pneumonectomy (EPP), pleurectomy/decortication (P/D), or general debulking are employed.

EPP, also known as *en bloc* resection, offers the best chance to potentially remove all of the cancer in patients with resectable mesothelioma of the epithelioid type, whose cancer has not yet metastasized to the lymph nodes. These extensive surgeries are usually performed at large tertiary referral centers, in which surgeons remove the pleura lining the chest wall, part of the diaphragm, the pericardium, nearby lymph nodes, and the whole lung on the side of the tumor. This allows for the delivery of concentrated hemithorasic radiotherapy postoperatively [2]. Pleurectomy is a less extensive operation in which all of the parietal pleura lining the chest wall (on the side of the tumor) are removed. The visceral pleura on the affected lung are also removed, as is the pleura coating the mediastinum and the diaphragm. Since the lung and diaphragm are not removed, one drawback of the procedure is that high dose radiotherapy can't be delivered due to the risks of lung toxicity. Decortication is mainly done for palliation of pain due to the rapid accumulation of pleural effusions. It involves the placement of a thoracotomy tube for pleural fluid drainage and followed by the obliteration of the pleural space with an irritant via video thoracoscopy.

Patients with diffuse malignant peritoneal mesothelioma (DMPM), who make up 20% of MM diagnoses, are usually also diagnosed in the late stages of the disease. The combination of cytoreductive surgery, followed by recent advances in hypothermic intraperitoneal chemotherapy with cisplatin and doxorubicin has shown to improve overall survival [3]. This procedure allows for the administration of high dose chemotherapy while minimizing systemic toxicity of the agents.

Chemotherapeutic agents

The current standard of care for patients with advanced level (non-resectable) MPM is systemic chemotherapy. The only first line chemotherapy regimen approved by the FDA is cisplatin with an anti-folate agent such as pemetrexed or raltritrexed [4,5]. Carboplatin, another platinum based analog, has also been shown to be an alternative in some phase II studies [6]. Regardless of this, it has to be emphasized that the median response rate of chemotherapy is still only 30% and its impact on overall survival rates has been insignificant [7]. Additionally, there has been no second-line treatment that has proven to be superior to supportive care.

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Novel & Experimental Therapies for Malignant Mesothelioma

Epigenetic modulations

It has been known for some time that direct genomic alterations are a major player in oncogenesis. But recent evidence has shown that modifications of DNA and their associated proteins that do not involve a change in the DNA sequence can have a major role in tumorogenesis. These changes (such as DNA methylation and/or histone deacetylation) are stable and heritable modifications in gene expression resulting in spatial and temporal control of gene activity required for homeostasis of complex organism [8]. Unlike genetic alterations, epigenetic modifications require active maintenance and are potentially reversible, making for therapeutic targets in MPM. Multiple DNA methyltransferases (DNMTs) and histone deacetylases (HDACs) control tumor suppressor genes via chromatin compaction and gene silencing. Thus, inhibition of these molecules can lead to alteration of gene expression and changes in cellular proliferation, differentiation, and apoptosis. HDAC inhibitors can induce cell death through caspase activation and also via the production of reactive oxygen species. Additionally, HDAC inhibitors cause hyperacetylation of non-histone proteins which inhibit angiogenesis, invasion, and motility of tumor cells [8]. Multiple studies have shown significant *in-vitro* apoptosis of MPM cells, and decreased tumorogenesis in xenograft mice models using DNMT and HDACs inhibitors, both alone and in combination [9].

Most clinical trials using these inhibitors have only reached phase I or early phase II due to their toxicity profiles and undesired side effects. In a phase II trial, Belinostat, a class I and II HDACs inhibitor was not effective as a monotherapy against recurrent MPM [10]. A promising phase II trial using the pro-apoptotic effects of valproic acid in combination with doxorubicin in refractory MPM patients showed good tolerability and a 16% response rate, with a rate of disease control of 36% [11]. A large randomized phase III trial comparing oral vorinostat, a HDAC inhibitor, to placebo in patients who relapsed after a first-line therapy failed to demonstrate overall survival benefits of patients with MPM (NCT00128102). A small phase I study combining vorinostat and first-line treatment regimen (cisplatin /pemetrexed) was started in patients with MPM, but was ended due to unclear reasons (NCT01353482).

It is clear from the available literature that clinical trials with HDAC inhibitors alone were discouraging. However, there may be some potential in combination of these inhibitors with conventional therapies, a possibility yet to be tested.

Signaling pathway inhibitors

Targeted molecular-level therapy has been studied extensively in MPM patients. It has been known for some time that MPM cells express high levels of epidermal growth factor receptor (EGFR), and secrete platelet derived growth factor (PDGF). Though, phase II trials using EGFR receptor tyrosine kinase (RTK) inhibitors such as gefitinib and erlotinib, or the PDGFR inhibitor imatinib as single agent first-line therapies have failed repeatedly [12,13]. The requirement of simultaneous activation of multiple RTKs (especially EGFR and MET), or modifications that cause activation of molecules downstream of RTKs have been implicated as reasons for the inefficacy of these single agent targeted therapies [14]. Also, it has been shown that mesothelioma patients lack mutations in the EGFR kinase domain, explaining the possible insensitivity to EGFR inhibitors [15].

Multiple inhibitors are currently under clinical trial: Dovitinib (Agent TKI258) is a potent small-molecule inhibitor of multiple class-III receptor tyrosine kinases (RTKs), fibroblast growth factor receptors (FGFR-1 to 3), VEGFR-1 to 3, PDGFR-β, and c-Kit. In previously studied in-*vitro* and *in-vivo* models, Dovitinib has exhibited inhibition of tumor cell proliferation, induction of apoptosis, and potent solid tumor-growth inhibition [16]. Multiple phase II trials are underway for different solid tumors such renal cell carcinoma (NCT01223027), advanced breast cancer (NCT00958971), and urothelial cancer (NCT00790426). A phase II trial testing Dovitinib as a single agent in second/third-line treatment for advanced MPM using progression-free survival is currently in the accrual phase (NCT01769547).

PF-03446962 (Pfizer) is a fully human monoclonal antibody against Activin receptor-like kinase 1 (ALK1) with dose-dependent antiangiogenic activity as demonstrated in studies in a human xenograft mouse model. ALK1 is a transforming growth factor β (TGF-β) type I receptor, and along with endoglin, a TGF-β co-receptor, plays an essential role in vascular development and pathological angiogenesis [17]. Previous studies have shown that patients with advanced malignancies tend to have increased numbers of ALK1-positive circulating endothelial cells [18]. A recently completed phase I trial (NCT00557856) testing the efficacy of the PF-03446962 in advanced malignancies showed that the anti-hALK1 antibody reduced the amount of these ALK1-positive circulating endothelial cells. Also of importance, partial responses were observed in three patients who had previously received antiangiogenic therapies. Based on these results, a Phase II clinical trial in patients with advanced MPM who have already been treated with cytotoxic chemotherapy is currently ongoing (NCT01486368).

Cixutumumab (Agent IMC-A12) is a fully human IgG1 monoclonal antibody that binds to insulin-like growth factor 1 receptor (IGF-1R), induces internalization, and causes degradation of the receptor. IGFs have long been implicated in the tumorogenesis of many different cancers. Previous studies have shown that signaling via the IGF-I binding to IGF-IR leads to activation of the phosphatidylinositol 3-kinase (pI3K)/Akt pathway, which results in cell proliferation, invasion, chemoresistance, and metastasis [19]. A recent study characterized the antiproliferative properties of Cixutumumab against IGF-IR expression in mesothelioma using tumor cells obtained from patients as well as established cell lines. The authors also demonstrated using *in-vivo* models that cixutumumab treatment attenuated the growth of mesothelioma tumor xenografts in mice compared to the control groups [20]. A phase II clinical trial of cixutumumab as a single agent in patients with MPM who have failed standard therapy is currently ongoing; it's determining the response rate as the primary measure and the progression-free survival as the secondary measure (NCT01160458).

NGR-hTNF-α is a peptide-tumor necrosis factor-α fusion protein, constructed by fusing the N terminal of TNF-α with the C terminal of the cyclic tumor-homing peptide NGR (asparagine-glycine-arginine). This peptide is a selective ligand of an aminopeptidase N/CD13 isoform overexpressed by endothelial cells of most solid tumors [21]. CD13 is a key metalloprotease involved in tumor invasion and angiogenesis, thus making for a good target. TNF-α has long been known to have antitumor activity, which is mainly mediated through apoptosis of tumor endothelial led by caspase activation [22]. An initial phase I trial testing the dose response, kinetics, and safety of the drug demonstrated good tolerability [23]. A phase II study of low dose NGR-hTNF-α versus placebo as maintenance treatment in patients with advanced

MPM (previously treated with pemetrexed) is currently in the accrual phase (NCT01358084). A randomized double-blind phase III study of NGR-hTNF-α plus Best Investigator's Choice (BIC) versus placebo plus BIC in previously treated patients with advanced MPM is also ongoing, with the primary measure of overall survival (NCT01098266).

GSK2256098 is a potent and specific small molecule inhibitor of focal adhesion kinase (FAK), which may prevent the integrin-mediated activation of several downstream signal transduction pathways, including ERK, PI3K/Akt, and JNK/MAPK, thereby inhibiting tumor cell migration, proliferation and survival, and tumor angiogenesis. Normal activation of FAK is via binding to integrins in the extracellular matrix, but is upregulated and constitutively activated in advanced level solid tumors and is correlated with poor prognosis. In tumor cells, attenuation of FAK expression results in lack of adhesion and apoptosis, suggesting that a FAK-dependent signal is required for tumor cell growth. Furthermore, an activated form of FAK leads to resistance to programmed cell death [24]. Interim clinical trials with the agent have determined that it is well tolerated with evidence of clinical activity; pharmacokinetic studies support BID dosing (**J Clin Oncol 30, 2012 suppl; abstract 3000**). A recently started phase I multicenter trial to determine maximal tolerated dose and the recommended Phase 2 dose and regimen for the combination of oral MEK inhibitor trametinib, and the oral FAK inhibitor GSK2256098, in MPM patients with advanced disesease is in the accrual phase (NCT01938443).

Anti-angiogenesis agents: The role of angiogenesis is well defined in MPM. It has been demonstrated that amongst solid tumors, MPM tumors express some of the highest levels of vascular endothelial growth factor (VEGF). Studies have further demonstrated increased angiogenesis, assessed via microvascular density, as an independent factor predicting poor prognosis [25]. VEGF RTK inhibitors, and chemotherapy along with single-agent monoclonal antibodies against VEGF (such as bevacizumab) have been tried in phase I/II clinical trials with failed results [26,27].

Cediranib (Agent AZD2171) is an oral pan-VEGF receptor tyrosine kinase inhibitor, which in a recently completed Phase II trial (NCT00243074) in patients with MPM who had received platinum-based systemic chemotherapy showed modest clinical activity as a single agent; 9% of patients had objective tumor response, 34% had stable disease, and 43% had disease progression [28]. Given these results, a new phase I/II trial looking at cediranib in combination with cisplatin and pemetrexed in chemo-sensitive MPM patients is in the accrual phase (NCT01064648).

Nintedanib (Agent BIBF 1120) is a triple angiokinase inhibitor. It is an indolinone-derived drug that targets VEGFRs 1-3, FGFR 1-3, and PDGFR α and β. Nintedanib inhibits mitogen-activated protein kinase and Akt signaling pathways in three cell types (endothelial cells, pericytes, and smooth muscle cells) contributing to angiogenesis, resulting in inhibition of cell proliferation and apoptosis. Compared to other drugs in its class, it also has a distinct pharmacodynamic feature, it shows sustained pathway inhibition after single dosing [29]. Multiple phase II and III clinical trials are underway for different solid tumors. Phase III trials (LUME-Lung 1 and 2) are investigating the use of nintedanib in combination with the existing chemotherapy agents patients with non-small cell lung cancer, and in combination with carboplatin and paclitaxel as a first line treatment for patients with ovarian cancer. A double blind randomized phase II trial was recently started in MPM patients with advanced disease. It's testing Nintedanib in combination with pemetrexed and cisplatin followed by continuing nintedanib monotherapy, versus placebo in combination with pemetrexed and cisplatin followed by continuing placebo monotherapy. Primary outcome is the progression-free survival measured from the time of randomization to the time of disease progression or death of any cause (NCT01907100).

Immunotherapy: Immunotherapeutic approaches in dealing with tumors have been gaining major ground due to their specificity for cancer cells, and low potential for harming normal tissue. Although a detail description of this subject is beyond the scope of this mini review, a few current ones are worth mentioning.

Tremelimumab is monoclonal antibody to cytotoxic T-lymphocyte antigen 4 (CTLA4) and has been shown to have therapeutic activity in different tumor types. First clinical trial of tremelimumab in MM patient (NCT01655888) showed small effect size but encouraging evidence in support of the clinical and immuniological activity of this antibody in pre-treated MM patients [30]. Based on findings from the first trial authors have launched another study to explore the effect of a more intensive tremelimumab treatment schedule in second-line MM patients and results are awaited [31].

WT1 vaccine is a transcription factor that is specifically overexpressed in MMs as compared to normal tissues. WT1 peptide analog vaccination in MPM patient induced immune response with minimal toxicity. Six out of 9 MPM patients tested showed CD4 T-cell proliferation in response to WT1 peptides [32]. Ongoing clinical trial is evaluating WT1 vaccine based immunotherapy in MM (NCT01265433).

SS1 (dsFv) PE38 (SS1P) is a chimeric recombinant immunotoxin comprising of anti-mesothelin disulfide-stabilized murine-antibody Fv fused to PE38, a 38-kDa portion of *Pseudomonas exotoxin*. Mesothelin is an important target for tumor specific immunotherapy as it is highly overexpressed in many cancers including MMs as compared to normal mesothelial cells. A response rate of 50% was observed in a trial of SSIP with 6 cycles of pemetrexed and cisplatin in front-line therapy for patients with advanced MM. Unfortunately generation of neutralizing antibodies to SSIP within 3 weeks ceased the trial. Recent developments indicate that host immune depletion can safely prevent anti-immunotoxin antibody formation [reviewed in] [33].

Amatuximab (MORAb009) is a fully humanized, high affinity monoclonal chimeric antibody targeting mesothelin. It has shown promise in preclinical studies and was well tolerated in phase I study with low incidence of immunogenicity [34].

Conclusions

There is no doubt that MM is a tumor of very complex nature associated with asbestos exposure. Abatement of asbestos use is the best way to curtail MM tumor development; however that is not always possible. The best possible next step is to understand this disease better so that more effective treatment options are made available. A coordinated approach by physicians and scientists to understand pathogenesis of MM may result in combined therapeutic options for this disease.

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