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New horizons from novel therapies in malignant pleural mesothelioma

Abstract

Malignant pleural mesothelioma (MPM) is a relatively rare, but highly lethal cancer of the pleural mesothelial cells. Its pathogenesis is integrally linked to asbestos exposure. In spite of recent developments providing a more detailed understanding of the pathogenesis, the outcomes continue to be poor. To date, trimodality therapy involving surgery coupled with chemotherapy and/or radiotherapy remains the standard of therapy. The development of resistance of the tumor cells to radiation and several chemotherapeutic agents poses even greater challenges in the management of this cancer. Ionizing radiation damages cancer cell DNA and aids in therapeutic response, but it also activates cell survival signaling pathways that helps the tumor cells to overcome radiation-induced cytotoxicity. A careful evaluation of the biology involved in mesothelioma with an emphasis on the workings of pro-survival signaling pathways might offer some guidance for treatment options. This review focuses on the existing treatment options for MPM, novel treatment approaches based on recent studies combining the use of inhibitors which target different pro-survival pathways, and radiotherapy to optimize treatment.

Key words: mesothelioma, chemotherapy, radiotherapy, targeted therapy, immunotherapy

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Introduction

Malignant pleural mesothelioma (MPM) is a rare and aggressive cancer with a reported worldwide incidence of only 10 to 30 cases per million [1]. This malignancy involves the mesothelial cells of the pleura and its pathogenesis is attributed to a direct causal relationship with prolonged exposure to airborne asbestos particles. Chronic exposure to asbestos leads to inflammatory changes in the pleural mesothelium, subsequently leading to malignant transformation [2]. The most common sub-type of MPM is the epithelioid variety, followed by the sarcomatous and biphasic types [3].

The current standard treatment strategies for MPM include surgery for resectable tumors in combination with radiotherapy (RT) and chemo-

therapy. In spite of recent advances and research focused towards novel approaches to manage MPM, the median survival of patients with MPM is still estimated to be 8 to 14 months [4]. With the emerging resistance of the MPM tumor cells to RT and chemotherapy, there is an even greater need for developing new treatment approaches which can bypass and overcome these obstacles. Cancer immunotherapy has shown tremendous promise in providing solutions which can aid in improving the poor outcomes that continue to be associated with MPM. A more detailed understanding of the molecular biological mechanisms in MPM has provided hope that novel combinations of targeted therapies along with administration of radiation can be successfully developed to enhance the immune response against this malignancy. In view of this, we evaluate the available treatment

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modalities for MPM, with a particular emphasis placed on the various cell survival pathways and the latest developments in the field of targeted chemotherapy and immunotherapy.

Current treatment approaches in MPM

The trimodality treatment involving surgery in combination with chemotherapy and/or radiotherapy continues to be the standard approach for management of MPM. Being an important and common treatment option in the treatment of MPM, surgery has been employed to either potentially cure the cancer or to provide palliation. The two main surgical methods include extra-pleural pneumonectomy (EPP) and pleurectomy with decortication (P/D). The preferred surgical of MPM continues to be widely debated with several studies showing conflicting results. Some retrospective studies have favored extended P/D, because it shows lower peri-operative mortality, morbidity, lower post-operative complications and better survival when compared to EPP (5, 6). Owing to the lack of randomized control trials, a clear conclusion of the optimal surgical procedure cannot yet be clearly determined. The National Comprehensive Cancer Network (NCCN) guidelines for MPM suggest that P/D is considered safer to EPP due to less post-operative complications and a higher quality of life.

RT is employed as an adjuvant or neoadjuvant treatment option in MPM and is mainly considered a palliative option [7]. Intensity modulated proton therapy has been suggested as a feasible option in the management of MPM in a recent study involving 7 patients [8]. Volumetric modulated arc therapy, a rotational form of intensity-modulated RT has also been considered in management of MPM [9]. Chemotherapy is considered a part of the trimodality regimen for MPM in patients, either before or after surgery and has shown to provide a median OS of 24 months [10]. In patients who refuse surgery and in medically inoperable patients, chemotherapy alone can also be considered [11]. The first-line treatment for MPM includes a combination of pemetrexed and cisplatin. Based on a recent study by Zalcman *et al.*, the NCCN guidelines recommended addition of bevacizumab to cisplatin-pemetrexed regimen for patients with unresectable MPM [12]. Pemetrexed-carboplatin and gemcitabine-cisplatin have also been recommended as acceptable first-line regimens based on relevant recent studies [13, 14].

Induction of cell survival pathways

Epidermal growth factor receptor (EGFR) pathway

EGFR is a transmembrane glycoprotein which belongs to the Her1 group of the ErbB family of tyrosine kinases [15]. This receptor forms an integral part of a complex signaling cascade which plays an important role in physiological pathways including controlling cell growth, proliferation and survival. Ligand binding to EGFR, phosphorylation of tyrosine residues, followed by receptor dimerization are the three steps which lead to cellular proliferation [16]. The overexpression of these receptors has been deemed significant in the pathogenesis of several cancers, which has led to the focus on development of targeted therapies towards these receptors [17]. Overexpression of EGFR is noted in about 70% of tissue specimens of MPM [18]. Asbestos, which is the major carcinogen associated with MPM, triggers aggregation of EGFR by forming reactive oxygen species, resulting in autophosphorylation and EGFR activation. This is subsequently followed by activation of the RAS/RAF/MAPK pathway leading to cellular proliferation and metastasis [19, 20]. There are several studies which have focused on EGFR gene mutations involved in MPM over the last few years. A study conducted in Japan demonstrated the presence of missense mutations of the EGFR gene in some cases of MPM [21]. Recent studies have suggested an epigenetic component involved in development of MPM. Moreover, oncogenic EGFR gene has been shown to cause downregulation and repression of Ten-eleven translocation enzymes (TET) DNA methylase, which leads to silencing of tumor suppressors [22].

The effect of radiation on the proliferation of tumor cells and association with EGFR has been studied extensively. The amplification of cellular proliferation after exposure to ionizing radiation is termed as accelerated repopulation and has been shown to be contributing partly to the development of radioresistance, especially in head and neck malignancies [23]. The possible mechanisms of EGFR phosphorylation and subsequent activation by radiation has been attributed to the release of TGF- α , which is an EGFR binding ligand [24]. A study detailing the effects of the combination of RT with ZD1839 (Iressa), which is a selective EGFR inhibitor in several cancers including mesotheliomas, conclusively showed that the combination arm yielded significant improvements in therapeutic index for radiation and enhanced tumor suppression compared to the radiation alone arm [25].

The two classes of drugs with established anti-EGFR targeted action are tyrosine kinase inhibitors (TKI) and monoclonal antibodies. TKIs such as gefitinib, afatinib, erlotinib, canertinib and lapertinib impart their action by acting as ATP analogues, competitively inhibiting the catalytic tyrosine kinase domain intracellularly. In-vitro studies have demonstrated that small molecule TKIs effectively decrease MPM cell proliferation [26]. However, initial clinical trials involving gefitinib showed no clinical efficacy in patients with MPM [27]. This contrast has been attributed to the theory that TKIs exert their action only in the presence of activating mutations of the EGFR gene, which are very rarely seen in MPM. As very few patients carry these mutations, the clinical efficacy of these drugs, when given individually, is lacking [28]. A Japanese study has been conducted in a patient harboring a rare EGFR mutation of G719C and S768I had been successfully treated with afatinib [29].

Monoclonal antibodies against the extracellular portion of EGFR such as cetuximab, nimotuzumab and panitumumab act by creating ligand inhibition, thereby blocking receptor dimerization and further downstream signaling. They also cause internalization and degradation of EGFR receptors leading to further downregulation [30]. The use of cetuximab, a chimeric mouse-human antibody, in rodent models has demonstrated significant tumor inhibition and improved survival [31]. Another monoclonal antibody, Nimotuzumab, approved for the treatment of colorectal and head and neck cancers, has demonstrated significant reduction in tumor volumes when compared to cisplatin-gemcitabine chemotherapy in animal models [32]. Novel EGFR targeted nanotechnology delivery techniques such as TargomiRs which are targeted minicells which are loaded with miR-16 mimic microRNA have also shown promise in preclinical models and clinical trials [33, 34].

Extracellular signal-regulated kinase (ERK) pathway

Mitogen-activated protein kinase (MAPK) pathway, which forms an integral link between upstream extracellular stimuli and downstream intracellular effectors, regulates cell differentiation, proliferation and death in both physiological and pathological milieus [35]. This cascade, which has been identified to be the most frequently mutated signaling pathway in humans, is composed of a RAS-RAF-MEK-ERK chain. Two types of distinct ERK proteins, ERK1 and ERK2,

are activated by MEK through phosphorylation of their tyrosine and threonine residues, which results in the activation of transcription factors and kinases which predominantly orchestrates cellular proliferation. Activation of several feedback loops between substrates and ERK further amplifies cell differentiation [36]. The significance of ERK has been clearly demonstrated in studies related to epithelioid type of MPM. ERK2 was conclusively shown to be critical in the transformation and homeostasis of mesotheliomas by controlling gene expression in animal studies [37]. An in-depth analysis of asbestos-induced signaling pathways also reiterated the importance of ERK in the development of malignant mesothelioma. The transcription factor activator protein-1 controls proliferation of mesothelial cells by elevation of ERK-dependent Fos-related antigen (Fra)-1 [38]. Thus, downstream ERK, which controls a critical juncture in this pathway, has been targeted as a potential opportunity for treatment of cancers, especially those with MEK, RAF and RAS mutations.

Radiation leads to activation of the ERK pathway by causing tyrosine and threonine phosphorylation of ERK1 and ERK2 by MEK, which prolongs cell survival and proliferation [39]. This activation of ERK by radiation leads to expression of anti-apoptotic proteins such as Mcl-1, and Bcl-xL [40]. It also inhibits some pro-apoptotic proteins such as caspase 9 and Bim, leading to the inhibition of tumor cell suppression [41]. A link between radioresistance and ERK5 has been established in a study by Jiang *et al.* which showed that ERK5 overactivation was noted in lung cancer development and G2/M cycle transmission. ERK5 was also identified as a potential regulator of radiosensitivity in cancer cells and supported its use as a biomarker to predict radiosensitivity [42].

In therapeutic targeting of the MAPK pathway, the initial design and development of newer drugs was focused on RAF and MEK proteins. The inevitable drug resistance that develops against RAF and MEK inhibitors has shifted the focus to novel ERK inhibitors. Use of a specific ERK5 inhibitor XMD8-92 in human MPM cells conclusively showed inhibition of ERK5 phosphorylation, which eventually led to attenuation of MPM tumor growth by an inflammasome-mediated mechanism [43]. A recent study demonstrated that zoledronic acid can potentially aid in restoring immune reactivity and chemosensitivity in MPM by decreasing RAS/ERK activity [44]. A single-arm clinical trial carried out in

8 patients with advanced MPM showed modest clinical activity and no significant toxic effects in patients who received zoledronic acid [45]. An *in vivo* microenvironment study showed that Pirfenidone can decrease proliferation and migration of MPM cells by causing inhibition of ERK [46]. Arsenic trioxide (ATO), an inorganic compound used in traditional Chinese medicine, has been shown to induce apoptosis in MPM cell lines by affecting MAPK pathways such as ERK and c-Jun NH₂-terminal kinase pathway [47]. In addition to these mechanisms, ATO has also demonstrated apoptosis in MPM cell lines by downregulating thymidylate synthase, Gli1 expression and E2F1 transcription factor [48, 49]. The potential benefits of these agents in all these studies provide a possible option in the future for repurposing them for use in MPM patients.

cAMP response element binding protein (CREB)

CREB, which belongs to the group of basic leucine zipper (bZIP) containing transcription factors, is a major regulator of basic cellular homeostasis, differentiation and growth [50]. After undergoing phosphorylation at its serine residues by other kinases, the transcriptional activity of CREB is activated [51]. Subsequently by regulating histone H3 and H4 methylation which controls chromatin recruitment, CREB modulates a number of physiological processes such as cell cycle, DNA repair, cell proliferation, angiogenesis, inflammation and immune responses [52, 53]. Overexpression of CREB has been implicated in many cancers such as glioblastoma, non-small cell lung carcinoma, breast carcinoma, hematopoietic malignancies and malignant mesothelioma, to name a few [54, 55]. CREB overexpression has also been shown to correlate with tumor recurrences, poorer prognoses and reduced survival in tumor patients [56, 57]. Several studies have emphasized the role of CREB in the pathogenesis of malignant mesothelioma. An *in vitro* study conducted on MPM cells showed that asbestos induced apoptosis also triggered the expression of several CREB target genes. It also demonstrated that doxorubicin increased the phosphorylation of CREB1 [58]. Another study using genetically CREB-silenced MPM cell lines and mouse xenograft models, conclusively proved that by regulating inflammatory signals, CREB plays a major role in controlling MPM tumor growth and development [59].

The activation of CREB following induction with radiation has been linked to radiosensitiv-

ity in several studies. A study by D'Auria *et al.* suggested that low dose radiation can trigger activation of CREB leading to cell survival. It also reviewed the pro-apoptotic role of CREB after exposure to ionizing radiation. This suggests that multiple mechanisms are involved in the radiation-CREB interaction and that future clinical trials involving this combination can provide a solution in cancer treatment [60]. Another study by Cataldi *et al.* showed that activation of CREB improves signal in leukemia cells which were exposed to ionizing radiation [61].

KG-501, a CREB inhibitor has been identified which can reversibly inhibit the interaction between CREB and CBP (CREB binding protein). The use of vandetanib, a tyrosine kinase inhibitor, along with doxorubicin in human MPM lines demonstrated that vandetanib alone decreased cell numbers in epithelioid cell lines and when used together synergistically resulted in increased doxorubicin toxicity in both epithelioid and sarcomatous cell lines [62]. This study suggested the combined use of these two drugs as a potential treatment option for MPM, owing to the impact on both ERK5 and CREB pathways. A new agent 666-15 has been identified as a CREB inhibitor with significant anti-tumor effects noted in both *in vivo* and *in vitro* studies and it holds promise as a future therapeutic option for MPM [63, 64].

Protein kinase B (AKT)

AKT is a serine/threonine kinase which exists as 3 isoforms and controls many cellular activities such as glucose metabolism, cell cycle progression and protein synthesis. It also blocks apoptosis by causing inactivation of several pro-apoptotic proteins [65, 66]. After being activated by phosphorylation, AKT induces a number of proteins located in the nucleus, cytosol and plasma membrane such as PRAS40, vimentin, palladin, p21 and p27 which enhance metastatic proliferation of cells [67, 68]. The system located upstream of AKT generates phosphatidylinositol triphosphate (PIP₃) with the action of phosphoinositide 3-kinase (PI3K) [69]. AKT over activation has been commonly noted in several human malignancies including ovarian carcinoma, gastric carcinoma and pancreatic cancer [70]. Some proteins in the AKT pathway such as PI3K, periostin, eIF4E function as oncoproteins when they are overexpressed. On the other hand, inactivation of tumor suppressor genes in the AKT pathway such as PTEN, TSC and FOXO leads towards malignancy causing paths, with PTEN mutations being the highest frequency [71, 72].

The role of radiation on AKT pathway has been analyzed in many studies. Li *et al.* conclusively proved in a study involving 8 cell lines of glioblastoma multiforme that induction of AKT activation by ionizing radiation led to an increase in radioresistance of the cancer cells. They showed that a serum factor may be involved and EGFR inhibition by AG1478 and PI3K inhibition with LY294002 can help increase radiosensitivity in tumor cells [73]. Toulany *et al.* pointed out that understanding the specific dysregulations of AKT such as gene amplification, point mutations and overexpression, which eventually lead to AKT activation might result in a clearer estimate of the outcome to radiation administration [74]. They demonstrated that the dual inhibition of AKT and MEK increased radiosensitivity in k-RAS mutated non-small cell lung cancer. They also emphasized the control of DNA double strand repair by AKT activation might serve as a future target to enhance radiosensitivity.

Several studies have dealt with the association between abnormalities in AKT/PI3K pathway and its role in the pathogenesis of MPM. In a study conducted by Suzuki *et al.* in 21 MPM cell lines, downregulation of PTEN was most frequently identified as the cause for activation of AKT pathway [75]. A study by Varghese *et al.* on the molecular nature of MPM conclusively proved that activation of PI3K and mTOR resulted in shortened survival in patients with MPM [76]. Zhou *et al.* demonstrated that the PI3K/AKT/mTOR pathway is a crucial cascade downstream of multiple activated receptor tyrosine kinases (RTK) suggesting the future potential of multi-point targeting of PI3K/mTOR as a therapeutic consideration in mesothelioma. Dual targeting of PI3K/mTOR by BEZ235 had a more significant effect on MPM inhibition compared to individual inhibition [77]. AKT kinase interacting protein (Aki1) is a scaffold protein for the PI3K–PDK1–AKT module. A study by Yamada *et al.* in cell-based assays showed that Aki1 silencing affected the CREB pathway and led to decreased cell viability in MPM tumors [78].

Programmed death-ligand 1 (PD-L1)

Programmed cell death receptor 1 (PD-1) is expressed on activated T cells and with its ligands PD-L1 and PDL2, it controls T-cell effector functions [79]. Several studies have demonstrated that PD-L1 overexpression is noted in around 30–40% of MPM patients, with a relatively greater incidence in non-epithelioid subtypes [80]. Moreover, MPM with PD-L1 positivity has significantly been associated with a poorer prognosis

than PD-L1 negative MPM (median survival of 4.8–5.0 months vs 14.5–16.3 months) [81, 82]. This finding led to the consideration that immune checkpoint inhibitors which affect PD-L1 can provide benefit in MPM.

Pembrolizumab, a humanized monoclonal antibody against PD-1, with a favorable safety profile and strong anti-tumor activity, has been approved for use in the management of several malignancies in more than 50 countries [83]. One of the first studies which involved pembrolizumab in MPM was the Keynote-028 Phase I trial conducted in 25 patients, and it showed a disease control rate (DCR) of 72%, a response rate of 20%, a median response duration of 12 months and was well tolerated [84]. Single arm phase II trials involving nivolumab, which also has PD-1 action showed objective response rates (ORR) between 15–29% and a median progression free survival (mPFS) between 2.6–6.1 months [85, 86]. Another agent avelumab, which has PD-L1 blocking activity, had a response rate of 9.4% in a study of 53 patients [87]. The CONFIRM trial, involving 336 patients with MPM randomized to nivolumab or placebo, which is ongoing in the UK hopefully will shed more light on this aspect [88].

Cytotoxic T lymphocyte-associated antigen (CTLA-4)

CTLA-4, an inhibitory receptor located on T lymphocytes, binds competitively to CD80 and CD86 ligands and attenuates CD28-mediated T cell activation. By inhibiting CTLA-4, there can be an increase in T cell activation which aids in mounting stronger anti-tumor immune responses. Ipilimumab and tremelimumab belong to the CTLA-4 family and have shown significant benefit in patients with advanced malignancies [89, 90]. Retrospective analysis of the phase II MESOT-TREM-2008 study revealed that the dosage of tremelimumab (15 mg/kg every 90 days) in chemotherapy-resistant advanced MPM was low [91]. This was followed by the MESOT-TREM-2012 trial with an increased dosage of tremelimumab (10 mg/kg every 4 weeks, and after 6 cycles every 12 weeks). Compared to 1 patient who achieved partial response in the 2008 study, 11 patients achieved disease control in the 2012 study [92]. Following the success of these 2 studies, the DETERMINE trial was conducted, a randomized controlled trial involving 571 patients who were randomized to tremelimumab or placebo arm. However, this study showed that tremelimumab did not significantly prolong survival or improve response in patients with previously treated MM [93].

A combination therapy of PD-L1 and CTLA-4 checkpoint inhibitors has also been studied with the aim to look for a more effective response in MPM patients. The MAPS-II trial, which included 125 patients with relapsed MPM across 21 hospitals in France, compared nivolumab (anti-PD1) with nivolumab plus ipilimumab (anti-CTLA4). It was concluded at the end of the study that nivolumab with or without ipilimumab showed an equally meaningful clinical response but higher drug-related adverse events were noted in the combination group (93% in combination vs 89% in monotherapy) [94]. A combination of tremelimumab and durvalumab in the NIBIT trial conducted in 40 patients with MPM showed comparable results to the MAPS-II trial [95]. The INITIATE trial, a single-arm phase II trial in 36 eligible patients with recurrent MPM, studied the combination of ipilimumab with nivolumab. A response rate of 38% and a DCR of 68% was noted at the study conclusion, but 94% reported experiencing an adverse event [96].

Dendritic cell (DC) therapy

DCs have often been referred to as “nature’s adjuvants” owing to the important role they carry out in initiating an immune response by capturing antigens and efficiently presenting them to lymphoid T cells. DCs also modulate humoral immunity by directly interacting with B cells and indirectly with CD4+ T helper cells [98]. Over the last decade, DCs have become an integral target in cancer immunotherapy. A study by Cornelissen *et al.* in 10 patients with MPM, DCs were administered with cyclophosphamide showed a promising overall mean survival of 37 months (98). A recently performed clinical trial in which 9 patients with MPM were administered DCs pulsed with allogenic tumor lysate, 2 patients showed a partial response and a median OS higher than 22.8 months in all the patients [99].

Conclusion

MPM is an aggressive cancer of the pleural lining and continues to present challenges in its management. Radioresistance of the tumor cells as well as increasing resistance to chemotherapeutic agents, have made the achievement of optimal response rates difficult. A better understanding of the various cell survival and pro-apoptotic signal pathways might open up new avenues in the treatment of MPM. Employing inhibitors targeting EGFR, ERK, CREB and AKT pathways, in combination with radiotherapy, might help in

overcoming the radiation resistance developed by tumor cells after administration of RT. Novel combinations of such small molecule inhibitors with existing approved chemotherapy regimens for MPM is also another possible alternative. Treatment options might also be available in the future in the domain of immunotherapy with several recent studies on inhibitors of PD-L1, CTLA-4 and dendritic cells showing promising results. There is a need to continue making efforts to further substantiate and deepen the understanding of the molecular mechanisms involved in MPM and to conduct clinical trials with the goal of optimizing treatment of MPM.

Conflict of interest

None declared.

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