The continual search for ideal biomarkers for mesothelioma: the hurdles

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J Thorac Dis 2013;5(3):364-366. doi: 10.3978/j.issn.2072-1439.2013.04.19

Malignant pleural mesothelioma (MPM) is an aggressive tumour predominately caused by exposure to asbestos. Asbestos consumption continues to increase worldwide, particularly among developing nations in Asia. Although actual data on mesothelioma incident rates are unavailable from several of the world's largest asbestos consuming nations including Russia, China and India (1), rates are predicted to surge in Asia reflecting the increased use of asbestos (2). Presently one person dies every four hours from mesothelioma in the United Kingdom.

There is a desperate clinical need for biomarkers that can aid the diagnosis of MPM, and/or predict survival and measure disease response to treatment. Mesothelioma is challenging to diagnose as phenotypic differentiation of malignant mesothelial cells from benign reactive ones are notoriously difficult. No immunohistochemical marker(s) can reliably define malignant mesothelioma either. Invasive pleural tissue sampling (e.g., by thoracoscopy) is often needed. Even then, MPM is the commonest cancer giving rise to false negative thoracoscopic biopsies (3). A reliable diagnostic marker will present a major aid to clinicians.

There is no cure for MPM. Although the median survival (9-12 months) for the MPM population as a whole is gloomy, about 5% of patients live for several years (4). Unusually long survivals (e.g., over 10 years) have also been seen. No reliable prognostic algorithm exists to predict survival in individual cases—a question that patients most wish answered. Chemotherapy may improve survival, but only 30% to 40% of patients respond (5). Thus finding a biomarker that may reflect disease burden and response to therapy, and hence prognosis, will be a significant advance. To date, there is no validated widely utilised biomarker for MPM. The report by Mori *et al.* in the *Journal of Thoracic Diseases* (6) provides another important step forward in the search for such a marker.

A biomarker is a characteristic that can be objectively measured and evaluated as an indicator of a pathogenic process. It may be a risk factor for a disease (on the causal pathway) or a risk marker, associated with the disease but not necessarily causally linked, or it may be a measure of the disease itself. The 'ideal' biomarker will increase pathologically in the presence of disease (yielding high sensitivity), will not increase in the absence of disease (high specificity), will be related to the disease burden and extent and will change with clinical evolution, reflecting treatment response, or progression and provide information about risk or prognosis. Further desirable test characteristics would include biological stability, technical reproducibility and reliability, and ideally the test would be easy and cheap to perform. There is intense interest in using mesothelioma-specific biomarkers to improve the clinical outcome for MPM patients. The majority of research to date has been of a case-control design to determine diagnostic accuracy of particular molecules. The report by Mori *et al.* examines the use of the mesothelioma biomarker N-ERC/mesothelin as a monitoring and prognostic tool in a treatment setting.

The nomenclature relating to the N-ERC/mesothelin marker as reported by Mori *et al.* can be confusing. The *mesothelin* gene, located on human chromosome 16p13.3, encodes at least four protein products, namely megakaryocyte potentiating factor (MPF) (7,8), and three isoforms of mesothelin; variant 1 (commonly known as mesothelin) (9), the as yet uncharacterised variant 2 (9,10) and variant 3 (known as soluble-mesothelin related protein (SMRP) (11). In the rat, the *mesothelin* gene is located on chromosome 10q12.21 and, based on similarity in sequence and predicted protein structure, is believed to encode MPF and the three variants of mesothelin. In the original report on sequencing of the rat *mesothelin* gene (12), the authors termed the gene *ERC* (expressed in renal cell cancer). The N-terminal domain of ERC (i.e. N-ERC) refers to

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Submitted Apr 19, 2013. Accepted for publication Apr 22, 2013.
Available at www.jthoracdis.com

ISSN: 2072-1439

MPF and the C-terminal domain to the predominant mesothelin isoform. Hence, in the report by Mori *et al.* the molecule of interest referred to as N-ERC is the same as (human) MPF.

To date, the majority of mesothelioma biomarker studies have focused on members of the *mesothelin* gene family. It has been nearly a decade since mesothelin (13) and MPF (14,15) were reported as candidate biomarkers for MPM, both providing similar diagnostic accuracy (16). A recent meta-analysis of serum mesothelin in the diagnosis of MPM determined that having a sensitivity of 32% at a 95% specificity was too low for diagnostic use and highlighted the need for ongoing research for better biomarker(s) (17).

There are unique challenges in this search. MPMs are heterogenous as evidenced by the lack of commonality in gene expression studies and lack of predominant mutations in common tumour suppressor and oncogenes. It is unlikely that a single MPM-specific biomarker will be found. The differences in protein expression among MPM subtypes also make finding a unique diagnostic marker unlikely.

A clinically useful biomarker for disease monitoring and prognostication is more likely to be uncovered than a diagnostic one. However the value of any monitoring or prognostic markers will be better assessed by the *changes* in its level within the same patient, an approach used by Mori *et al.* and in an increasing number of other studies (18-21).

The study by Mori *et al.* highlights further problems and limitations with published reports on biomarkers of MPM. Most biomarker, immunohistochemistry and gene expression studies examining prognosis in MPM share inherent limitations including small sample size, selection bias and a lack of external validation (22). For instance, many studies employed specimens from radical surgical resections when only a small proportion of MPM patients are fit for such operations (23). Similarly many clinical trial populations favour the epithelial sub-type of MPM, producing bias.

Relatively limited sample size does not allow adequate examination of the proportionally less common variants of MPM such as biphasic and sarcomatoid sub-types. These histological phenotypes have contributed to the limitations of validated biomarkers, such as mesothelin (17).

The results of Mori *et al.* as well as those of other studies (18-21) show that longitudinal changes in mesothelin-family biomarkers can in some patients reflect chemotherapy response. A simple, affordable, blood-based assay for monitoring treatment response has major advantages over existing radiological response measures (24) which require CT scans and are confounded by benign pleural thickening and prior pleurodesis. Further work is needed in this area as published data often includes limited patient numbers with significant heterogeneity in their disease (e.g., subtype, staging etc) and treatments.

The past decade has brought substantial advances in identifying and exploring MPM-specific biomarkers. More potential biomarkers are being identified (25,26) on a regular basis. For these targets to attain their professed clinical potential, independent externally validated studies with large, representative patient cohorts will be required. A combination of potential biomarkers should also be evaluated. The next stage will need studies to determine how to integrate promising markers into clinical diagnostic and/or management algorithms (27), a process essential in the evaluation of markers.

Acknowledgements

Disclosure: The authors declare no conflict of interest.

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Cite this article as: Brims FJ, Lee YC, Creaney J. The continual search for ideal biomarkers for mesothelioma: the hurdles. J Thorac Dis 2013;5(3):364-366. doi: 10.3978/j.issn.2072-1439.2013.04.19