Editorial

Biomarkers in malignant mesothelioma—an unfulfilled need or a waste of resources?

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The search for a molecular biomarker in malignant mesothelioma is as old as its first proven effective therapy (1,2). A definitive diagnostic biomarker could aid in establishing the diagnosis of malignant mesothelioma in patient. The benefit of such diagnostic biomarker is clear: the location of the tumor inside the thorax in pleural space is more challenging to biopsy than for example a biopsy of a breast tumor. Furthermore, more invasive procedures like video assisted thoracic surgery (VATS) and even CT guided biopsy of the pleura can cause more complications than a needle biopsy of a well reachable tumor. In addition, pleural thickening can be minimal or absent in malignant mesothelioma making it even harder to establish the final diagnosis in for example a patient with asbestos exposure presenting with only cytology negative pleural fluid. In addition to the benefits of a perfect diagnostic biomarker in patients presenting with pleural thickening or pleural fluid, a diagnostic biomarker could be used to screen the asbestos exposed population. The link between asbestos exposure in the past and the development of malignant mesothelioma, after a 30 to 40 interval in most patients, is well known. But even in the highest asbestos exposed workers, only 1 in 4 will develop malignant mesothelioma (3), with a much lower incidence of malignant mesothelioma when asbestos exposure was less. A perfect diagnostic biomarker could be the ideal tool to screen this entire asbestos exposed population to find the disease in an earlier stage. On the other hand, it is a well-accepted paradigm that screening or early diagnosis is only indicated in diseases where early diagnosis can increase the prognosis of the patient. Unfortunately, at this point of time this is not clearly the case in malignant mesothelioma as we will discuss further in this editorial. But this raises immediately the ethical question whether the search for a biomarker to diagnose a disease early where it is uncertain whether early diagnosis improves prognosis is just apart from a waste of resources, putting patients and their relatives into an enormous burden of emotional distress without affecting the prognosis.

Sun and colleagues describe the current biomarkers in malignant mesothelioma with regard on their potency to be used as a diagnostic marker as well as a prognostic tool for patients. Well known biomarkers such as soluble mesothelin and osteopontin are extensively discussed, as well as lesser known biomarkers as the use of micro-RNA or proteomics. They conclude that the classic biomarkers soluble mesothelin-related proteins in diagnosis have a high specificity, but a dismal sensitivity, where osteopontin had a sensitivity/specificity around 70–80%. Where mesothelin is non-prognostic, osteopontin shows promise. Fibilin-3 showed very promising results in the first publication in the *New England Journal of Medicine* with a sensitivity and specificity over 95% (4). However, the validation cohort showed worse outcomes in the same publication and in independent validation no better outcomes were found than the classic biomarkers mesothelin and osteopontin. Prospective validation is needed for fibulin-3 to act as a prognostic biomarker. High-mobility group box 1, micro-RNA and proteomics are also discussed, with promising

results, especially for the latter. Furthermore, markers of chronic inflammation, such as lymphocyte-to-monocyte ratio have been tested as a prognostic tool.

The lingering question is if there is an unfulfilled need for a diagnostic biomarker at this moment, even if it is a definitive diagnostic biomarker with a specificity and sensitivity that is high enough to be considered potential useful in aiding to establish the diagnosis of malignant mesothelioma. But to be considered clinically useful, a molecular diagnostic biomarker must lead to diagnosis malignant mesothelioma without substantially increasing the number of procedures performed on patients with benign pleural abnormalities or fewer procedures for patients with benign pleural abnormalities without substantially delaying the diagnosis of cancer in patients with malignant mesothelioma. However, regarding the possibility of an early diagnosis we must consider how an early diagnosis could alter the treatment choice for the patient in which the diagnosis is made. Currently there are only three positive randomized controlled phase III trials in malignant mesothelioma (2,5,6). These phase III led to the current standard treatment in mesothelioma being cisplatin combined with an antifolate (either pemetrexed or raltitrexed), and more recently, the addition of bevacizumab thus showed an extra overall survival benefit of nearly 3 months and this triple therapy is considered standard treatment now in parts of the world. Early diagnosis does not alter this treatment. The MED trial showed that even in patient presenting with malignant mesothelioma and stable symptoms after pleural fluid control, no significant survival benefit can be expected when chemotherapy is started immediately instead of delaying treatment to the point where patients have symptomatic progression (7). These results have some limitations at this moment; in addition to a trend that indeed was found in a benefit of immediate treatment initiation, the MED trial did not use the current treatment combinations. Given the very limited treatment options in malignant mesothelioma, and the relative small overall survival benefit these treatment options have, additional, non-randomized controlled proven treatments are being used worldwide. Given the location of the tumor in one hemithorax and the fact that distant metastasis are infrequent at the time of diagnosis, the interest in surgery is vast and mesothelioma surgery is being performed in a large number of mesothelioma centers worldwide based on the results of multiple phase II trials or case series (8,9). Some surgeons advocate the use of surgery as a standard of treatment for malignant mesothelioma patients and consider it as evident as the use of a parachute when jumping from a plane (10). Indeed, the median survival in most surgical studies is around 20–24 months. When comparing this to the outcome of the first phase III trial that showed the benefit of cisplatin in combination with pemetrexed, i.e., 13 months, this looks promising. However, patients are thoroughly selected for surgery using histologic subtype and stage of the tumor in addition to age and performance status of the patients. When these parameters are applied on the non-surgery population the benefit of surgery seems to be absent as was demonstrated in a large retrospective patient series by Bovolato *et al.* (11). The only randomized controlled trial that randomized extra-pleural pneumonectomy versus no extra-pleural pneumonectomy, the Mesothelioma and Radical Surgery (MARS) trial was actually a feasibility study (12). Therefore, no definitive conclusions can be drawn for effectivity of the surgical treatment opposed to the non-surgical treatment. Nevertheless, the surgical arm did perform comparable to historical data and did not show improved results compared to the non-surgical treatment arm. Lung sparing surgery in the form of pleurectomy decortication is now more widely advocated than extra-pleural pneumonectomy. This choice in altering surgical treatment seems a result of the combination of the publication of the MARS study and following articles and retrospective analysis of extrapleural pneumonectomy versus pleurectomy decortication data, in which pleurectomy decortication is better tolerated than extra-pleural pneumonectomy and no suggestion of a better survival in extra pleural pneumonectomy was found (13). However, retrospective patient series are prone to selection bias even for comparing two non-proven effective treatment arms. To firmly establish the benefit of surgery in mesothelioma, a randomized clinical trial is the only option. The MARS2 study is currently enrolling mesothelioma patients and is randomizing between pleurectomy decortication versus no pleurectomy decortication and the world is waiting for their results (ClinicalTrials.gov Identifier: NCT02040272). However, this is again a feasibility study. Therefore, interpretation of the final data will be prone to discussion like the first MARS trial.

In this light, the application of a biomarker as a diagnostic tool to detect malignant mesothelioma early is vastly different in for example lung cancer, where treatment and treatment outcomes of early stage disease consists of definitive treatment using surgery of stereotactic ablative radiotherapy (SABR) yielding a high 5-year overall survival versus systemic treatment in late stage disease having hardly

any survivors after 5 years (although this is improving with the introduction of immunotherapy and targeted therapy). In pleural abnormalities, a false positive biomarker result in a patient might actually lead to harm done in the following diagnostic procedures. Therefore, the application of a diagnostic biomarker in asbestos exposed subjects could even be detrimental to this entire population unless we as a medical community can provide an improved treatment when the disease is found in an early stage.

In the patient that already had presented him or herself with a suspicion of malignant mesothelioma, a diagnostic biomarker could indeed assist in the persistence of the clinician for the need for making the final diagnosis. A histologic diagnosis is still mandatory, given that none of the biomarkers have a diagnostic accuracy to replace a histologic sample. It should be noted that thoracoscopic biopsies have a diagnostic yield of over 90% (14), and thus in about than 1 of 10 patients will be false negative. When a biomarker result is very suspicious of mesothelioma, clinicians might be more eager to perform a repeat procedure to establish the final diagnosis of malignant mesothelioma.

A prognostic biomarker is useful for the prediction in individual variation in survival. In the review the prognostic value of each biomarker is discussed. Some biomarkers could be used on combination with the well-known European Organisation for Research and Treatment of Cancer (EORTC) prognostic score to increase the prognostic value. However, in clinic, there is more need for a predictive biomarker. Surgical and non-surgical studies have one common characteristic; the survival curves show patients that survive just weeks after starting trial inclusion and patients that survive for multiple years. Currently, it is unknown if patients exist that would survive longer using either surgery or non-surgical treatment. A predictive biomarker might aid in choice for therapy. Therefore, biomarker research should focus on predictive biomarkers. For example, the recent study of Patil *et al.* focused on the tumor microenvironment (15). Three different groups of immunological parameters were found; all three groups could differently react to immunotherapy on the basis of the different immunological parameters found. Multiple clinical trials are currently ongoing, for example in the field of immunotherapy (16). Following the negative randomized large phase IIb DETERMINE trial using the CTLA4 antibody tremelimumab (17), a number of trials are currently ongoing mostly using PD-1 or PD-L1 antibodies with or without anti CTLA4 inhibitors (18). It is now pivotal to test for example the three-group hypothesis in these patients that are being treated with immunotherapy. This could indeed lead to a useful predictive biomarker and selection of immunotherapeutic strategy for a patient.

When comparing to lung cancer biomarker utility, a recent review by Mazzone *et al.* report the results that should be reported in various phases of biomarker evaluation (19). These are in clinical validation of the sensitivity and specificity of a technically validated biomarker, the clinical features of the cancer and control groups in clinical validation studies of the biomarker compared with the intended use population, the biomarker results for relevant clinical subgroups and the biomarker performance compared with and combined with clinical calculators, standard practice, and/or clinician judgment.

In clinical utility, the frequency with which the biomarker result impacts a clinical decision and the impact of patient management decisions on patient outcomes when the biomarker is used. In cost-effectiveness the biomarker compared with the currently accepted standards for the clinical application.

Clearly, in mesothelioma, the biomarkers are clinically being evaluated. No biomarker currently impacts clinical decisions, let alone cost-effectiveness.

In conclusion, the current biomarkers in mesothelioma yield variable results as diagnostic and prognostic tool. Research is ongoing in new biomarkers, but clinical utility is dependent on how the test result affects subsequent clinical decisions and outcomes. Currently, no biomarker available in mesothelioma holds that promise. This is of course linked to the very limited treatment options that are currently available. However, multiple trials are currently ongoing in mesothelioma and this could lead to novel therapies being introduced in the coming years. Without an improved treatment in early stage mesothelioma however, we call upon researchers to preferably focus on detection of and validation of predictive biomarkers to select the most effective treatment for each individual patient. Because at this moment, this most useful tool to the clinician is missing and greatly needed.

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Footnote

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