Editorial

Mesothelioma and mesothelin—an underused diagnostic biomarker becoming a treatment target

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The origins, development and story of mesothelin as well as a short account on other mesothelioma biomarkers is outlined in the thorough and interesting review by Creaney and Robinson (1).

Mesothelioma is in most cases an asbestos-induced cancer of the serosal linings of pleura, which is the most common (>80%), peritoneal cavity which is less common (>20%), and of the tunica vaginalis testis that is extremely rare (2). Importantly, its incidence is still increasing in Europe, showing that the latency of asbestos exposure is more than 40 years, actually 20–60 years. Therefore, one must expect a new wave of mesotheliomas in countries that recently banned asbestos or that still use it. These are among the most populous in the world, the BRICS countries (2). This man-made cancer epidemic is very challenging, and has many similarities with the tobacco associated cancers on the rise.

Mesothelioma has three main subtypes, the epithelioid, the sarcomatous and the biphasic type which is a mixture of the two first. As a group survival is approximately 12–14 months when state-of the art chemotherapy can be given, but one can see cases surviving for several years with chemotherapy or multimodal treatment of chemotherapy, surgery and radiotherapy (2). The role of surgery remains controversial after the MARS study, most authors now favouring pleurectomy-decortication (3), but some are cautious about recommending surgery except within the frame of clinical trials (4,5).

Diagnosis

Early diagnosis could change this outlook. An old study published in 1993 on mesothelioma diagnosis by medical thoracoscopy showed that when only parietal pleura was affected, the median survival was 32 months while when affection of both parietal and visceral pleura, the survival dropped to 7 months, defined by the 7th IASLC staging system as T1a and T1b (6). The 8th IASLC staging, using a newer and larger patient material, could not find any survival difference in these two groups, and now stage T1 is defined as confined to either pleura. Stage IA (T1N0M0) with no nodal affection has a 5-year median survival of 16% while stage IV the 5-year survival is 0% (7). Thus, early diagnosis actually can save some patients, but we will not know for sure because stage IA stage rarely is diagnosed as symptomatic mesothelioma presents in later stages.

Biomarkers with diagnostic, predictive or prognostic value, even as effective targets for cancer are rare. Mesothelin is one of these few markers for this relatively rare disease.

Mesothelin, or soluble mesothelin-related protein (SMRP) a glycoprotein normally expressed on the surface of mesothelial cells, was very promising as an early detection marker due to elevation in serum of mesothelioma patients as well as in a few subjects some years prior to diagnosis (8). In a collaborative study with Creaney and Robinsons group back in 2008 on pre-diagnostic serum from the Janus Serum-bank in Oslo 1–30 years before diagnosis, we

could not verify this but we speculated it could be due to the long median lag-time of 15 years to diagnosis (9). A subsequent study with serial pre-diagnostic blood samples on asbestos exposed population by Creaney's group found elevated mesothelin in 17 of 106 cases in the last blood test before diagnosis, but overall it could not justify a full-scale screening (10). Thus, for screening/early diagnosis mesothelin alone should not be recommended.

The authors have recently published findings showing that ENOX2 could be a true early marker in the blood 4–10 years before frank diagnosis. This could be a major step forward, but needs validation.

It is timely to emphasize the definitive role of immunohistochemistry in the correct diagnosis of mesothelioma by biopsy and cytology, this is not discussed in the current review but currently two positive and two negative markers are needed to establish a mesothelioma diagnosis, where mesothelin do not play a role (11).

In contrast, as an adjuvant diagnostic in patient with a pleural mass or pleural fluid and suspected malignancy, mesothelin can indeed be helpful. Mesothelioma diagnosis is often delayed due to lack of histological or cytological findings, or problem to obtain biopsies in comorbid patients. In such cases an elevated mesothelin in serum is a clear signal of malignancy. However, a negative mesothelin, which is the case in roughly 50% of mesothelioma patients, does not mean lack of malignancy. Thus, as an adjuvant diagnostic, mesothelin or SMRP is a great tool, but has to be handled with care. Mesothelin in pleural fluid can also be a useful test as pleural fluid levels of mesothelin are significantly higher in patients with MPM compared to patients with pleural metastasis of carcinomas or benign pleural lesions. Pleural fluid concentrations of mesothelin were significantly higher in epithelioid mesothelioma compared to sarcomatous type, a finding in total accordance with serum mesothelin. Caution should be taken as pleural fluid levels of mesothelin are higher than the respective serum values. Interestingly, pleural fluid mesothelin measurement has higher sensitivity than cytological examination, 71% *vs.* 35% and a specificity of 89% *vs.* 100% respectively (11).

Monitoring

Monitoring disease in mesothelioma by CT scan can be challenging particularly due to the non-circular tumor growth pattern, and modified RECIST-criteria have been developed for mesothelioma (7). An elevation or reduction in serum or pleural mesothelin is a clear indication of tumor growth or reduction and in this setting mesothelin is helpful. In this review, several monitoring papers are shown, and all are positive, either regarding tumor volume change or prognosis. Therefore, mesothelin, like other "classical" tumor markers is useful only in the patients where there is an elevation before treatment.

Finally, is may be its role as a drug target that will be the most important, as pointed out in the article, impressive responses have been seen on a case-basis and one await results from studies on more patients (12). However, one phase II study on mesothelin-toxin conjugate anetumab-ravtansine, presented at the World Lung Cancer Congress in Yokohama, October 2017, showed no significant difference in progression-free survival compared to vinorelbine. However, the survival was longer than expected in this group of patients indicating some effect. More studies on various compounds targeting mesothelin as well as vaccine studies are awaited.

The review touches upon most of the promising biomarker candidates, as hyaluronate, fibulin-3, osteopontin, the SOMAmers and microRNAs, but do not mention two very new promising markers in the blood, the HMGB1 (13) and calretinin (also known as an immunohistochemical marker in tumor) (14) that seem to outperform previous markers in smaller studies and validation results are awaited.

In summary, among all mesothelioma biomarkers so far, only mesothelin has made it to become a commercially used clinical biomarker, but its potential as an adjuvant diagnostic and follow-up tool has, in my opinion, been underestimated. Still it is not in general use in Norway or in Denmark where mesotheliomas are fairly common, and one cannot say it is less useful than CEA, CA-125 and other "classical" but unspecific tumor markers that are in routine use for colorectal, ovarian and other solid tumors.

The important message of this review is that the road from a very promising biomarker to a clinical biomarker may be long, in the case of mesothelin, discovered in the early 90s, was granted FDA approval in 2007 and still it is not in general clinical use in 2017. However, as researchers have a tendency not to give up, mesothelin can turn out to be a very important treatment target, not only in mesothelioma but ovarian and pancreatic cancer as well, where mesothelin is expressed (9). Finally, as mesothelioma is on the rise almost world-wide, we urgently need more research to advance screening, diagnosis, monitoring and treatment of our patients.

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