Malignant pleural mesothelioma (MPM) is a neoplasm originating from mesothelial cells, which form the membranes surrounding the lung cavities. It is currently a disease mainly of the industrialised world, closely linked to asbestos exposure.1 Seldom diagnosed prior to the advent of widespread asbestos mining in the early to mid twentieth century, it has risen in incidence over the last five decades.2,3 According to the most recent Australian Institute of Health and Welfare data, in 2009 there were 666 cases of malignant mesothelioma diagnosed in Australia.4 This review will provide a brief overview of the diagnosis, current treatment modalities and some novel systemic treatment strategies that have been explored in MPM.

Abstract

Malignant pleural mesothelioma is a relatively uncommon disease associated with asbestos exposure. Its incidence increased markedly following the widespread mining and use of asbestos in many industries. The legal aspects regarding compensation cases for those who have developed this disease has raised its profile in the media, but also compounds the stress of diagnosis for patients. It has an insidious onset and may clinically and pathologically mimic other benign or malignant processes, complicating diagnosis. Radical surgery may be used for a highly selected population of malignant pleural mesothelioma patients in the context of multimodality treatment in an experienced thoracic surgical centre, but there is no randomised evidence to support its benefit. In most cases surgery is used to treat symptoms or obtain tissue for diagnosis. Combination of a platinum agent and pemetrexed is now widely used and shown to prolong life. Other treatments including radiotherapy, analgesics and supportive interventions are an integral part of the treatment of this disease. Further research is being undertaken on promising novel therapies for use in this disease, which will be discussed in this review.

Diagnosis

Clinical features of MPM usually develop gradually and may consist of constitutional symptoms including weight loss, fatigue and night sweats, as well as local symptoms such as dyspnoea and chest pain.7 Initial investigations should include chest X-ray and computed tomography. The most frequent finding on initial investigations is that of a pleural effusion. As MPM has different histological patterns (three major subtypes: epithelioid, sarcomatoid or mixed/biphasic),8 and may resemble benign mesothelial disease, malignant lung disease or sarcoma, formal diagnosis on a tissue biopsy by a pathologist experienced in the diagnosis of MPM is recommended.9 The pathological diagnosis of MPM requires the observation of invasion of the neoplastic mesothelial cells into surrounding tissue on histological sections,8 and the diagnosis should be supported by appropriate immunohistochemical labelling (two positive mesothelial markers and two negative carcinoma markers).9 Cytology-only diagnosis of epithelioid MPM on aspirated effusion fluid remains controversial, although cytological diagnosis is achievable in many cases with supportive immunohistochemical investigation, particularly when the cytological findings can be correlated with imaging studies (evidence of nodularity of the pleural disorder and evidence of invasion).10 However, due to the low sensitivity of cytology only diagnosis reported in the literature,5,11 it is generally recommended that video-assisted thoracoscopic surgery be performed to obtain pleural biopsy tissue, as it also allows for drainage of pleural effusion and access for pleurodesis.12

Malignant pleural mesothelioma (MPM) is a disease with particular relevance to Australia. Asbestos was first mined in Australia in the 1880s near Jones Creek, a town in NSW.5 It was not until the late 1940s when the insulating properties of asbestos rendered it a useful product in the building industry during the post war building boom, and subsequent demand for asbestos saw mining production rise exponentially in mines in NSW, Tasmania, South Australia and Western Australia.5 There has also been widespread exposure within the building and transport industries in which asbestos was broadly utilised.6

Asbestos mining ended in Australia in 1983, and it is expected that malignant mesothelioma related to occupational exposure will plateau in the coming decade. In a Western Australian study, however, a significant increase was noted in the number of people being diagnosed with malignant mesothelioma whose only exposure to asbestos must have occurred in a non-occupational setting (most likely during home maintenance and renovation). Between 2005 and 2008, 8% of males and 5% of females diagnosed with malignant mesothelioma in this series reported non-occupational exposure as their only exposure to asbestos.6 These observations ask for confirmation in a case-controlled epidemiological study.
From a prognostic perspective, epithelioid histological type provides the best outlook. Other favourable prognostic factors include an Eastern Cooperative Oncology Group performance score of 1 or less, absence of anaemia or thrombocytopenia, and a normal lactate dehydrogenase. Emerging inflammatory markers, such as neutrophil-to-lymphocyte ratio may also assist in the prognostication of MPM patients.

**Current treatment strategies**

Treatment of an MPM patient should be provided by a multidisciplinary team ensuring multidisciplinary care, although there is no direct high-level evidence suggesting the benefit of the multidisciplinary approach. It may involve a single or multiple modality therapy involving surgery, chemotherapy, radiotherapy, and best supportive care. Recently, the draft of the Australian National Guidelines for Diagnosis and Management of Pleural Malignant Mesothelioma, prepared under the auspices of the National Health and Medical Research Council, has been released, and currently is open for public consultation.

**Surgery**

Surgery may be used to palliate symptoms of pleural effusion, or bulky pleural disease. More radical surgery with the intent to prolong survival may be used in selected patients with limited disease confined to one hemithorax. The most extensive radical surgery is extrapleural pneumonectomy (EPP), which involves excision of the pleura, lung, lymph nodes, diaphragm and pericardium en bloc. Pleurectomy and decortication is arguably a less radical procedure, in which the parietal pleura is removed and the lung is examined for any macroscopic evidence of disease, which if found is subsequently resected. As it is impossible to achieve a clear microscopic surgical margin, treatment strategies have been developed to consolidate further control from surgery. In the case of EPP, typically chemotherapy is given as induction treatment, followed by surgery and then hemithoracic adjuvant radiotherapy.

The MARS trial published in 2011 examined the survival benefits of EPP in comparison to no EPP after chemotherapy, as a secondary outcome. Twelve centres in the UK randomised 50 patients into the two arms of the study. In the trial, patients in the EPP arm had lower overall survival than those who were randomised not to have EPP. One of the main controversies of the trial was the high perioperative mortality rate of 18% in those undergoing EPP, which compares poorly to other documented rates worldwide – in the Australian experience, the 30 day mortality rate post-EPP is 5.7%. Further, perioperative chemotherapy regimens were not standardised and there was a significant proportion of patients who were not treated to the study protocol. On this basis, the results of this trial cannot be generalised to other experienced centres. However, in view of the lack of randomised evidence for definite benefit, multimodality approach incorporating EPP should be considered experimental and restricted to institutions with significant surgical experience with high volumes of cases.

**Chemotherapy**

It is only since 2003 that MPM has been shown to be responsive to chemotherapy agents. Vogelzang et al demonstrated that when patients received pemetrexed and cisplatin compared to cisplatin as monotherapy, they received a survival benefit (median overall survival 12.1 months v 9.3 months) and longer time to progression (median 5.7 months v 3.9 months). This combination chemotherapy was also found to improve patients’ symptoms and health-related quality of life, compared to cisplatin alone. Retrospective analysis published in 2008 demonstrated similar 12 month overall survival rates between the combinations of cisplatin and pemetrexed, and carboplatin and pemetrexed (63% and 64% respectively), suggesting carboplatin equivalence with cisplatin in this regimen. Raltitrexed, another antimetabolite, in combination with cisplatin, demonstrated similar improvements in median overall survival when compared with cisplatin monotherapy (11.4 months v 8.8 months). Therefore, the first line standard of care for MPM patients currently is a platinum doublet with an antimetabolite, either pemetrexed or raltitrexed.

The role of maintenance chemotherapy following combination chemotherapy with platinum and pemetrexed has not been prospectively evaluated. A small non-randomised study demonstrated that pemetrexed maintenance therapy is well tolerated and is feasible to administer. There is an ongoing randomised phase II trial evaluating the role of maintenance pemetrexed in patients with stable disease after first-line chemotherapy (NCT01085630).

Once patients progress after first-line chemotherapy, there is currently no standard of care in this setting, as there are no agents with randomised evidence demonstrating a survival benefit. Agents tested in the second line setting include pemetrexed alone in pemetrexed-naïve patients, and vinorelbine. However, in a recent retrospective review from Memorial Sloan-Kettering Cancer Centre, the response rate for vinorelbine in a cohort of MPM patients who progressed after platinum-based therapy was found to be 0%. Retreatment with pemetrexed-based therapy could be considered in patients with durable responses from previous pemetrexed-based treatment. Patients should be encouraged to participate in clinical trials in this setting.

**Radiotherapy**

Radiotherapy has a role in palliating symptoms of pain associated with chest wall involvement or metastatic nodules. The evidence for the use of radiotherapy prophylactically on biopsy tracts to prevent seeding remains inconclusive, and the two systematic reviews showed no significant effect on overall survival by prophylactic radiotherapy and therefore it is not recommended.

**Supportive care**

Symptom management of MPM is complex. Pain and dyspnoea are the most common symptoms which are reported in greater than 90% of MPM patients. These symptoms interface with psychological symptoms such as depression and anxiety, which may be heightened in
an environment where patients are commonly involved in legal proceedings related to their occupational exposures. Initial management of dyspnoea should include addressing the patient’s environment. Using fans to blow air across the face, opening doors and windows to create a sense of space and using cool face washes can all reduce the sensation of dyspnoea. Additionally, low dose oral opioids have also been shown to reduce symptomatic breathlessness. Domiciliary oxygen has historically been used in the palliative setting to alleviate dyspnoea, however there is little evidence for its use in the absence of hypoxaemia. Underlying causes of dyspnoea should be considered and managed appropriately. Most often, this involves draining recurrent pleural effusions and performing pleurodesis.

Pain should be managed with simple analgesics such as paracetamol, with the addition of opioids, and anti-inflammatory medications for nociceptive pain. Neuropathic pain may coexist with nociceptive pain and requires the use of co-analgesics such as antiepileptics or tricyclic antidepressants. Patients with refractory pain should be referred to a palliative medicine specialist, nerve blocks or intrathecal injections should be considered.

Legal and compensation issues affect the majority of people diagnosed with MPM. Patients should be provided with practical information of how to navigate through the often complicated local system.

**Novel systemic therapy**

Despite the promise of personalised treatment in other solid tumours, the approach of ‘precision medicine’ is not yet a reality for MPM patients, despite international efforts over the last decade. Although targeting EGFR, VEGF and PDGFR pathways has been successful in some other solid tumours, agents targeting these pathways have failed to demonstrate benefit in MPM patients. Here, we will discuss some of the molecular pathways that have been tested in the last decade and selected, and promising potential pathways that could be targeted.

**Signalling Pathway Inhibition**

Although EGFR is over-expressed in most MPM, the EGFR-tyrosine kinase inhibitors, gefitinib and erlotinib, have been found to be ineffective in the treatment of MPM in two phase II trials in the first line setting. Furthermore, two phase II trials using imatinib mesylate, a potent inhibitor of PDGFR receptor signalling and C-Kit, have shown a lack of efficacy and poor tolerability.

**Anti-angiogenesis**

Agents targeting the VEGF pathway that have been tested in MPM include anti-VEGF antibody (bevacizumab) and small molecule tyrosine kinase inhibitors. Bevacizumab in combination with cisplatin and gemcitabine in a randomised phase II trial, has been shown not to prolong survival in MPM patients. As cisplatin with gemcitabine is typically has a poor prognosis, the preliminary result of this study is difficult to interpret.

**Other promising targets**

Other important new targets in MPM are being examined and MPM is molecularly characterised by the loss of tumour suppressor genes, rather than gain of function mutation. An example is the inactivation of neurofibromatosis type 2 (NF2) in MPM which typically has a poor prognosis, the preliminary result of this study is difficult to interpret.

**Epiogenetic modulations**

The recent discovery of the relatively common (25%) inactivation of the BRCA 1- associated protein 1 (BAP1) is of interest, as BAP1 has a role in control of gene expression through histone modification. Vorinostat is a histone deacetylase inhibitor that alters gene expression and protein activity. The VANTAGE 014 study randomised MPM patients who failed prior pemetrexed and platinum therapy to either vorinostat or placebo. Disappointingly, vorinostat did not significantly extend the overall survival in the second line setting. However, a phase II trial examining first line vorinostat with cisplatin and pemetrexed is ongoing (NCT01353482).

**Mesothelin**

Mesothelin is expressed abundantly in the epithelioid subtype of the MPM tumour cells, which makes this an appealing therapeutic target. There are several mesothelin-targeted immunotherapeutic approaches currently being tested, including SS1P (NCT01144593) and amatuximab (NCT00738582). Amatuximab (MORAb-009) is a chimeric monoclonal antibody that binds mesothelin and elicits antibody-dependent cellular cytotoxicity. It is currently the only agent in phase II development. The single arm clinical trial of amatuximab in combination with cisplatin and pemetrexed is ongoing (NCT01353482).

Tyrosine kinase inhibitors inhibiting the VEGF receptors tested in unselected MPM patients include sorafenib, sunitinib, cediranib and vatalanib. These agents were all examined in single-arm phase II trial fashion and yielded a response rate from 0 to 12%, and progression free survival from 1.8 to 4.1 months. It is difficult to know if these agents have definitive activity, as no randomised trials have been done to date. Identification of predictive markers for these types of agents has been elusive, making selection of patients who are likely to benefit difficult.

Lastly, thalidomide (an angiogenesis inhibitor and cytokine modulator) in combination with cisplatin and gemcitabine, or alone, has been tested in two phase II studies and suggested some hint of prolongation of stability of disease. However, a subsequent randomised trial evaluating maintenance thalidomide in non-progressing patients after initial pemetrexed based chemotherapy, failed to show a benefit in delaying tumour progression.
number of signalling pathways, with an NF2 loss leading to activation of mammalian target of rapamycin complex 1 (mTORC1) and the focal adhesion kinase (FAK). Clinical interest in these drugs targeting these pathways is now high due to the availability of mammalian target of rapamycin (mTOR) inhibitors and FAK inhibitors. A phase I trial of GDC9980 (PI3K/mTOR inhibitor) showed some encouraging anti-tumour activity (tumour regression and prolonged disease control) in a subgroup of six MPM patients, reported in the 2012 International Mesothetaoma Interest Group conference. The use of FAK inhibitors in MPM is currently being considered.

Conclusion

Progress in the treatment of MPM has been slow and the systemic treatment of MPM remains unchanged since the approval of pemetrexed used in conjunction with cisplatin in 2003. Beyond the first line treatment, there is currently no standard of care. The promise of ‘precision medicine’ is yet to arrive in the clinic for the treatment of MPM patients. Significant work is required through multidisciplinary research input into this devastating disease, starting with surgeons collecting high quality annotated specimen, translational scientists uncovering important molecular pathways and development of novel pathway or protein targeted drugs, as well as committed clinicians designing and conducting practice-changing clinical trials.

References


