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Scientific Advances and New Frontiers in Mesothelioma Therapeutics

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Abstract

Malignant pleural mesothelioma (MPM) is a rare and aggressive cancer that arises from the mesothelial surface of the pleural and peritoneal cavities, the pericardium, and rarely, the tunica vaginalis. The incidence of MPM is expected to increase worldwide in the next two decades. However, even with the use of multimodality treatment, MPM remains challenging to treat, with a 5-year survival rate of less than 5%. The International Association for the Study of Lung Cancer has gathered experts in different areas of mesothelioma research and management to summarize the most significant scientific advances and new frontiers related to mesothelioma therapeutics.

Keywords

Malignant pleural mesothelioma; Oncology therapeutics; Biomarkers; Immunotherapy; Chemotherapy

Introduction

Malignant pleural mesothelioma (MPM) is a rare and aggressive neoplasm primarily affecting the pleural cavity.[1,2] MPM is a male-predominant disease, with approximately 80% of cases resulting from occupational or environmental asbestos exposure.[3–7] Asbestos is a name that was used for regulatory purposes in the United States to identify six of about 400 mineral fibers that were used commercially; thus, many millions of people have been exposed to asbestos worldwide.[8] Although in most of the Western countries the use of asbestos is presently forbidden, MPM incidence is expected to increase in many countries in which asbestos either has not yet been banned or is still largely used. Moreover, increased development of rural areas, has caused exposure to carcinogenic fibers that are naturally present in the environment, including asbestos and nonregulated fibers,[9,10] and there is evidence of a third wave of mesothelioma in industrialized countries owing to renovation of asbestos-containing buildings.[11] It is anticipated that 500,000 new cases of MPM among men with occupational exposure will be diagnosed in Europe alone.[12]

MPM is characterized as having a very poor prognosis, with a median survival between 12 and 18 months and a 5-year survival rate less than 5%. Survival time is considerably shorter for patients in whom sarcomatoid mesothelioma has been diagnosed (median survival 12 months).[12–16] This poor prognosis is mostly due to a lack of reliable tools for screening and the lack of effective systemic therapy.[13,14] Moreover, surgery with curative intent can be attempted in only a minority of patients because of the stage at which the diagnosis is made.[17,18] Significant insights about the carcinogenesis of asbestos and other fibers and the genetics of MPM have been achieved in recent years,[16,19–24] and preclinical results[25–27] have also paved the way for innovative therapies.[28] In contrast, immunotherapy, which has achieved significant results in a subset of patients with cancer (i.e., melanoma, lung cancer, and renal carcinoma), has not shown the same efficacy in MPM.[29] Therefore, more

translational research and biological models are needed to move forward and improve the survival of patients with MPM.

This review article will discuss the most significant scientific advances and new opportunities related to mesothelioma research and management (see Fig. 1 and Table 1[30]).

Mesothelioma Biomarkers

Biomarkers are generally a useful clinical tool and can be used to search for risk, for early detection, and for prediction of the effectiveness of treatment of MPM. Of these blood-based biomarkers, mesothelin is the one that has been extensively studied.[31–33]

Mesothelin is a cell surface protein with normal expression limited to mesothelial cells lining the pleura, peritoneum, and pericardium, but it is also highly expressed in many cancers, including malignant meso thelioma.[34] Mesothelin can be shed from the cell surface and is found in the blood, urine, and tumor-associated fluids.

In the first study of mesothelin as a potential diagnostic biomarker for mesothelioma, 87% of patients with mesothelioma had increased levels in the serum compared with healthy asbestos-exposed and non-asbestos-exposed controls and individuals with other malignant or inflammatory lung and pleural diseases. The high specificity of serum mesothelin for mesothelioma has been confirmed in additional studies.[35] Increased levels of mesothelin in pleural effusion may be useful in the context of the cytological findings suggestive of malignancy (atypical, nonmalignant, or nondiagnostic) as an adjunct to the diagnosis of pleural mesothelioma. In one study, effusion mesothelin had a sensitivity of 67% for pleural malignant mesothelioma at 95% specificity.[36] In more than 47% of cases of pleural malignant mesothelioma, the level of mesothelin was increased in effusions obtained before a definitive diagnosis of pleural malignant mesothelioma had been established. Serum mesothelin level may be useful for monitoring response to treatment. In a study of 55 patients who received chemotherapy, a change in mesothelin level correlated with radiological response and change in metabolically active tumor volume. The median survival for patients with a reduction in mesothelin level after chemotherapy (19 months) was significantly longer than that for patients with increased mesothelin levels (5 months [$p < 0.001$]).[37]

The search for a good biomarker for early detection of MPM is a priority, especially for subjects with high levels of asbestos exposure. However, prospective studies have shown that monitoring serum mesothelin levels in these cohorts shows increased levels in only around 14% of individuals before diagnosis.[38] The recent description of ecto-NOX disulfide-thiol exchanger 2 as a potential early detection marker is encouraging.[39] Osteopontin, cancer antigen 125, hyaluronic acid, fibulin 3, and high mobility group box 1 (HMGB1) are some of the other biomarkers that have been studied in mesothelioma. They may have some value in prognostication, but they lack specificity.[40,41] On the whole, in many laboratories these results are prompting further research for novel, more sensitive biomarkers.[42]

Current Standard of Care

Patients with stage I or II disease and selected patients with stage III disease may benefit from an operation, at least to improve symptoms. However, randomized trials have been difficult to conduct, as was demonstrated by the Mesothelioma and Radical Surgery) randomized feasibility study, which suggested that radical surgery within trimodal therapy not only offers no benefit but possibly harms patients.

This trial was a feasibility study that highlighted the difficulty of randomizing patients to an extensive surgical procedure such as extrapleural pneumonectomy (EPP).[43] The goal of surgery is macroscopic complete resection with either an extended pleurectomy-decortication or an EPP. Because surgery alone is not curative, it is usually performed in the context of multimodality therapy with chemotherapy and/or radiation therapy.

Patients with unresectable disease are often treated with palliative systemic chemotherapy. Currently, four to six cycles of combination chemotherapy with platinum and antifolates is the standard treatment for patients with MPM. Tumor response rate with this combination is up to 30% in the randomized phase 3 trial; with this combination therapy, improvement in some cancer-related symptoms is possible and the overall survival (OS) time is approximately 1 year.[44] Carboplatin is a good alternative to cisplatin, especially in elderly patients.[45] Currently, there is no clear evidence supporting neoadjuvant or adjuvant chemotherapy,[14] and there are no approved second- or third-line agents. Clearly, there is a desperate need to improve therapies for MPM.

New Frontiers in Mesothelioma Treatment

Neoadjuvant and Adjuvant Therapies

Designing and conducting neoadjuvant studies in MPM is a challenging effort that requires extensive multidisciplinary involvement. In addition, there is a knowledge gap, as well as a great need to develop clinical trials that yield predictive or prognostic biomarkers for mesothelioma.

Although there are very few randomized studies about possible therapies for MPM, it is standard practice to administer four cycles of cisplatin-pemetrexed (CP) as adjuvant or neoadjuvant therapy. However, the benefit of systemic therapy has been demonstrated in the unresectable setting and most single-arm trials have shown a survival benefit over historical controls with the addition of systemic therapy. Trimodality therapy (systemic chemotherapy, surgical resection, and radiation) yields median OS times between 16.6 and 25.5 months.[46–53] It has been surmised that although surgical and radiotherapy techniques can be optimized for mesothelioma, the greatest challenge is eliminating microscopic disease; therefore, there is a critical need to improve systemic therapies and clarify the best sequence of therapies.

Although the neoadjuvant and adjuvant setting provides significant opportunities to conduct translational research with the acquisition of blood and tissue, successfully conducting trials in this space has remained a challenge. Neoadjuvant platinum-doublet chemotherapy has

given response rates between 29% and 44%,[48,51] and prospective trials suggest that the responders have improved survival outcomes.[48] However, in mesothelioma, neoadjuvant therapy carries inherent risks of potentially delaying surgery or predisposing patients to postoperative complications. This is of concern in MPM, as EPP completion rates in prior clinical trials conducted at high-volume centers have ranged from 42% to 84%.[46–48,50–52,54,55] Although adjuvant systemic therapy does not affect the surgical resection, there are significant concerns that it is often inadequate on account of dose reductions, treatment delays, or cessation of therapy secondary to poor tolerance by patients. Adding novel agents to trimodality or bimodality therapy may improve outcomes; however, it is essential that these agents (if given in the neoadjuvant setting) contribute to an antitumor effect with tumor shrinkage while maintaining nonoverlapping or relatively low toxicity. In addition, to assist with reducing residual microscopic disease after resection, these agents must have a reasonable adverse event (AE) profile that will allow them to potentially be administered in the adjuvant maintenance setting.

This article reviews three distinct examples of mesothelioma trial designs that have incorporated novel agents or immunotherapies into multimodality treatment. These examples include an adjuvant vaccine trial, a neoadjuvant window of opportunity biomarker-based trial, and a neoadjuvant chemotherapy with an oral antiangiogenic agent.

Memorial Sloan Kettering Cancer Center has been pioneering the use of an adjuvant Wilms tumor 1 (WT1) vaccine (galinpepimut-S), which consists of four peptides (three to stimulate common HLA-DR expressing cells and one for HLA-A0201 cells) with an immunologic adjuvant called Montanide ISA 51 UFCH (Seppic, Fairfield, NJ). It is administered every other week for 10 weeks postoperatively. Eligible patients were required to express WT1 (according to immunohistochemistry [IHC]) on their mesothelioma tumor cells. A phase II randomized study that was presented at the American Society of Clinical Oncology (ASCO) meeting in 2016 included data from 40 patients with mesothelioma who were IHC positive for WT1, had completed trimodality therapy, and had no evidence of disease. Galinpepimut-S was administered every other week for 10 weeks postoperatively. Galinpepimut-S showed a trend toward an improved median progression-free survival (PFS) (11.4 versus 5.7 months, hazard ratio [HR] = 0.69, $p = 0.3$) and median OS (21.4 versus 16.6 months, HR = 0.52, $p = 0.14$) over the placebo control arm. According to the subgroup analysis, the largest benefit was in the group of patients with an R0 resection, in which the median OS time was 39.3 months compared with 24.8 months in the control arm ($p = 0.04$).[56]

In the second example, a biomarker-based window of opportunity trial that was conducted at the University of Texas M. D. Anderson Cancer Center, demonstrated that it is feasible and safe to orally administer neoadjuvant tyrosine kinase inhibitor (TKI) agents before surgical resection, adjuvant radiation therapy, and adjuvant chemotherapy and then as a maintenance agent. This trial was based on preclinical studies showing that MPM cell lines and tumor cells have overexpression of activated Src kinase, and preclinical studies demonstrated antitumor efficacy of dasatinib that corresponded to dephosphorylation of the biomarker p-Src^{Tyr419}.[57] The primary end point was modulation of p-Src^{Tyr419} in tumor cells. Patients who exhibited biomarker modulation or a response to 4 weeks of administration of neoadjuvant dasatinib were eligible for maintenance dasatinib for 2 years. This study

demonstrated that distinct patterns of platelet-derived growth factor receptor alpha and platelet-derived growth factor receptor beta expression according to IHC were predictive of sensitivity or resistance to dasatinib treatment.

Buikhuisen et al. reported (at the ASCO 2013 meeting) on the combination of neoadjuvant CP with and without axitinib (an oral vascular endothelial growth factor receptor [VEGFR] inhibitor) for three cycles of therapy before pleurectomy. Axitinib was administered (at a dose of 5 mg twice daily on days 2 to 19) with standard CP.[58] Two tissue collections, before and after neoadjuvant therapy, were utilized with corresponding blood sampling. In the 31 patients enrolled (20 with axitinib and 11 without it), there was a higher response rate (35% versus 27%) with axitinib but no difference in median PFS or OS. The axitinib arm had higher rates of grade 2 hypertension (43% versus 0%) and grade 3 to 4 neutropenia (45% versus 9%), which did not translate into a higher rate of infectious complications. Four patients did not proceed with pleurectomy; a pulmonary embolism developed in one patient, and an arrythmia developed in one patient. Biomarker analysis for vascular endothelial growth factor (VEGF) and VEGFR is pending. This study indicates that the antiangiogenic agent was safely given with neoadjuvant chemotherapy with a low complication rate. Other antiangiogenic agents have recently become prominent in mesothelioma. For example, the French Cooperative Thoracic Intergroup Mesothelioma Avastin Cisplatin Pemetrexed Study trial reported that the addition of bevacizumab to CP significantly improved objective response rate, PFS, and OS in patients with unresectable MPM.[58] There are currently ongoing trials in the neoadjuvant setting in which immunotherapies are being used in window of opportunity trials (NCT02592551 and NCT02707666) and in combination with neoadjuvant chemotherapy-atezolizumab (SWOG 1619; NCT03228537).

Radiation

Mesothelioma has been shown to be sensitive to radiation in in vitro studies and in animal models. Clinically, radiation therapy has thus been used in three different settings in MPM: (1) prophylactically for the prevention of procedure tract metastasis after large-bore pleural biopsy; (2) palliatively for treatment of pain or an area at risk of compression, such as the esophagus or superior vena cava; and (3) radically in the form of highdose hemithoracic radiation to improve local control and possibly improve survival.

Prophylactic radiation directed to large-bore biopsy sites has been performed sporadically after one small randomized study demonstrated significant reduction of port site metastasis in 19 9 5.[59] After this study, two small randomized trials failed to confirm the potential benefit in prevention of port sites metastasis.[60,61] A recently completed large multicenter, open-label, phase 3, randomized controlled trial (SMART) studied 203 patients who received either immediate radiotherapy (n = 102) or deferred radiotherapy after diagnosis of procedure tract metastasis (n = 101). The study demonstrated no benefit, thus suggesting abandoning this concept.[62]

Palliative radiation in MPM has been used for pain management, treatment of dysphagia, or relief of superior vena cava compression.[63] A prospective phase II study was recently completed to assess the impact of a standardized radiation regimen of 20 Gy in five fractions on pain control at 5 weeks (SYSTEMS). Of 40 patients, 14 (35%) had improvement in pain

and five (12.5%) had complete pain resolution.[64] These encouraging results led to a new multicenter phase II randomized dose escalation study (SYSTEMS-2) to determine whether a higher dose of radiation (36 Gy in six fractions over 2 weeks) could provide additional benefit in terms of pain control.

Radical hemithoracic radiation in a dose of more than 50 Gy in a prospective phase II trial after EPP was reported by Rusch et al.[65] Local control was excellent, with a rate of recurrence in the radiation field of only 12%. These results led to a trimodality approach with induction chemotherapy followed by EPP and radical hemithoracic radiation. The median survival time among all studies ranged from 14 to 24 months in an intention-to-treat analysis with a rate of completion of all three therapies of 33% to 71%.[66] Two small multicenter randomized trials[43,67] attempted to determine the benefit of EPP compared with that of chemotherapy alone (the Mesothelioma and Radical Surgery randomized trial) and the benefit of hemithoracic radiation after chemotherapy and EPP (SAKK 17/04). Both trials had limitations related to the small sample size and raised concerns about the quality of the surgery or the radiation therapy, thus precluding definitive conclusions.[68,69]

Over the past 10 years, radical hemithoracic radiation has evolved toward two new paradigms: (1) the use of radical hemithoracic radiation as part of a lung-sparing multimodality approach (IMPRINT) and (2) the use of an accelerated course of hemithoracic radiation before EPP (SMART).[70,71] Both approaches use intensity-modulated radiation therapy and have been evaluated in prospective single-arm clinical trials. The trials have demonstrated the safety of these new radical approaches in experienced centers.[72–74] Further studies are currently ongoing to evaluate the potential long-term benefit of these therapeutic approaches.

In summary, prophylactic radiation of large-bore pleural biopsy sites is not superior to radiation to the biopsy tract after diagnosis of procedure tract metastasis. Palliative radiation is an option for MPM when there is a specific symptomatic site to target, but the optimal radiation regimen remains to be defined and radical hemithoracic radiation should be part of clinical trials in the context of a multimodality approach and performed in expert centers only.

Antiangiogenic Drugs

The results of earlier trials assessing antiangiogenic drugs in MPM were negative; they included the phase III study of thalidomide as maintenance treatment after CP[75] and a phase II trial of bevacizumab (anti-VEGF antibody) combined with first-line cisplatin plus gemcitabine.[76] To test CP with bevacizumab (CPB) or CP alone, a phase III trial (the Mesothelioma Avastin Cisplatin Pemetrexed Study trial) randomized 448 patients with unresectable MPM who had not received previous chemotherapy.[77] The patients were 18 to 75 years of age, had an Eastern Cooperative Oncology Group performance status of 0 to 2, and had no substantial cardiovascular comorbidity. Patients with nonprogressive disease who had been treated with CPB received bevacizumab maintenance until progression or toxicity. The primary end point, OS time, was longer in the CPB arm: 18.8 versus 16.1 months in the CP arm, (hazard ratio [HR] = 0.77, $p = 0.017$). Median PFS was also increased in the CPB arm: 9.2 versus 7.3 months (HR = 0.61, $p < 0.001$). Moreover, there was no detrimental

effect of bevacizumab on quality of life despite its higher frequency of toxicities. Overall, 158 of 222 patients given PCB (71%) and 139 of 224 patients given PC (62%) had grade 3 to 4 AEs. There were more cases of grade 3 or higher hypertension (51 of 222 [23%] versus 0) and thrombotic events (13 of 222 [6%] versus 2 of 224 [1%]) with PCB than with PC. Thus, CPB provided a significantly longer survival in MPM with acceptable toxicity, making this triplet a potential treatment paradigm for these patients, and it was included in the 2016 National Comprehensive Cancer Network guidelines.[78]

On the basis of a similar rationale, nintedanib, which is a drug targeting VEGFR, fibroblast growth factor receptor, and platelet-derived growth factor receptor, is currently being tested versus placebo in patients with MPM treated with first-line CP in a phase II/III trial (the LUME-Meso trial). In the phase II trial, 87 patients were randomly assigned to up to six cycles of pemetrexed and cisplatin plus nintedanib (200 mg twice daily) or placebo followed by nintedanib plus placebo monotherapy until progression. Primary PFS favored nintedanib (HR = 0.56, 95% confidence interval [CI]: 0.34–0.91, $p = .017$), which was confirmed in updated PFS analyses (HR = 0.54, 95% CI: 0.33–0.87, $p = .010$). A trend toward improved OS also favored nintedanib (HR = 0.77, 95% CI: 0.46–1.29, $p = .319$). Neutropenia was the most frequent grade 3 or higher AE (43.2% with nintedanib versus 12.2% with placebo); the rates of febrile neutropenia were low (4.5% in the nintedanib group versus 0% in the placebo group). AEs leading to discontinuation were reported in 6.8% of those receiving nintedanib versus in 17.1% of those in the placebo group. Another anti-VEGFR TKI inhibitor, axitinib, failed to improve median OS and PFS in combination with CP versus chemotherapy alone.[79] Additional VEGFR TKIs have been studied with frontline chemotherapy. Axitinib, a multi-targeted antiangiogenic TKI, failed to improve median OS and PFS in combination with CP versus chemotherapy alone. However, SWOG0905, which was a phase I/II trial that combined cediranib (a VEGFR inhibitor) with CP, reported a median PFS time of 8.6 months and a median OS time of 16.2 months.[80] The randomized SWOG0905 phase II trial has completed enrollment and will be presented at the ASCO meeting in 2018.

In summary, the triplet CPB is a new option for selected patients and is recommended in the National Comprehensive Cancer Network guidelines.

Targeting Stem Cell Pathways

Cancer stem cells is a term often used to identify a subpopulation of cells within each tumor that display properties of self-renewal, pluripotency, a high proliferative capacity, and a higher ability to resist standard chemotherapy and radiation. The resistance of MPM to conventional cytotoxic drugs is due in part to subpopulations of drug-resistant stem cells, and new therapeutic strategies that specifically target this stem cell population and improve the efficacy of cytotoxic drugs are needed.[81]

Focal adhesion kinase (FAK) is overexpressed in epithelial and mesenchymal tumors and regulates cell adhesion, proliferation, migration, and survival in addition to being critical for cancer stem cell survival and maintenance. FAK signaling is associated with resistance to cytotoxic chemotherapy, and FAK inhibition enhances cancer cells' sensitivity to taxanes.[82] Cells with Merlin deficiency, which is common in mesothelioma, are sensitive to FAK inhibition.[83] The small molecule FAK inhibitor defactinib showed promising results in

preclinical studies; however, a phase II clinical trial of defactinib in mesothelioma was ended in late 2015 after interim analysis failed to show any benefit. Other FAK inhibitors remain in development, and targeting the FAK pathway in combination with other treatment strategies continues to be an area of interest.

Several other stem cell pathways, including Wnt, Hippo, and Sonic Hedgehog are active areas of drug development with promising preclinical results in mesothelioma. Wnt pathway signaling is deregulated in a large variety of cancers, promotes stem cell self-renewal in hematopoietic stem cells, and is necessary for cancer stem cells to maintain their tumorigenic potential.[84,85] In mesothelioma, combining cisplatin with Wnt pathway inhibitors in vitro improves the efficacy of standard chemotherapy and induces synergistic cell cycle arrest and colony formation.[86]

The Hippo pathway is a highly conserved regulator of organ size and stem cell proliferation and mainte-nance.[87] It is of interest in mesothelioma, as there are multiple genes in the Hippo pathway that are frequently mutated in mesothelioma.[88]

Another pathway of interest in mesothelioma is the Sonic Hedgehog pathway and its downstream effectors Smoothened and Gli, which control progenitor cell migration, differentiation, and proliferation and play an important role in carcinogenesis. Vismodegib, a Smoothened inhibitor that is approved for use in basal cell skin cancer, impairs MPM growth in rat models.[89] The final effector of the pathway, Gli, has been shown in vitro and in xenograft models to be up-regulated in mesothelioma.[90] A novel Gli inhibitor that is currently in preclinical development suppresses mesothelioma cell growth and works synergistically with pemetrexed and the Smoothened inhibitor vismodegib in mesothelioma.[90]

Immunotherapy

It has been known for some time that MPM is a cancer that can be sensitive to immunotherapy, and some immunotherapies are currently being tested.[91] Nonetheless, at the moment there are no randomized clinical trials examining immunotherapy versus standard therapy that could provide strong support for the use of immunotherapy for MPM.

Antibodies blocking immune checkpoints that function as negative regulators of T-cell function, cytotoxic T-lymphocyte-associated antigen 4 (CTLA4), programmed death 1 (PD-1), and programmed death ligand 1 (PD-L1) have been approved in several different cancers. In two nonrandomized studies, the anti-CTLA4 antibody tremelimumab showed preliminary evidence of activity in patients with previously treated mesothelioma.[92,93] On the basis of these results, a phase 2b, randomized, double-blind, placebo-controlled study investigated tremelimumab in patients with mesothelioma (the DETERMINE trial). This trial did not meet the primary end point of OS. There was no difference in OS between the tremelimumab group (median OS 7.7 months [95% CI: 6.8–8.9]) and the placebo group (median OS 7.3 months [95% CI: 5.9–8.7]).[94]

In the KEYNOTE-028 trial, previously treated patients with PD-L1-positive MPM received pembrolizumab (which is an anti-PD-1 antibody) in a dose of 10 mg/kg every 2 weeks for

up to 2 years or until confirmed progression or unacceptable toxicity. PD-L1 positivity was defined as expression in 1% or more of tumor cells by IHC. In the preliminary results, five of 25 patients (20%) had a partial response (for an objective response rate of 20%) and 13 (52%) patients had stable disease. Responses were durable (median duration of response 12.0 months [95% CI 3.7-not reached]).[95] The NivoMes study, which evaluated the anti-PD-1 antibody nivolu-mab in unselected patients with previously treated mesothelioma reported response rates of 28%.[96] The JAVELIN study of the anti-PDL-1 antibody avelumab in unselected patients with previously treated mesothelioma reported a response rate of 9.4% with a median PFS of 17.1 weeks. Subgroup analysis in the PD-L1-positive population (cutoff >5%) showed a response rate of 14%.[97] Novel vaccine approaches using MPM neoantigens identified by gene sequencing are also entering clinical trial on the basis of early animal studies.[98]

Overall, the preliminary data on PD-1- and PD-L1-targeting monoclonal antibodies in MPM suggest that single-agent immunotherapy may have some benefit in this disease, possibly because of its complex biology. Additional studies are ongoing (in particular, studies assessing combinations of PD-1- or PD-L1-targeted therapies with anti-CTLA4 antibodies or with chemotherapy.[99]

Targeting Inflammation

MPM is causally linked to exposure to asbestos and other carcinogenic mineral fibers such as erionite and antigorite.[8,100] The deposition of mineral fibers in tissues triggers a chronic inflammatory process that over the course of many years, drives asbestos carcinogenesis.[19] Inflammatory cells, particularly macrophages, play an important role in this process by releasing mutagenic reactive oxygen species and various cytokines that are mutagenic and/or support inflammation.[101–106] In the pleura and peritoneum, the chronic inflammation caused by asbestos is causally linked to the release of HMGB1 by primary human mesothelial cells after asbestos exposure. Human mesothelioma cells undergoing necrosis passively release HMGB1 into the extracellular space, where HMGB1 recruits macrophages, induces the secretion of tumor necrosis factor alpha and other cytokines, and initiates inflammation.[107] These same pathways contribute to MPM growth.[20,108] The prolonged bio-persistence of asbestos fibers lodged in the pleura initiates a vicious cycle of chronic cell death and chronic inflammation that over a period of many years, can lead to MPM.[105] In addition, asbestos fibers can activate NLR family pyrin domain containing 3 inflammasome and interleukin-1β (IL-1β) production.[109,110] Given the established role of chronic inflammation in asbestos-induced mesothelioma and the long latency between fiber exposure and cancer development, asbestos-induced inflammation is a potential therapeutic target for MPM prevention. Malignant mesothelioma biopsy specimens often show a marked inflammatory infiltrate that contains a large number of tumor-associated macrophages. Moreover, the growth of most MPM cells is dependent on HMGB1, and the tumor phenotype of HMGB1-secreting mesothelioma cells requires HMGB1 for continued growth.[111] Therefore, HMGB1 is an attractive novel target to identify patients with malignant mesothelioma and possibly to treat MPM.[112]

Several reagents that block HMGB1 activity have been investigated and have shown promising results in vitro and in animals. These anti-HMGB1 reagents include anti-HMGB1 and anti-receptor for advanced glycation end products monoclonal antibodies, HMGB1 antagonist BoxA, and ethyl pyruvate (which inhibits HMGB1 secretion).[111] In addition, HMGB1 is a novel target of aspirin (acetylsalicylic acid [ASA]) and its metabolite salicylic acid (SA); it has been found that ASA treatment may delay MPM development and inhibit its progression by inhibiting HMGB1 activity.[113] Daily ASA has been shown to have a protective effect against colorectal cancer and against cancers in other sites, such as breast, stomach, and prostate cancer. Although to our knowledge, the possible therapeutic effects of ASA in MPM have not been studied, we found some evidence supporting a role of ASA in preventing or possibly delaying the growth of malignant mesothelioma. Specifically, the Physician's Health Study suggests that there may be a possible association between ASA use and reduced incidence of malignant mesothelioma.[114]

In addition to ASA, several other anti-inflammatory drugs have also been studied. For example, flaxseed lignan was found to be able to reduce acute asbestos-induced inflammation and thus may be a promising agent for MPM chemoprevention.[115] Celecoxib, a cytochrome c oxidase assembly factor COX20 inhibitor, was shown to be able to inhibit MPM tumorigenic potential in vitro and in vivo, and it was used in a clinical trial and also tested in combination with adenovirus (ADV)-interferon and chemotherapy.[116,117] IL-4R expression was found to be associated with poor survival and promotion of tumor inflammation. In addition, the IL-4/IL-4 receptor axis was proposed to be potential therapeutic target in MPM.[118] Similarly, it was also recently proposed that use of anti-IL-6 be considered a potential therapeutic strategy.[119]

Virotherapy for MPM

The concept of using viruses for cancer therapy emerged on the basis of numerous anecdotal case reports demonstrating disease remission in patients acquiring natural viral infections. The potential therapeutic effects of these viruses have been attributed to different mechanisms. In addition to causing direct oncolytic cell death, targeted infection, and killing of the tumor cell by the virus, viral tumor cell infection is also known to trigger antitumor immune responses (viroim-munotherapy).[120,121] In addition, viruses can be used to therapeutically change the infected tumor cells by gene transfer (gene therapy).[120,121]

Recent advances in genetic engineering have resulted in the rapid improvement of therapeutic viruses, including enhanced tumor cell-specific targeting and introduction of cargo genes to enhance the therapeutic effect of these agents. Although the inherent impairment of the type I interferon pathway in many malignant cells augments tumor cell-specific oncolysis, innate and adaptive antiviral immune responses limit the effects of oncolytic viruses.[120] On the basis of promising preclinical data, various viruses, including herpes simplex virus (HSV), vaccinia virus, ADV, measles virus, reovirus, and others, have been evaluated in clinical trials across different malignancies. Many of these studies have established the safety of virotherapy and demonstrated some promising clinical response.[120] In 2015 the U.S. Food and Drug Administration approved talimogene laherparepvec (also

known as T-VEC or OncoVEX$^{GM\text{-}CSF}$), which is a granulocyte macrophage colony-stimulating factor-expressing variant of HSV type 1, for patients with melanoma.[122]

For MPM, virotherapy currently represents an experimental treatment strategy, and additional data are needed. Local confinement of tumor growth within the chest cavity in the absence of distant metastasis and easy access to local delivery through the pleural space have made MPM an interesting target for virotherapy. Therapeutic viruses are most commonly delivered through an intrapleural catheter. The most frequently used viral vectors in MPM have been recombinant replication incompetent ADV. Different ADV vectors encoding the suicide gene HSV thymidine kinase (Ad.HSVtk) in conjunction with gancyclovir (intravenous delivery), and interferon beta (Ad.IFNβ) or interferon alfa (Ad.IFNα) either alone or in conjunction with chemotherapy and cyclooxygenase inhibition have been investigated in several phase I/II trials.[117,123–126] Studies investigating the intrapleural administration of a modified vaccine strain measles virus encoding the sodium iodine symporter (MV-NIS, NCT01503177), the modified HSV type 1 strain HSV1716 (SEPREHVIR, NCT01721018), and the attenuated modified vaccinia virus (GL-ONC1, NCT01766739) encoding several tracking genes, green fluorescent protein (GFP), β-galactosidase, and β-glucuronidase are currently ongoing. Disease responses, prolonged periods of disease control, and extended OS have been observed in virotherapy studies in mesothelioma. Combinatorial approaches with immunosuppression and cellular viral carriers to avoid viral neutralization and combinations with immune checkpoint inhibitors, chemotherapy, and radiation to enhance the effects of the viruses on antitumor immunity are currently being considered.

Other Approaches

Preclinical studies and early-stage clinical trials have validated mesothelin as an attractive target for therapy of patients with mesothelioma, given its high and uniform expression in patients with epitheloid mesothelioma and limited expression on normal human tissues. Currently, several approaches targeting mesothelin are in clinical trials; they include immunotoxin LMB-100 (a recombinant protein consisting of antimesothelin Fab conjugated to a truncated *Pseudomonas* exotoxin A) and the antibody drug conjugate anetumab ravtansine (antimesothelin monoclonal antibody linked to the antitubulin DM4) In addition, phase I clinical trials of mesothelin-directed chimeric antigen receptor T cells given intravenously or in the pleural cavity are being conducted.[127]

Another source of hope might come from the arginine dependence that is exhibited by argininosuccinate synthetase 1 tumors such as mesothelioma, and the good results of pegylated arginine deiminase alone or in combination with CP in the phase I TRAP trial.[117] A phase II/III trial (Polaris) comparing first-line CP with pegylated arginine deiminase or placebo was started in 2017 for biphasic (mixed) or sarcomatoid MPM only because they exhibit argininosuccinate synthetase 1 defect twice as frequently as the epithelioid subtype.

Finally, other innovative drugs are also candidates for first-line treatment after preliminary positive clinical trials, include gene therapy[117] or cell therapy using chimeric antigen receptors or dendritic cells.[128] For example, in 2018 the European DENIM phase III trial

will start to test dendritic cell-based immunotherapy with allogenic tumor cell lysate as maintenance treatment after CP chemotherapy in patients with MPM.

Future Perspectives

Despite MPM being a relatively rare cancer, there are a number of ongoing clinical trials of novel therapies in MPM, including large randomized clinical trials. As we learn more about the biology of mesothelioma, it will become possible to target those mechanisms that are most critical and most commonly altered in these malignancies: it is hoped that such targeted therapies will lead to improved outcomes for patients with mesothelioma. It is also very important to conduct randomized clinical trials, which given the rarity of this malignancy, requires cooperation among expert medical centers, as in the absence of such trials it is impossible to judge with any degree of reliability the possible benefit of novel therapies.

From a clinical point of view, the translational trials should be stratified and aimed at reaching strong primary end points (e.g., OS), thus avoiding the risk recently demonstrated with surrogate end points, and the establishment of larger patient cohorts will allow a new understanding of the efficacy of the new treatments.[129]

From preclinical point of view, it is critical that a better understanding of MPM biology could allow us to move forward and gain ground against this disease. Amid other characteristics, the mesodermal origin of MPM offers intriguing opportunities, and likewise, the role of the microenvironment in affecting the growth of tumor cells and the immune response also offers interesting possibilities.[130,131]

Lastly, even though MPM cells show a relatively low mutational load that can affect the sensitivity to immunotherapy, there is no doubt that the genetics, gene-driven metabolism, and immune characteristics of this tumor are likely to unravel translational implications within the next few years.[23,29,132] It will be useful in clinical trials to obtain germline and tumor samples for detailed molecular analysis of genes that may influence disease occurrence or outcomes, such as BRCA1 associated protein 1 gene (*BAP1*), and mutations and transcriptomes that might inform therapeutic choices and prognosis and clarify the molecular basis of response or progression.

Ultimately, although there have been repeated failures in the development of novel therapeutics for mesothelioma, we have recently achieved a better understanding of the basic biology behind mesothelioma development, and this is paving the way for better therapeutics and patient outcomes.

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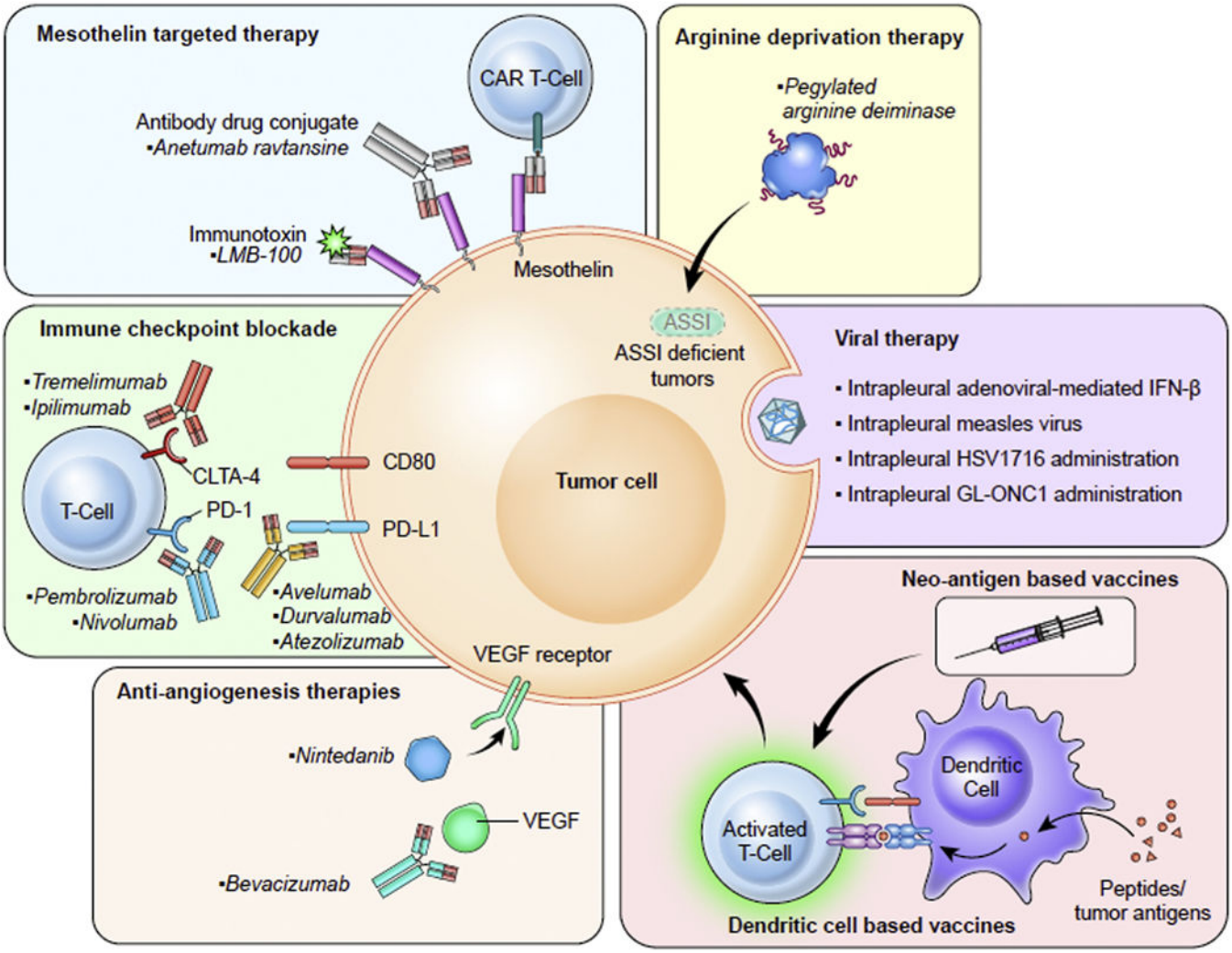

Figure 1.

Different approaches to treating mesothelioma that are currently in clinical trials. Nintedanib, in addition to targeting VEGF receptor, also targets fibroblast growth factor receptor and platelet-derived growth factor receptor. Abbreviations: CAR, chimeric antigen receptor; CTLA4, cytotoxic T-lymphocyteassociated antigen; PD-1, programmed death 1; PD-L1, programmed death ligand 1; ASS1, argininosuccinate synthetase 1; IFN-β, interferon beta; VEGF, vascular endothelial growth factor.

Table 1.

Prospective Therapies and Trials for Mesothelioma

Therapy	Treatment	Identifier/Reference	Phase	Status/Outcome
Angiogenesis inhibition	Thalidomide	ISRCTN13632914	III	No noted benefit in time to disease progression
	Bevacizumab	NCT00027703	II	Addition of bevacizumab to gemcitabine/cisplatin treatment did not improve overall or progressionfree survival in advanced malignant mesothelioma
	Bevacizumab	NCT00651456	II/III	Addition of bevacizumab to cisplatin and pemetrexed improved significantly overall survival (by 2 mo) in newly diagnosed pleural mesothelioma
	Axitinib	NCT01211275	II	Axitinib was well tolerated, but there was a lack of clinical benefit
	Nintedanib	NCT01907100	II/III	Improvement of progression-free survival/recruiting
	Cediranib	NCT00243074	II	End point was not achieved
	Cediranib	NCT00309946	II	End point was not achieved
	Cediranib	NCT01064648	I	Active but not recruiting
FAK inhibition	Defactinib	NCT02004028	II	Completed, no results posted
	Defactinib	NCT01870609	II	Terminated
	Defactinib	NCT02758587	I/II	Recruiting—study will assess combination of defactinib with PD-1 inhibition
Antimesothelin	Amatuximab	NCT00738582	II	Amatuximab in combination with pemetrexed and cisplatin was well tolerated; however, no significant difference in progression-free survival was seen
	SS1P immunotoxin	NCT01362790	I/II	Study ongoing
Arginine deprivation	ADI PEG 20	NCT01279967	II	Improvement in progression-free survival
	ADI PEG 20	NCT02709512	II/III	Recruiting—study will assess combination of ADI PEG 20 with cisplatin/ pemetrexed
Immunogene therapy	Intrapleural adenoviral-mediated interferon-alfa 2b	NCT01119664	I/II	Study ongoing—study will assess combination of intrapleural adenoviral-mediated interferon-alfa 2b in combination with chemotherapy
		NCT01212367	I	Intrapleural administration of adenoviral-mediated interferon-alfa 2b showed potential therapeutic benefits
	IL-2 administration	Astoul et al.[30] (1998)	II	IL-2 administration was well tolerated and had an antitumour activity in patients with MPM
	CP-870, 893 (CD40-activating antibody)	ACTRN12609000294257	I	Objective response rates were similar to those with chemotherapy alone (rather than CP-870,893 in combination with chemotherapy), but 3 patients achieved long-term survival
Cell therapy	Dendritic cell vaccination	NCT01241682	I	Treatment was well tolerated and showed signs of clinical activity
Immune checkpoint inhibition	Tremelimumab	NCT01843374	II	No statistically significant difference in survival
	Pembrolizumab	NCT02054806	I	Study ongoing, but preliminary results show common side effects and a partial response of 20%

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Therapy	Treatment	Identifier/Reference	Phase	Status/Outcome
	Nivolumab	NCT02899299	III	Recruiting—study will assess combination of nivolumab with ipilimumab
		NCT02497508	II	Study ongoing
		NCT02341625	I/II	Recruiting—study will assess BMS-986148 (antimesothelin) with or without nivolumab
		NCT02716272	II	Study ongoing
	Pembrolizumab	NCT02707666	I	Recruiting—study will assess the use of pembrolizumab and cisplatin and pemetrexed
	MEDI4736	NCT02592551	II	Recruiting—study will assess MEDI4736 (PD-1 inhibitor) with or without tremelimumab
WT1 vaccination	SLS-001	NCT01265433	II	Results presented at ASCO indicated that a trend toward survival was observed; however, the trial was originally not powered to determine this effect
Tyrosine kinase inhibition	Dasatinib	NCT00652574	I	Study ongoing
Radiotherapy	Prophylactic radiotherapy	ISRCTN72767336	III	No benefit observed
	Palliative radiotherapy	ISRCTN66947249	II	Radiotherapy as pain relief was effective for a proportion of patients
	Radical hemithoracic radiation	Rusch et al. (2001)[65]	II	Trial assessed the role of radical hemithoracic radiation after surgery and showed prolonged survival in early-stage tumors
	Hemithoracic intensity-modulated pleural radiation therapy (IMPRINT)	NCT00715611	II	Hemithoracic IMPRINT was safe with an acceptable rate of radiation pneumonitis
	Accelerated intensity-modulated radiation therapy followed by extrapleural pneumonectomy	NCT00797719	I/II	Median survival for all patients was 36 months, and this approach has become the preferred option for resectable MPM
Viral therapy	Intrapleural adenoviral-mediated interferon beta	NCT00066404	I	The approach was safe, promoted disease stability, and induced immune responses; however, side effects were seen at all doses
	Intrapleural measles virus	NCT01503177	I	Recruiting—study will assess the side effects and doses for the use of a measles virus encoding a thyroidal sodium iodide symporter
	Intrapleural administration of HSV1716 (mutated herpes simplex virus)	NCT01721018	I/II	Study ongoing
	Intrapleural administration of GL-ONC1 (genetically modified vaccinia virus)	NCT01766739	I	Study ongoing

ADI PEG 20, pegylated deiminase; FAK, focal adhesion kinase; PD-1, programmed death 1, MPM, malignant pleural mesothelioma; IL-2, interleukin 2; WT1, Wilms tumor 1; ASCO, American Society of Clinical Oncology.