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Malignant pleural mesothelioma: current perspectives

Abstract

The objectives of this study are to review epidemiology, novel methods of detection, novel diagnostics, and novel therapeutic options of malignant pleural mesothelioma (MPM) in the literature that were published between 1977 and 2019. Malignant pleural mesothelioma, associated with prolonged respirable-asbestos-fiber exposure is a rare cancer with constantly increasing incidence and poor prognosis due to lacking the effective treatment options. The median survival ranges from 8 to 14 months. Sarcomatoid histological subtype has the worst prognosis. Video-assisted thoracoscopy plus mediastinoscopy is the current gold standard for staging malignant pleural mesothelioma and is superior to computerized tomography of the chest for assessing the tumor size and suspected nodal metastases. Several circulating biomarkers are detected in MPM patients, such as mesothelin, osteopontin, fibulin-3, high mobility group B1, vascular endothelial growth factor, reactive oxygen species, reactive nitrogen species, micro-ribonucleic acids, tumor deoxyribonucleic acid, etc.Surgery is controversial and restricted to patients with early stage disease and good functional status. There is still no curative treatment whereas chemotherapy is the only treatment modality that improve patients' survival. Radiotherapy is beneficial as a palliative treatment and an adjuvant to chemotherapy and surgery in the context of trimodality treatment. In conclusion, there is potential for the development of biomarkers and radiological imaging in the years to come. Several novel therapeutic options are under studied and it is likely to involve highly personalized treatment. Its incidenceis expected to decrease in the next decade.

Keywords: pleural, mesothelioma, malignant, diagnosis, treatment, epidemiology

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Abbreviations: BALF, bronchoalveolar lavage; BAP1, BRCA-associated protein 1; CFAP45, Cilia and flagella associated protein 45; CT, computed tomography; CTCs, circulating tumor cells; ctDNA: circulating tumor deoxyribonucleic acid; DNA, deoxyribonucleic acid; FDG, 18-fluoro-deoxy-glucose; HMGB1, high mobility group B1 ; miRNAs, micro-Ribonucleic acids; MPM, malignant pleural mesothelioma; MRI, magnetic resonance imaging ; MSLN, mesothelin; PDGF, platelet-derived growth factor; PET-CT, positron-emission technology-computed tomography;RNS, reactive nitrogen species; ROS, reactive oxygen species; RR2, ryanodine receptor 2; SETDB1: set domain bifurcated 1; SETD2, set domain containing 2; SMRP, soluble mesothelin-related peptide; TGF-β, tumor growth factor-β ; TNM, tumor-nodes-metastases;UICC, the union for international cancer control; UK, united kingdom; ULK2, Unc-like autophagy activating kinase; USA, united states of america; US FDA, united states food and drug administration; VATS, video-assisted thoracoscopic surgery; VEGF, vascular endothelial growth factor

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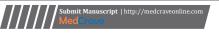
Introduction

Malignant pleural mesothelioma, a tumor originated from the submesothelial or mesothelial cells of pleura, pericardium, or peritoneum accounts for more than 80% arising from the pleura that the majority are male patients.[1,2] MPM, a rare cancer with increasing incidence and poor prognosis because of lacking the effective therapeutic interventions.[1,3,4] MPM is associated with previous long-term asbestos exposure of about 40 years of latency period.[5–9] The total incidence is highest in the UK and USA whereas the global incidence has increased constantly over the past decade, and is predicted to reach the estimated peak in 2020,[5,6] The median survival of MPM ranges from 8 to 14 months from the diagnosis.[5–7,10] Male is predominant of 4 : 1.[10] Four main histological subtypes of MPM are classified as the following : 1) epithelioid (most favourable prognosis with a median survival of 13.1 months), 2) sarcomatoid(worst outcomes with a median survival of 4 months), 3) biphasic or mixed, and 4) desmoplastic.[5,6,10]

Pathogenesis

Prolonged exposure to respirable asbestos fibers triggers an increase in inflammatory cytokines and reactive oxygen species (ROS) in the pleural microenvironment, both of which facilitate MPM carcinogenesis.[11,12] Naturally, asbestos occurs in the form of silicate mineral with two different forms : 1) curly serpentine fibers of chrysotile or " white " asbestos and 2) sharp, needle-like fibers of amphibole asbestos. Amphibole asbestos is divided into : 3) crocidolite (blue) asbestos, 4) amosite (brown) asbestos, 5) anthophyllite, 6) actinolite, and 7) tremolite. The risk of MPM development is associate with the type of fibers and heaviness and duration of exposure.[5]

Nevertheless, MPM is characterized by a low mutation load,[13] with the most frequently mutated genes involved in MPM pathogenesis, " tumor suppressors (BAP1, CDKN2A, LATS2, NF2).[14] After asbestos fibers are inhaled and migrate to the pleural

space causing pleural irritation and a repeated cycle of tissue damage and repair. Asbestos fibers that penetrate mesothelial cells that cause cell mitosis interference, generating DNA mutation, and altering chromosome structure. These mesothelial cells release inflammatory cytokines, such as platelet-derived growth factor (PDGF), tumor growth factor-β (TGF-β), and vascular endothelial growth factor (VEGF) that facilitate tumor growth.[9] Asbestos fibers also induce the phosphorylation various protein kinases (extracellular signal-regulated kinase 1 and 2 and mitogen-activated protein) that increases the expression of proto-oncogenes and facilitating abnormal cellular proliferation,[15] In PMP tumor, there is reduced expression of key molecules in the p53 tumor-suppressor gene pathway (p14, p16, and NF2-MERLIN).[15] There are deletions and loss mutations of BAP1 (BRCA-associated protein 1), CFAP45 (cilia and flagella associated protein 45), DDX3X, DDX51,RR2 (ryanodine receptor 2), SETDB1 (set domain bifurcated 1), SETD2 (set domain containing 2), and ULK2 (unc-like autophagy activating kinase).[16] Nevertheless, MPM has a low frequency of protein-altering mutations, approximately 25 mutations per tumor,[17] and contributing to the limitations of the potential for molecular targeted therapy.[18]

Clinical manifestations, investigation and diagnosis

Chest radiological imaging should be performed in all MPM-suspected patients for diagnostic and staging information. Characteristically radiological findings may be nodular pleural thickening, pleural plaques, a localized pleural-mass lesion, pleural effusion, irregular fissural thickening, or loss of hemithoracic volume. Nevertheless, further radiologically imaging tools, such as bedside chest ultrasonography, computed tomographic imagingare usually required due to insensitive and nonspecific chest radiographic features in general.[19–22] Positron-emission technology-computed tomography (PET-CT) combines high-resolution computed tomographic (CT) scanning injected with a radioactive metabolic tracer (such as 18-fluoro-deoxy-glucose (FDG)) or magnetic resonance imaging (MRI).[23–25] Nevertheless, PET-CT has low sensitivity for the diagnosis of extrapleural lesions due to its poor spatial resolution.[26] In addition to CT scanning of the chest, surgical information by video-assisted thoracoscopic surgery (VATS) plus mediastinoscopy which is the current gold standard for staging in MPM and is superior to CT for assessing tumor size and suspected nodal metastasis,[27,28] is the consensus by using the International Mesothelioma Interest Group staging classification,[29] whereas the European Pneumological Society,[30] recommends using the tumor-nodes-metastases (TNM) classification of the Union for International Cancer Control (UICC).[31] VATS reveals the sensitivity and specificity of 95%-98% and 100%, respectively and enables the removal of specimens under visual observation, as well as pleurodesis in the same procedure.[28] VATS also enables the assessment of its respectability.[32]

By pleural puncture and cytological diagnosis, tumor cells are identified in pleural effusion more than 50% of patients with MPM, with the likelihood of positive cytology depending on the MPM subtypewith the limited cytological diagnosis.[33] Percutaneous needle biopsy without image guidance reveals the sensitivity and specificity of 7%-47% and 100%, respectively.[28]

There are several circulating tumor proteins identified in patients with MPM, such as mesothelin (MSLN, a cell-surface glycoprotein expressed by mesothelial cells),[34–36] osteopontin(an integrin-binding protein implicated in cell-matrix interaction and overexpressed in several types of cancers),[37,38] and fibulin-3 (a secreted glycoprotein implicated in cell proliferation and migration correlated with advanced disease, also identified in pleural fluid).[39, 40] Soluble mesothelin-related peptide (SMRP), a soluble form of mesothelin is secreted by the tumor cells into the blood circulation.[41–43] SMRP seems to be effective in predicting response to chemotherapy and patient survival although it is not specific for MPM and cannot be considered an early diagnostic biomarkers for MPM surveillance program.[41,44–48] Several studies revealed that plasma osteopontin is a more reliable and stable biomarker than serum osteopontin and the data involving its diagnostic accuracy are inadequate.[49–51] Combined measurement of circulating SMRP and osteopontin is not more informative than measurement of circulating SMRP alone.[49,50,52,53] Several previous studies demonstrated that fibulin-3 was not beneficial for differentiating patients with MPM from patients affected by other diseases,[54] and was not effective as mesothelin.[55]

Other biomarkers for detecting MPM are inflammatory and angiogenic factors (High Mobility Group B1 (HMGB1) and VEGF), biomarkers of oxidative stress (Reactive Oxygen Species (ROS) and Reactive Nitrogen Species (RNS)), circulating micro-ribonucleic acids (miRNAs), circulating tumor deoxyribonucleic acid (ctDNA), circulating methylated deoxyribonucleic acid (circulating methylated DNA), and circulating tumor cells (CTCs).A previous study indicated that HMGB1 and its receptors were highly expressed in MPM cell lines and tissues.[56] VEGF, a key stimulator of tumor neoangiogenesis, is overexpressed in MPM tissues.[57–59] In comparison to patients with lung cancer or non-malignant pleural diseases, circulating VEGF levels are increased in pleural effusions of patients with MPM.[60] ROS and RNS are key mediators of asbestos toxicity.[61] Bronchoalveolar lavage (BALF) of patients with asbestos exposure demonstrated an increase in various biomarkers of inflammation and altered ROS and iron homeostasis (i.e., iron, lactoferrin, ferritin, transferrin, and transferrin receptors)compared to controls.[62] A previous study on the levels of miR-103a-3p and miR-30e-3p in extracellular vesicles demonstrated that the combination of these two biomarkers discriminated patients with MPM from asbestos-exposed controls with a sensitivity of 95.5% and specificity of 80% and were confirmed by normalizing the data to RNU48, miR-99a, miR-638, miR-720, and miR-1274a.[63] In consideration, these miRNAs could be biomarkers of asbestos exposure rather than disease. Upregulation ofmiR-2053 could be a good prognostic biomarker of MPM.[64] Detection ofctDNA variants in patients with MPM could be a potential biomarker for the diagnosis of MPM.[65–67] Detection ofchanges in ctDNA methylation could be an early diagnostic and prognostic tool of MPM.[68] CTCs countsin the blood circulation is very low at the early stage and increases in advanced stage of cancer.[69]" CTC-chip " test that developed by Chikaishi et al. demonstrated better performance than CELLSEARCH®test that is approved by the United States Food and Drug Administration (US FDA).[70, 71]

Chest pain is common and usually heavy and dull and sometime called a " dragging " sensation,[5,72] Breathlessness is also common and is usually due to a pleural effusion that is identified in about 70% of MPM patients in early stage of disease.[73] Other clinical features include anorexia, weight loss, malaise, sweats, and fatigue.[5,6,72–78]

Management

Systemic treatment options include targeted therapy, chemotherapy, and radiotherapy, provided separately or as part of multimodality treatment, whereas surgery is controversial and restricted to patients

with good functional status and early stage disease. Treatment of MPM patients should be discussed at a specialist mesothelioma multidisciplinary team meeting.[5,79,80] There are several unanswered questions regarding chemotherapy in MPM patients, such as whether immediate chemotherapy is more effective than chemotherapy delayed until the appearance of clinical manifestations, the unclear optimum number of cycles of chemotherapy, the role of maintenance pemetrexed, and the benefit from continuing pemetrexed as maintenance therapy following an initial response.[81] Nevertheless, chemotherapy is the only treatment modality that improve survival in MPM patients, but there is still no curative treatment for MPM.A recent study demonstrated that bevacizumab, an anti-VEGF monoclonal antibody in targeted therapy was effective in the treatment of MPM and is warranted alongside first-line standard chemotherapy in patients with unresectable MPM.[82,83] Radiotherapy is beneficial in two main types : 1) as a palliative treatment, and 2) an adjuvant to chemotherapy and surgery in the context of trimodality treatment.In consideration the benefit of surgery, there is a need for large-scale randomized trial data to investigate its efficacy.[5,84,85] For controlling pleural fluid, chemical pleurodesis is a procedure that can obliterate the pleural space and preventing pleural fluid re-accumulation. Good palliative care foe MPM patients is emphasized by the British Thoracic Society, the European Respiratory Society, and the International Mesothelioma Interest Group to manage clinical symptoms, emotional or spiritual, and psychological support for maintaining quality of life and dignified life.[5,6]

Discussion

Several circulating biomarkers are investigated for screening and detection of MPM, such as mesothelin, osteopontin, fibulin-3, HMGB1, VEGF, ROS, RNS, miRNAs, ctDNA.[34–68] Additionally, " CTC-chip " test developed by Chikaishi *et al* revealed better results than " CELLSEARCH® " test that approved by the US FDA. CTCs counts increases in the MPM patients with advanced stage.[69] The mentioned miRNAs are beneficial biomarkers of asbestos exposure rather than advanced stage MPM. Detection of changing ctDNA methylation could be beneficial in early diagnosis and prognosis of MPM,[68] whereas upregulation of miR-2053 could be a good prognostic biomarker of MPM.[64] For detection of asbestos toxicity, both ROS and RNS are the key mediators.[61] Breathlessness, identified in around 70% of MPM patients and chest pain are common symptoms in addition to weight loss, anorexia, sweats, fatigue, and malaise.[5,6,72–78].

Surgery is controversial and limited to MPM patients with early stage disease and good functional status. The efficacy of surgery is urgently needed for large-scale randomized trial data.[5,84,85] Although there is no curative treatment, chemotherapy is the only treatment modality that improve MPM patients' survival. Nevertheless, there are still several questionable issues, e.g. whether immediate chemotherapy is more effective than chemotherapy delayed until the appearance of clinical features, the unclear suitable number of the cycles of chemotherapy, the role of maintenance pemetrexed, and the benefit from continuing pemetrexed as maintenance therapy following an initial response,[81] whereas the roles of radiotherapy are only two main types, palliative treatment and adjuvant to chemotherapy and surgery in trimodalitytreatment. Numerous novel therapeutic agents for MPM have been studied, such as EGFR antagonist targeted therapy and PDGF inhibitor targeted therapy.[86–89] Mesothelin-targeted treatments, such as chimeric antigen receptor T-cells targeted to mesothelin, mesothelin tumor vaccine (CRS-207),

anti-mesothelin immunotoxins (e.g. SSIP), and mesothelin-specific monoclonal antibodies (e.g. amatuximab) are another interesting area in MPM treatment.[90–94] Checkpoint inhibitors, the immunotherapeutic agents, such as pembrolizumab and tremelimumab have demonstrated prolonged disease stability and impressive disease control rates when used as first-, second-, and third-line treatment,[95–99] Further exploration in synergistic effects of the combination of chemotherapy with immunotherapy or multiple immunotherapy agents in MPM treatment.[100–102] In fact, the latency of MPM can be as long as 60 years, the patient' s occupational history must be investigated extensively by an properly qualified health personnel and it must be kept in mind that MPM can be caused by short-term, low-level asbestos exposure.[103,104]

Conclusion

MPM, a complex disease can cause important morbidity and mortality. MPM remainsa diagnostic and therapeutic challenge ambulatory and in-hospital care. There is potential for the development of biomarkers and radiological imaging in the years to come. Several novel therapeutic options are under investigated and it is likely to involve highly personalized treatment. Its incidence has been constant in recent years and expect to decrease in the next decade.

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Conflicts of interest

The authors declare there are no conflicts of interest.

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