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Molecular-Targeted Therapy For Malignant Mesothelioma

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Abstract

Malignant pleural mesothelioma (MPM) is an intractable disease associated with asbestos exposure, and the number of affected patients will increase in the coming decades. The clinical outcome associated with current treatments is unsatisfactory, and the chemotherapy regimen for mesothelioma has remained unchanged for the past 10 years. Emerging molecular-targeted therapies are a novel way to treat other types of tumors and have been shown to drastically improve clinical response and patient prognosis. Some of these targeted agents had promising effects on MPM at the preclinical level and in various clinical trials that have been conducted over the last decade. Contrary to our expectations, results from the majority of these studies were disappointing and many were terminated at an early stage. No useful predictive or prognostic biomarkers were identified for mesothelioma treatment. Nevertheless, some novel strategies involving focal adhesion kinase inhibitors and immune checkpoint targeting agents showed some antitumor effects. In this article, we review the outcomes of previous clinical trials using molecular-targeted agents and discuss several hurdles that need to be overcome, which hopefully will contribute to a better understanding of this rare malignancy.

Keywords

biomarker, mesothelioma, molecular-targeted therapy

Introduction

Malignant pleural mesothelioma (MPM) is a rare tumor with a dismal prognosis, which is associated with asbestos exposure for the majority of affected patients. Many industrial countries have already prohibited asbestos use, but its use in developing countries is increasing. Russia, China, and Brazil, for example, use large amounts of chrysotile, an asbestos mineral, and export it to other countries and areas that do not have strict controls on its usage. Therefore, the numbers of patients with MPM are increasing, and there are concerns that MPM will be a worldwide health care problem in the future.[1]

Malignant pleural mesothelioma has a long latency period of 20 to 40 years, and morbidity is expected to peak within the next 2 decades in industrialized countries such as the United States and the European Union countries. The majority of patients are diagnosed at an advanced stage because the signs and symptoms are nonspecific during the early stages. Malignant pleural mesothelioma diffusely invades the thoracic wall, disturbs the functions of vital organs such as the heart and great vessels, and causes pericardial and pleural space effusions, all of which can cause considerable deterioration of a patient's quality of life (QOL).

Current Therapy for Mesothelioma

Extrapleural pneumonectomy (EPP) is a standard surgical procedure for MPM and is suitable only for those with early-stage disease and a good performance status. However, such an aggressive procedure impairs the patient's QOL and restricts daily life because it decreases the respiratory capacity. In addition, intrathoracic recurrence frequently occurs even after this radical operation. Pleurectomy/decortication (P/D), a peeling-off procedure to free the lung from the tumor, is a less invasive surgery than EPP, but postoperative recurrence is inevitable. Thus, the operation is recommended in palliative care to relieve dyspnea or thoracic pain.

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Abbreviations

MPM	(malignant pleural mesothelioma)
RR	(response rate)
TTP	(time to progression)
PFS	(progression free survival)
OS	(overall survival)
CR	(complete response)
PR	(partial response)
SD	(stable disease)
PD	(progressive disease)
ORR	(objective response rate = CR+PR)
DCR	(disease control rate = CR+PR+SD)
TKI	(tyrosine kinase inhibitor)
CTCAE	(Common Terminology Criteria of Adverse Events)

Furthermore, a recent study showed that EPP did not prolong patient survival when compared to P/D.[2] Collectively, these data indicate that surgical procedures have little clinical benefit, and surgery as a monotherapy is not an option for patients with MPM.

Current therapeutic modalities involve a combination of surgery, irradiation, and chemotherapy. Recently, a trimodality therapy consisting of induction chemotherapy, followed by EPP and sequential irradiation demonstrated favorable long-term outcomes for those who completed all of the treatment, and some patients survived for more than 2 years.[3] However, although 65% of the registered patients received all of the modalities, the study excluded those at an advanced stage or those who had a low performance status. Consequently, this aggressive combination therapy is suitable only for patients with early-stage disease.[4]

The current treatment for advanced-stage MPM is chemotherapy. Few agents have achieved an objective response rate (ORR) greater than 10%, and these results were based on small-scale phase II studies.[5] Nevertheless, the combination of cisplatin and pemetrexed achieved a favorable outcome in terms of response rate (RR), time to progression (TTP), and overall survival (OS) compared with cisplatin alone (RR, 41.3% vs 16.7%; TTP, 5.7 months vs 3.9 months; and OS, 12.1 months vs 9.3months).[6] Therefore, this phase III trial has been regarded as a benchmark study for the last 10 years, and the combination of cisplatin and pemetrexed is accepted as the first-line regimen for MPM. Carboplatin plus pemetrexed is another option for those who are intolerable to cisplatin-mediated toxicity, since this combination has a similar efficacy to the cisplatin-based regimen (disease control rate [DCR], 65.7%; TTP, 6.5 months; OS, 12.7 months).[7] Raltitrexed, another antifolate agent, was tested in combination with cisplatin and achieved an almost equivalent clinical outcome to pemetrexed.[8] Although raltitrexed is more cost effective than pemetrexed, the latter is still commonly used in clinics worldwide.

Almost all inoperable cases progress to an advanced stage, even during chemotherapy, or show recurrence after completion of first-line chemotherapy. No clinical study has demonstrated a feasible second-line agent, and none have been approved by the United States Food and Drug Administration.[9] Repeat chemotherapy with the same first-line agents is generally acceptable as a treatment for small cell lung cancer, where the TTP is greater than 3 months. The efficacy of treating such sensitive relapse cases with the same agent has not been demonstrated in MPM studies. Pemetrexed can be included as a second-line agent if it has not been already administered and it is frequently used as a first-line treatment, and either gemcitabine or vinorelbine is used as a second-line treatment.[10] However, a study has shown that the efficacy of gemcitabine or vinorelbine is in fact lower than that previously reported. The overall ORR was 2%, and the progression-free survival (PFS) and OS rates for gemcitabine were 1.6 and 4.9 months, respectively, and those for vinorelbine were 1.7 and 5.4 months, respectively.[11]

Advances in the molecular analyses of non–small-cell lung cancer led to the development of a new agent that blocks tumor-specific molecules. Tyrosine kinase inhibitors (TKIs) target the mutated epidermal growth factor receptor (EGFR) or the echinoderm microtubule-associated protein-like 4 anaplastic lymphoma kinase fusion gene.[12] The TKIs dramatically changed cancer treatment resulting in a shift from cytotoxic chemotherapy to molecular-targeted therapy. The efficacy of antiangiogenic agents in several types of cancer was also examined, and some were used at a clinical level.[13-15]

Most recently, inhibition of immunological checkpoints such as cytotoxic T lymphocyte-associated protein 4 (CTLA-4) and programmed cell death 1 (PD-1) molecules produced long-lasting antitumor effects, and consequently, we realized that immunotherapy can play a central role in cancer treatment.[16] Similarly, an investigation into MPM at the molecular level led to several clinical trials with molecular-targeted agents.

Antiangiogenic Agents and Kinase Inhibitors

A number of preclinical models have demonstrated an important role for angiogenic factors in the progression of MPM.[17] Currently, several clinical trials are examining angiogenesis inhibitors for use as first-line agents or for those who failed to respond to an initial treatment modality. In other types of cancer such as lung cancer, monotherapy with antiangiogenic agents showed only modest effects, and consequently, they are used in combination with chemotherapy.

Bevacizumab

Bevacizumab is a humanized monoclonal antibody against the vascular endothelial growth factor (VEGF) and is widely used in various types of cancer including colorectal cancer, non–small-cell lung cancer, breast cancer, and gynecologic cancer.[13-15] The VEGF stimulates mesothelioma cell growth

in vitro in a dose-dependent manner, and the anti-VEGF antibody inhibits the growth.[18] Furthermore, immunohistochemical staining (IHC) of MPM surgical specimens showed high expression levels of VEGF in all of the solid tumors tested, and these levels were negatively correlated with the prognosis.[19] These data indicated that VEGF was an ideal target in MPM treatment. One phase I and 2 phase II trials studied the effect of adding bevacizumab to the cisplatin and pemetrexed,[20] carboplatin and pemetrexed,[21] and cisplatin and gemcitabine[22] chemotherapy regimens in patients with MPM. Patients in each study showed good tolerability to adverse events including exacerbation of hypertension, proteinuria, and stomatitis. Nevertheless, none of the studies demonstrated an improvement in the RR or OS rates. Further analysis of patient subpopulations showed that those with high circulating serum VEGF levels had a shorter PFS and OS than those with low VEGF levels,[22] but the other 2 studies did not support this conclusion.[21]

Thalidomide

Thalidomide is an oral antiangiogenic agent used for the treatment of multiple myeloma. It is a multitargeted inhibitor of VEGF and fibroblast growth factor (FGF). A phase II study with thalidomide as a monotherapy was conducted on 40 patients with MPM. None of the patients showed a partial response (PR), and 27.5% showed stable disease (SD) that lasted 6 months, and the median OS was only 7.6 months. The adverse effects were relatively mild, mostly grade 1 or 2 (Common Terminology Criteria for Adverse Events, version 3.0) nonhematologic toxicities including drowsiness, constipation, and dry mouth.[23] Maintenance therapy with thalidomide after first-line chemotherapy did not produce additional benefits when compared to best supportive care.[24] Patients with decreased VEGF levels during the treatment showed a long survival period,[25] although the clinical usefulness of serum VEGF levels as a predictive marker remains unknown.

Dasatinib

Dasatinib is an orally administrable agent that inhibits BCR/Abl and the Src family of tyrosine kinases and also suppress the kinase function of the platelet-derived growth factor receptor (PDGFR). It is approved as a first-line drug for patients with chronic myelogenous leukemia (CML). In general, inhibition of c-Src induces apoptosis and cell cycle arrest and reduces migration of cancer cells.[26] The PDGF promotes the growth of MPM cells in vitro in an autocrine and paracrine manner.[27] The efficacy of dasatinib as a monotherapy was investigated in a phase II study that enrolled 46 inoperable patients with MPM. The PR, SD, and PD rates were 5%, 28%, and 42%, respectively. The DCR (DCR = CR + PR) was 32.6% and the PFS rate at 24 weeks was only 23%. The adverse events including gastrointestinal symptoms, peripheral edema, pleural effusion, and general malaise were tolerable. Thus, the clinical efficacy of dasatinib was limited and a further study was not reported thereafter.[28]

Sorafenib

Sorafenib was originally developed as a Raf kinase inhibitor. It is an oral multitargeted TKI of the RAS/RAF/MEK and c-Kit pathways. In addition, it has antiangiogenic effects as it inhibits Vascular Endothelial Growth Factor Receptor VEGFR1/2 and Platelet-Derived Growth Factor Receptor Beta PDGFRβ. This agent has been used clinically as part of the standard treatment for renal cell carcinoma, hepatocellular carcinoma, and thyroid cancer. The efficacy of sorafenib was examined in 51 patients with MPM. The PR and SD rates were 6% and 54%, respectively, and the median PFS and OS were 3.6 and 9.7 months, respectively. No *BRAF* mutations were detected in any of the MPM biopsy samples used in this study. Toxicities greater than grade 3 were general fatigue and hand–foot skin rashes. As demonstrated in hepatocellular carcinoma, high expression of ERK1/2 detected by IHC staining in clinical specimens correlated with a long survival period, although the expression level did not predict response to sorafenib.[29] Recently, another group conducted a phase II study of patients pretreated with platinum-containing chemotherapy and showed that the median PFS period was 5.1 months, and the treatment was well tolerated.[30]

Sunitinib

Sunitinib is an orally administrable small-molecule multitargeted inhibitor of receptor tyrosine kinases (RTK) that affects VEGF- and PDGF-mediated signaling. Sunitinib was approved as an agent for renal cell carcinoma and imatinib-resistant gastrointestinal stromal tumors (GIST). Its efficacy was examined in 35 patients with MPM who were either previously treated with cytotoxic chemotherapy (cohort 1) or remained untreated (cohort 2).[31] The PFS and OS were 2.8 and 8.3 months, respectively, for cohort 1, and 2.7 and 6.7 months, respectively, for cohort 2. Toxicities were relatively mild and included gastrointestinal complaints, hand–foot skin rashes, and general fatigue. The ORR was not reported. The investigators concluded that the existence of some patients who were high responders suggested a feasible clinical application for this agent, but further study was required to identify biomarkers for this subset of patients.

Cediranib

Cediranib is an oral pan-VEGF receptor (VEGFR1/2/3) TKI. In addition to VEGFR, it inhibits c-Kit and PDGFRβ kinases. Phase III studies with cediranib were conducted on non–small-cell lung cancer,[32] colorectal cancer,[33] and relapsed ovarian cancer.[34] Its efficacy was also examined in a phase II clinical trial of 47 patients with MPM. The PR, SD, and PD rates were 9%, 34%, and 43%, respectively. The median PFS and OS were 2.6 and 9.5 months, respectively.[35] The

toxicities were similar to those caused by bevacizumab, which included hypertension, proteinuria, general fatigue, and gastrointestinal symptoms. The effects were similar to other antiangiogenic agents, and there were some high responders in the study with an improved clinical response.

Vatalanib

Vatalanib is an oral inhibitor of all of the VEGF receptors, especially VEGFR2, and PDGFRβ and c-Kit. The efficacy of vatalanib was examined in 47 chemo-naive patients with MPM in a phase II clinical trial. The PR and SD rates were 6% and 2%, respectively. The median PFS and OS were 4.1 and 10 months, respectively. Toxicities greater than grade 3 were mainly gastrointestinal symptoms such as nausea and vomiting. The serum levels of VEGF, PDGF, and mesothelin were not associated with the RR or patient prognosis.[36] No further studies on MPM treatment with vatalanib have been conducted.

Other Types of Molecular-Targeted Agents

Bortezomib

Bortezomib is a proteasome inhibitor used in the treatment of multiple myeloma, and it is currently under clinical investigation in various types of malignancy.[37,38] Bortezomib increased the in vitro cytotoxicity of cisplatin and pemetrexed in MPM cells.[39] Acquired resistance to bortezomib was attributed to the upregulated Bcl-2 protein interacting with the mediator of cell death (Bim) protein.[40] There were 2 clinical trials evaluating the effects of bortezomib on MPM: one involved first-line monotherapy but did not produce any objective response in 10 patients, and the other involved second-line treatment for 23 patients where the PR and SD rates were 4.8%, and 4.8%, respectively, while the majority had PD. The median PFS and OS were 2.1 and 5.8 months, respectively.[41] Bortezomib was also tested in combination with cisplatin and pemetrexed in 82 patients, and the study showed that the ORR was 28.4%, and the median PFS and OS were 5.1 and 13.5 months, respectively.[42] The toxicities of bortezomib were numerous and included hyponatremia, hypokalemia, fatigue, thrombocytopenia, neutropenia, and peripheral neuropathies. The investigators in these 2 trials concluded that a further study was not warranted unless there was appropriate patient selection for monotherapy or combination treatment.

Imatinib

Imatinib mesylate is an inhibitor of the breakpoint cluster region-Abelson (BCR/Abl), PDGF, and c-Kit tyrosine kinases and has been used to treat CML and GIST. The majority of MPM specimens showed high expression of PDGFβ following IHC staining.[43] The efficacy of imatinib monotherapy was examined in 25 patients with MPM in a phase II clinical trial. The PR and SD rates were 0% and 12%, respectively, and the median OS was 398 days.[44] The adverse events, which included nausea, diarrhea, constipation, and edema were relatively mild. Recently, the results of a phase I study of imatinib in combination with cisplatin plus pemetrexed were reported.[45] High expression of PDGFα by IHC staining correlated with a long OS. Unfortunately, the majority of participants could not tolerate this triplet therapy, and further studies have not been carried out.

Epidermal Growth Factor Receptor TKIs

Epidermal growth factor receptor TKIs are key drugs for the treatment of non–small-cell lung cancer with constitutively active EGFR mutations. The EGFR is highly expressed in many types of cancers and in malignant mesothelioma. At the preclinical level, both gefitinib and erlotinib inhibited cell proliferation and cell migration induced by transforming growth factor (TGF) α.[46] The efficacy of gefitinib was investigated in 42 previously untreated patients with MPM in a phase II trial. The CR, PR, SD, and PD rates were 2%, 2%, 49%, and 35%, respectively, and thus, the ORR was only 4%. The median survival and failure-free survival rates were 6.8% and 2.6 months in epithelial-type MPM, respectively, and 2.7% and 1.7 months in sarcomatoid-type MPM, respectively.[47] Erlotinib was administered to 33 patients with MPM, and SD and PD were observed in 42% and 45% of patients, respectively, but there was no ORR. The median PFS and OS were 2 and 10 months, respectively, while the 1-year survival rate was 43%.[48] A study using a combination of erlotinib and bevacizumab in 24 patients with MPM showed that the ORR was 0%, and the median PFS and OS were 2.2 and 5.8 months, respectively.[49] There was no correlation between the EGFR expression levels in the tumor specimens and treatment effects. Previous studies have demonstrated that *EGFR* mutations in the kinase domain were associated with a good response to EGFR-TKI therapy in non–small-cell lung cancer, but EGFR expression and gene amplification levels were not.[50,51] Similarly, a poor response to EGFR-TKI treatment in cases with MPM can be attributable to the fact that the majority of MPM cell overexpress EGFR but do not have active *EGFR* mutations. The clinical significance of the EGFR expression levels in MPM remains unclear, and it has not been shown to be a prognostic factor. Nevertheless, EGFR expression is often associated with a good performance status, and it is detected in epithelioid—but not sarcomatoid-type MPM, which are both favorable prognostic indicators.[52]

Histone Deacetylase Inhibitors

Inhibition of histone deacetylase (HDAC) induces histone acetylation and results in gene expression associated with apoptosis and cell cycle arrest. It also inhibits tumor angiogenesis mediated by VEGF. Vorinostat is a small molecule inhibitor of HDAC I and II, and it is approved for the treatment of cutaneous T-cell lymphoma. Vorinostat downregulates the expression of an antiapoptotic protein, a caspase 8

inhibitor, and FLICE-like inhibitory protein[53] and increases sensitivity to chemotherapeutic agents in a 3-dimensional spheroid culture system.[54] A phase I clinical trial evaluated the efficacy of vorinostat in 13 patients with MPM, and 2 non-MPM patients showed a PR (ORR = 15.3%).[55] Belinostat, another HDAC I and II inhibitor, was tested in 13 patients with MPM. The ORR and SD rate were 0% and 15.4%, respectively, which did not meet the criteria to proceed with a further clinical study. The median PFS and OS were 1 and 5 months, respectively.[56] The investigators concluded that belinostat was not effective as a monotherapy for MPM, and its efficacy should be evaluated as part of combination therapy or in an alternative treatment schedule.

Mammalian Target of Rapamycin Inhibitors

The phosphatidylinositol 3 kinase (PI3K)/Akt/mammalian target of rapamycin (mTOR) pathway plays a central role in cell growth, cell metabolism, immunity, and angiogenesis. Everolimus is an oral mTOR inhibitor that is used as an immunosuppressant in organ transplantation and also for the treatment of renal cell cancer, hepatocellular carcinoma, angiomyolipoma, and lymphangioleiomyomatosis.[57,58] The PI3K/Akt/ mTOR pathway is often activated in MPM cell lines, and its inhibition enhances the apoptosis of MPM cells in vitro.[59] Two phase II trials evaluating the effect of everolimus on MPM are ongoing (NCT00770120, NCT0102946) and their conclusions have not yet been reported.

Amatuximab

Mesothelin is a cell surface antigen highly expressed in epithelial-type MPM, and the serum level of mesothelin is a good prognostic indicator for these patients.[60] Expression of mesothelin is not limited to mesothelioma but is also detected in ovarian, lung, and pancreas cancers.[61] However, tumor specificity is especially high in MPM compared to the solid tumors, indicating that mesothelin is an ideal target for MPM treatment. The efficacy of amatuximab, an antimesothelin chimeric antibody, in combination with cisplatin plus pemetrexed was investigated in a phase II trial.[62] After 6 cycles of chemotherapy, patients who responded to chemotherapy or who had SD received amatuximab as a maintenance therapy until disease progression. The study enrolled 89 inoperable patients with MPM and showed that the PR and SD rates were 40% and 51%, respectively, and PFS and OS were 6.1 and 14.8 months, respectively. The study showed no significant improvement in PFS compared to the controls. The investigators concluded that a predictive biomarker was required before further clinical trials could take place.

Fibroblast Growth Factor Inhibitor

Fibroblast growth factor is involved in a variety of cellular processes including cell migration, cell proliferation, drug resistance, and angiogenesis, and it has an antiapoptotic effect. Squamous cell carcinoma of the lung, and head and neck, highly express FGF receptors 1 and 2 (FGFR1 and FGFR2).[63] The FGF is secreted by cancer cells and surrounding tissues and supports tumor growth in an autocrine and paracrine manner. High expression of FGF in the serum or pleural fluid was associated with poor survival in patients with MPM.[64] Half of MPM cell lines tested coexpressed FGF2 and FGFR1 and a FGF TKI, ponatinib, inhibited cell proliferation, clonogenicity, migration, and spheroid formation in vitro and in vivo.[65] In addition, suppression of FGF-mediated signaling have synergistic effects together with radiotherapy and chemotherapy. Thus, FGF inhibitors are promising agents for MPM treatment and a phase Ib clinical trial on solid tumors with a FGF inhibitor (FP-1039 GSK 3052230) as a monotherapy or in combination with cisplatin and pemetrexed chemotherapy commenced in 2013 (NCT01868022).

Focal Adhesion Kinase Inhibitor

Focal adhesion kinase (FAK) is phosphorylated in response to integrin engagement and stimulation by growth factors and mitogenic neuropeptides. The FAK signaling plays a role in attachment and migration of cells, and inhibition of the FAK pathway reduces cell migration and the metastatic ability of a breast cancer cell line.[66] Pathways activated by the extracellular matrix are crucial for the proliferation of cancer stem cells and for the maintenance of a favorable microenvironment or niche. Therefore, a FAK inhibitor can eliminate cancer stem cells. Defactinib is one of the FAK inhibitors and a COMMAND study, examining defactinib as a maintenance therapy to control mesothelioma is underway in the United Kingdom. In that study,[67] patients with MPM treated with 6 cycles of platinum plus pemetrexed will be stratified according to merlin expression and defactinib will be administered as a maintenance therapy. Merlin is the product of the neurofibromatosis type 2 (*NF2*) tumor suppressor gene and inhibits cell proliferation. Somatic mutations in *NF2*[67] which inhibit merlin expression are often found in samples with MPM. It will be interesting to know how merlin expression affects treatment with this FAK inhibitor.

Anti-CD26 Antibody

CD26 is a type II glycoprotein known as dipeptidyl peptidase IV. Expression of CD26 is detected on the cell surface of activating T cells and is found in various types of cancers including MPM. Indeed, 70% to 80% of MPM tissues express CD26 molecules, and stimulation of CD26-mediated signals enhances cell migration and proliferation, and inhibits cell apoptosis.[68] Expression of CD26 is limited to epithelial-type MPM, and its expression level is associated with sensitivity to chemotherapeutic agents.[69] At the preclinical level, anti-CD26 antibodies were effective in eradicating orthotopically implanted MPM tumors by antibody-dependent,

cell-mediated cytotoxicity, in addition to its direct antitumor effects.[70] A phase II study to evaluate the efficacy of the anti-CD26 antibody in MPM has been launched. Toxicity in a phase I study was mild, and there were no immunologic adverse reactions. Some patients had a long PFS, although the final outcome has yet to be reported.

Antibodies Targeting Immuno Checkpoints

Cancer uses several systems to evade host immune surveillance and antitumor immunity. Evasion mechanisms include loss of major histocompatibility complex antigens, secretion of immunosuppressive cytokines such as TGF-β and interleukin (IL)-10, recruitment of tumor-supporting macrophages (M2-macrophages), and elimination of T-cell responses through modulation of an immune checkpoint pathway. Previous immunotherapy for mesothelioma was focused on enhancing the inflammatory response; for example, instillation of IL-12 or interferon (IFN) α into the thoracic cavity directly induced tumor cell death and subsequently activated antitumor immunity.[71,72] However, this was often accompanied by adverse events such as fever, shivering, headache, and arthralgia.

Recently, novel immunotherapies targeting immune checkpoints that restore the host immune system and eliminate tumor cells have been developed. These immunotherapies have been tested in a variety of malignancies including melanoma, renal cell carcinoma, and non–small-cell lung cancer and are changing the therapeutic direction of cancer treatment.[16] Drugs targeting CTLA-4 and PD-1, and PDL-1, a key ligand for PD-1, are now being investigated in clinical trials.

Anti-CTLA-4 Antibody

Cytotoxic T lymphocyte-associated protein 4 is expressed on the surface of both cytotoxic and regulatory T cells. The extracellular domain of CTLA-4 resembles the CD28 ligand (L). The CD28–CD28L interactions induce co-stimulatory signals for the activation and proliferation of T cells. The CTLA-4 signaling pathway inhibits T-cell activation and induces a negative feedback mechanism. The TGF-β also induces expression of CTLA-4. Thus, inhibition of CTLA-4 restores antitumor immunity that were dampened by the tumor.[73]

The efficacy of tremelimumab, a monoclonal antibody against CTLA-4, was investigated in 29 chemotherapy-resistant advanced cases.[74] The CR and PR rates were 0% and 7%, respectively, but some patients showed a PR longer than 6 months. The median PFS and OS were 6.2 and 10.7 months, respectively. One patient achieved a PR although PD was diagnosed initially. Radiographic exacerbation during the initial phase seemed to be due to an activated immune response against the tumor. The clinical study did not produce any antitumor effects, but a stable PR was present after disease progression. Similar cases were also observed in a study on patients with melanoma, indicated that further investigation was required. A large-scale global study that will evaluate the efficacy of tremelimumab as a second- or third-line therapy has launched (NCT01843374).

Another CTLA-4 antibody, ipilimumab, has been widely tested in a variety of tumors including melanoma and lung cancer, but a study with mesothelioma has not yet been reported.

Anti-PD-1 and anti-PDL-1 Antibodies

The coinhibitory receptor, PD-1, and its ligand, PDL-1, play a key role in the downregulation of activated T cells as part of the immune response. Suppression of activated T cells in turn reduces autoimmunity and promotes self-tolerance in cancer immunology. Interestingly, many types of cancer cells express PDL-1 and evade host antitumor immunity by inducing the apoptosis of tumor-infiltrated T cells. Antibodies that block PD-1/PDL-1 signals reactivate the immune system and augment preexisting antitumor responses. A PD-1 inhibitor was used to treat metastatic non–small-cell lung cancer, melanoma, renal cell carcinoma, head and neck cancer, and Hodgkin lymphoma.[75,76] A possible association between the PDL-1 expression levels in the tumors and the prognosis or treatment responses was reported for lung cancer and melanoma, but further investigations are required to finalize the conclusions. There are more than 10 PD-1 antibodies including nivolumab which is available currently, but no MPM clinical trials have commenced. The expression level of PDL-1 in human mesothelioma cell lines varies and is not dependent on histological type. Also, the immunological significance of PD-1/PDL-1 signaling in mesothelioma needs further study.

Discussion

In the last decade, emerging molecular-targeted therapies changed the landscape of non–small-cell lung cancer treatment and shifted the focus to personalized medicine. EGFR-TK and anaplastic large cell kinase (ALK) inhibitors dramatically improved the PFS of patients with less toxicity than conventional chemotherapy. These advances in lung cancer treatment contributed to the further understanding of molecular abnormalities in MPM, and preclinical studies demonstrated the clinical feasibility of targeted therapy for patients with MPM. Based on these studies, a number of MPM molecular therapies were used as monotherapies or in combination with other modalities, mainly chemotherapeutic agents. In general, the ORR of these studies was approximately 10%, and more than 40% of patients achieved SD, although the clinical outcomes varied in the respective studies. The PFS was approximately 2 to 3 months, and these data did not indicate any significant advantage over controls treated with platinum-based chemotherapy.[77] Nevertheless, we need more time to accurately determine the efficacy of these molecular-targeted agents in MPM treatment because

a long test period was required for non–small-cell lung cancer. For example, it took up to 10 years to discover that a predictive factor for EGFR-TKI effectiveness was linked to a gain-of-function mutation in the *EGFR* in tumors, which was not present in nontumorous tissues. Similarly, studies on targeted therapy for malignant mesothelioma require meticulous classification of genetic differences and the identification of an appropriate biomarker, in contrast to conventional clinical studies with unrestricted patient enrollment. However, a comprehensive genetic analysis of mesothelioma found no active mutations in the *EGFR*, *EML-ALK*, *K-ras*, or *BRAF* genes,[78] and consequently, no specific targets have been identified.

One of the most difficult hurdles for a mesothelioma study is the relatively small number of eligible patients. We cannot expect high-quality medical evidence from clinical studies that have only enrolled 20 to 30 patients. Different conclusions have been reported by studies using such small numbers. We need to accumulate cases with MPM from clinical centers in each country or to establish an international consortium for clinical studies like the Lung Cancer Mutation Consortium for non–small-cell lung cancer. In the interim, this could be coordinated by the International Mesothelioma Interest Group.

In addition, we should develop a system to evaluate treatment efficacy. The use of radiographic responses to determine treatment efficacy is difficult for MPM because of the complex configurations of the tumor shapes. The modified Response Evaluation Criteria In Solid Tumors system is commonly used, but different assessments by different medical institutions and practitioners are inevitable.[79] The use of fluorodeoxyglucose positron emission tomography as an evaluation method is not well established, although it is now being introduced in a number of clinics. Semiquantitative analysis of metabolic response is more useful to evaluate treatment effects compared with conventional radiological assessments. The viability of tumor cells in the residual mass, especially during the early treatment period, may help when choosing the most appropriate chemotherapy regimen.[80] The implication of standardized uptake value changes following immunotherapy requires further study since the antitumor response is sometimes followed by a temporary exacerbation. Improved imaging technology is beneficial for large-scale studies to standardize criteria among institutes.[81]

Study enrollment according to histological types plays a crucial role in clinical evaluation. Almost all of the clinical trials enrolled patients with both epithelial and sarcomatoid types and analyzed the outcomes assuming that they were the same clinical entity. The sarcomatoid type is resistant to most treatment options, and these patients have a very poor prognosis compared with epithelial-type patients.[82] In fact, the current version of the MPM guidelines does not recommend clarification of the histological subtypes when evaluating treatment efficacy. However, the ORR for sarcomatoid MPM was at least half of those with the epithelioid phenotype, irrespective of the treatments used. Accordingly, studies that include a high population of the sarcomatoid type showed worse clinical outcomes than those with fewer numbers. A clinical study should be conducted which differentiates between the histological subtypes, similar to those that were carried out for lung cancer, to determine any differences between them.

We do not have a suitable prognostic biomarker for MPM, and currently, the serum mesothelin level is used worldwide since it reflects tumor volume and possibly, disease progression. However, its expression is limited to the epithelial type, and its diagnostic value is uncertain in the case of the sarcomatoid type or biphasic mesothelioma. Conjugation of the antimesothelin antibody with an anticancer agent (amatuximab) or mesothelin-targeted vaccination (CRS-207 [commercial name, GVAX])[83] may be a rational choice, as there is minimal mesothelin expression on the mesothelium. In addition, mesothelin-targeted therapy combined with either surgery or irradiation needs to be examined in a clinical setting.

At present, therapies targeting immune checkpoints are one of the promising MPM treatment strategies. Durable antitumor effects are desirable, especially after surgical resection. Mesothelioma cells produce a large amount of extracellular matrix by secreting TGF-β, which allows tumors to escape from immune cell-mediated attacks. This evading mechanism has hampered immunotherapy and inactivated IL-12 or IFN-α administered via the intrathoracic cavity. It is not yet clear how regulatory T cells suppress the immune response and contribute to immune tolerance in MPM. Emerging approaches using immunotherapy either as a single agent or together with other treatment modalities should result in a favorable outcome in the future. However, long-term prognosis and safety are important issues to be considered also.

Conclusion

Contrary to our initial expectations, most of the current molecular-targeted therapies only showed a modest benefit for patients with MPM and were not ready for use in clinical practice. The preclinical studies were promising, but the therapeutic benefits found in clinical studies, even when conventional treatments were also used, were limited as studies on other types of cancer have demonstrated. Further laboratory research is needed to find a more reliable biomarker and to collect genetic information of the invasion ability, possible interaction with surrounding tissues, cell death, drug sensitivity, and prognosis. Finally, global collaborative research is required so that a large-scale clinical trial can be conducted in the future.

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