Editorial

Biomarkers in malignant pleural mesothelioma: current status and future directions

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Malignant pleural mesothelioma (MPM) is an uncommon but highly aggressive tumour of the mesothelial lining of the thoracic cavity that is associated with asbestos exposure (1). It can develop from inhaled needle-like asbestos fibers that can become trapped in the lungs. Over time, these asbestos fibers migrate from the lungs to the pleural lining and can trigger genetic changes in the mesothelial cells, where they can become cancerous. The characteristic morphology of MPM is usually a rind that encases and locally invades the sub-pleural lung tissue (2). MPM is a challenging malignancy to manage as it is often difficult to diagnose, it is generally associated with poor prognosis, there are a lack of effective targeted therapies and significant proportion of patients do not benefit from available treatments (3). With these factors in mind, it was timely to read the recent review by Sun *et al.* (4), which highlights the importance of biomarkers, both tumoural and blood-based, and their potential to assist in the clinical management of MPM.

Early diagnosis of MPM is difficult because the disease is typically asymptomatic until later in its course. When it becomes symptomatic, the constellation of symptoms can be vague and nonspecific and often mimics other more common presentations such as chest infection or pleurisy. This in turn means MPM is frequently diagnosed at an advanced stage. Diagnosis of MPM currently requires pathological examination and immunohistochemical analyses that are supplemented with radiological examination such as chest X-rays and computed tomography scans (1). Pathological confirmation can either be achieved by cytological examination of the pleural fluid or more typically by obtaining tissue via invasive surgical biopsy (1). Given MPM is highly heterogeneous and the pleura is a common site for other metastatic diseases, accurate pathological diagnosis of MPM can be challenging (3).

There are three main histological subtypes for MPM that have validated prognostic significance: epithelioid, sarcomatoid and biphasic. Epithelioid MPMs are the most common (around 50–60% of all cases) and have longer survival than the other subtypes (12 to 27 months) (3). They appear morphologically similar to carcinomas (1,3) and commonly present with pleural effusion. Sarcomatoid MPMs make up around 10–20% of all cases (1) and have the worst prognosis. They appear similar to sarcomas and commonly present with a pleural mass. Biphasic MPMs are defined as a mixture of epithelioid and sarcomatoid types (1). MPM patients generally have poor prognosis, with typical survival of around 1 year from diagnosis (1,2). However, with up to 10% living for 5 years or more (3), discussion of prognosis in individual patients at the time of diagnosis remains a challenge.

Treatment options for MPM patients are limited because MPM is usually detected at an advanced stage. Currently available treatment options for MPM include surgery, chemotherapy and radiation therapy or a combination of these modalities. The appropriate treatment is determined by the clinical stage and patient characteristics (3). Patients

who are candidates for surgery undergo either extra-pleural pneumonectomy (EPP), which involves macroscopic removal of the diseased pleura together with the lung, pericardium and hemi-diaphragm, or a radical pleurectomy/decortication (P/D) (1). Surgical management is typically combined with chemotherapy and/or radiotherapy as surgical microscopic clearance is difficult to achieve (1,2). However, most patients are not suitable candidates for surgery, making systemic chemotherapy the mainstay treatment for most patients (1). Currently, there are only two Food and Drug Administration (FDA)-approved chemotherapeutic drugs for MPM: cisplatin and pemetrexed (3). They have been used as standard of care in MPM for over a decade. No second-line treatments for MPM have yet been approved for standard of care treatment. Combining cytotoxics with an anti-vascular endothelial growth factor (VEGFA) approach has shown promise. The addition of bevacizumab (MAPS study) (5) or nintedanib (LUME-Meso study) (6) to chemotherapy has been investigated with some success in clinical trials.

Currently, there is intense interest in the use of immunotherapy in MPM due to the promising results of KEYNOTE-028 using single agent pembrolizumab, a programmed death protein 1 (PD-1) antibody (7). PD-1 is expressed on effector lymphocytes, while its natural ligands, PD-L1 and PD-L2, are expressed on tumour cells or in the surrounding microenvironment (1). The PD-1/PD-L1 pathway downregulates T-cell function, which can facilitate tumour rejection by the immune response (1,3). These receptors can be targeted by monoclonal antibodies that block PD-1/PD-L1 pathways. Currently there are several international trials using the PD-1/PD-L1 approach, typically in combination with chemotherapy [pembrolizumab and chemotherapy in a Canadian trial (NCT02784171) and durvalumab and chemotherapy (DREAM; ACTRN12616001170415)] or with other immunotherapy agents [nivolumab and ipilimumab (CheckMate743; NCT02899299)].

It is clear that there are several clinical challenges with MPM. There is an urgent and unmet need for non-invasive biomarkers that can assist in early diagnosis, better define prognosis and predict patient responses to available treatments. A biomarker is a characteristic that can be measured and that gives an indication of the biological state of the patient. Diagnostic biomarkers can differentiate the disease of interest from other diseases or normal state; prognostic biomarkers inform us about the pace of disease progression and outcome regardless of treatment; and predictive biomarkers tell us whether a patient will benefit from a particular treatment. An ideal biomarker for MPM should be inexpensive, reproducible, easy to obtain and easily sampled with a minimally invasive technique, making blood-based tests prime for investigation.

The search for mesothelioma biomarkers has been ongoing for the last 30 years. So far, three blood-based biomarkers have been extensively investigated for MPM for their diagnostic potential: soluble mesothelin, osteopontin and fibulin-3, as discussed in the review by Sun *et al.* (4). Soluble mesothelin, also known as soluble mesothelin-related peptide (SMRP), is a glycoprotein encoded by the *MSLN* gene. It is expressed on the surface of normal mesothelial cells in limited amounts and overexpressed by tumour cells in most MPM tumours and other cancers (1,2). The regulation of mesothelin expression is not fully understood, however it has been observed that mesothelin can be shed from the cell surface and can be detected in the blood (2). SMRP is currently the only blood-based biomarker that has been clinically validated and FDA-approved for mesothelioma. It is marketed under MESOMARK® and indicated for monitoring of patients diagnosed with epithelioid or biphasic mesothelioma. Although SMRP has been validated as a diagnostic biomarker, its clinical utility is limited by its apparent poor sensitivity, with meta-analysis reporting sensitivity of 32% at 95% specificity. The clinical utility of SMRP is also limited by its apparent high false-positive results (1,2).

Osteopontin and fibulin-3 are two additional secreted proteins that have been investigated as diagnostic biomarkers in MPM. Osteopontin is a glycoprotein that is encoded by the *SPP1* gene and is involved in immune regulation, cell migration and other biological processes (8). In a meta-analysis involving 360 MPM cases, the overall diagnostic sensitivity of osteopontin was reported at 65% and a specificity of 81%. It therefore currently lacks the sensitivity and specificity to be as a standalone diagnostic biomarker (2,8). Fibulin-3 is an extracellular glycoprotein that is involved in the regulation of cell proliferation and migration. In early studies (9), Fibulin-3 was able to accurately diagnose MPM from asbestos-exposed individuals, but it has proved difficult to independently validate these initial results (10). A recent meta-analysis involving 468 MPM cases yielded a diagnostic sensitivity of 62% at a specificity of 82% (11). Therefore, the use of fibulin-3 as a diagnostic biomarker is currently not ready for prime time and requires further validation studies prospectively.

More recently, an increase in the levels of the High

Mobility Group Box 1 (HMGB1) protein in serum has demonstrated potential as a diagnostic biomarker in MPM (12). HMGB1 is a protein that is released by mesothelial cells during necrotic cell death. When released, HMGB1 proteins initiate inflammatory response in the extracellular space. One study demonstrated that the specific hyperacetylated isoform of HMGB1 was highly sensitive and specific in differentiating MPM patients from asbestos-exposed and healthy controls (13). However, larger prospective studies are required to validate the diagnostic accuracy of HMGB1.

All four blood-based markers mentioned above have also been investigated for their prognostic value. SMRP, osteopontin and HMGB1 have been associated with poor prognosis and show potential as prognostic markers in MPM (14,15). However, none of them are currently used routinely in clinic for this purpose, as majority of them have not been validated prospectively and their superiority used alone has not been proven over the conventional prognostic EORTC or CALGB models (16). The prognostic value of fibulin-3 in MPM patients has not yet been demonstrated (11). Other peripheral blood-based markers involving inflammation-based prognostic scores have also been explored as candidate biomarkers, such as lymphocyte-to-monocyte ratio (LMR) and neutrophil-to-lymphocyte ratio (NLR). LMR has been reported as an independent prognostic marker for overall survival in MPM patients and there are reports that low NLR could be an independent predictor of better survival (17).

MicroRNAs (miRNAs) are another group of markers being investigated as diagnostic and prognostic biomarkers owing to their tissue specificity and ability to classify several types of tumours (18). MicroRNAs are short non-coding RNAs (typically 19–25 nucleotides) that are involved in multiple cellular processes including development, proliferation and apoptosis. It has been shown that deregulated miRNAs have potential as diagnostic and prognostic markers for MPM. For example, in a study of 142 tumour samples, higher expression of miR-29c was found to predict longer survival (9). In a subsequent study involving MPM patients undergoing EPP or P/D, a six-miRNA signature including miR-21-5p, miR-23a-3p, miR-30e-5p, miR-221-3p, miR-222-3p, and miR-31-5p was found to predict an overall survival of more than 20 months with an accuracy of 92.3% for EPP and 71.9% for P/D (19). Circulating miRNAs are also being investigated in MPM because of their stability in circulation (18), however larger studies are required to validate the diagnostic and prognostic values of miRNAs.

While there has been a focus on diagnostic and prognostic biomarkers in MPM, in common with other solid tumours, there is a lack of reporting on predictive biomarkers in MPM. Although not covered in the review by Sun *et al.*, it could be argued that predictive biomarkers are the most important as they have the potential to personalise treatments for MPM patients. The thymidylate synthase (TS) protein, encoded by the gene TYMS, is the main target for pemetrexed-based chemotherapy, however treatment responses do not appear to be strongly correlated with tumoural TS expression levels (18). So far, no predictive biomarkers have been recommended for clinical practice and none have been validated in independent and prospective studies. The discovery of predictive biomarkers for the anti-VEGF therapeutic approach has been elusive. Despite intensive international effort, no reliable biomarkers have been found to predict for response to bevacizumab (20). Similarly, a range of angiogenic factors have been investigated as potential biomarkers for nintedanib in the LUME-Meso study, but none were predictive of nintedanib response (6).

As discussed earlier, immunotherapy approaches using checkpoint inhibitors are actively being investigated in MPM. Checkpoint inhibitors are antibodies that trigger the anti-tumour immune response and the genes involved could provide new predictive biomarkers. PD-L1 expression in the tumour tissue has emerged as a predictive biomarker in lung cancer, where ≥50% tumour proportional score predicts for response to pembrolizumab in lung cancer (21). Similarly, PD-L1 has been examined in MPM. It has been consistently shown to be a robust prognostic marker with high PD-L1 expression associated with poor prognosis (22-24). The predictive role of PD-L1 for checkpoint inhibitors in MPM is yet to be prospectively defined, although one retrospective international study suggests that high tumour PD-L1 expression is associated with pembrolizumab response (25). The challenge of defining the predictive role of a biomarker is that in order to differentiate its predictive role for the treatment from simply suggesting prognostic differences, it has to be studied in the context of a prospective, randomized clinical trial using the treatment of choice.

Overall, there is still a long way to go in the discovery and clinical implementation of new biomarkers in MPM. Given MPM is a rare and aggressive disease, international collaboration is important to expedite biomarker research and biomarker validation. While there are some promising

diagnostic and prognostic biomarkers reported in MPM, these all require independent validation, and more research effort needs to focus on predictive biomarkers for old and new treatments in MPM patients.

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Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

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