The challenge of prognostic markers in pleural mesothelioma

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ABSTRACT Malignant pleural mesothelioma (MPM) is a very aggressive tumor, highly resistant to chemo- and radio-therapy. Treatment of MPM patients is often disappointing, regardless of the modality used.

Inter-individual variability of response to multimodal treatment remains a challenge and generally the MPM prognosis continues to be poor. Knowledge of predicting factors of outcome is currently insufficient; therefore, it would be highly desirable to find specific prognostic markers for MPM. Translational research projects are to be implemented.

KEY WORDS Malignant pleural mesothelioma (MPM); prognostic factors; translational research

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Malignant pleural mesothelioma (MPM) is a very aggressive tumor, highly resistant to chemo- and radio-therapy. Treatment of MPM patients is often disappointing, regardless of the modality used. Median survival remains less than 1 year, with less than 5% 5-year survivors (1). Currently, therapeutic management of MPM is heavily dependent on patient performance status and is expected to be potentially effective predominantly in the epitheliod subtype. The association of pemetrexed with cisplatin resulted in significantly improved efficacy of chemotherapy (2). The multimodal treatment including surgery (extrapleural pneumonectomy, or pleurectomy/decortication or extended pleurectomy/decortication) combined with chemotherapy that was introduced in the 1990s improved the long-term survival in selected operable patients (3). However, inter-individual variability of response to multimodal treatment remains a challenge and generally the MPM prognosis continues to be poor. Knowledge of predicting factors of outcome is currently insufficient even if many clinico-radiographic and molecular variables have been studied, usually with limited numbers of patients (4); therefore, it would be highly desirable to find specific prognostic markers for MPM.

New biomarkers are needed to improve the three aspects of the clinical management of MPM: early diagnosis, prognosis, and prediction of response to treatment (5). Some promising biomarkers (osteopontin, mesothelin, fibulin-3) have been described to predict prognosis and likelihood of response to therapy, in order to tailor treatment regimens on the basis of patients' individual features (6-8). However, these biomarkers are yet to be fully validated. For example, despite promising initial results, plasma osteopontin levels did not discriminate between chronic pleural inflammatory disease and MPM (9).

In a recent issue of the *Journal of Thoracic Disease*, Mori *et al.* retrospectively assessed the prognostic value of what they term "N-ERC index" in a small group of inoperable MPM patients (10). ERC, previously identified by the authors in a rat renal carcinoma and also known in humans as human megakaryocyte potentiating factor (MPF) or mesothelin, is a 71-kDa protein that can be found in the serum (11). These authors previously identified serum N-ERC level as a marker for early MPM diagnosis and noted that it increased as a function of disease stage (12). The N-ERC levels of MPM patients at diagnosis show wide inter-individual variance. Using baseline pre-treatment N-ERC level and post-chemotherapy treatment level, Mori *et al.* developed an index they term "N-ERC index". The latter was defined as Log_2 of the post-/pre- N-ERC ratio, which normalizes baseline N-ERC variability and post-chemotherapy changes. From the results of their study, Mori *et al.* concluded that "*… The N-ERC index is considered to be a useful biomarker for predicting not only the chemotherapeutic response, but also the prognosis in patients with advanced MPM.*" (10). While this may represent an important step in the direction of finding a useful MPM biomarker, a limitation of the study of Mori *et al.*, as in similar studies is methodology, reproducibility and small sample size. The importance and validity of a prognostic factor is much

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greater when it is identified in a prospective randomized trial with univariate and multivariate analysis, rather than in a retrospective series review as was the Mori study. Further, to correctly assess the effects of treatment for MPM, clinical trials should stratify patients according to prognostic group (13). In MPM, detailed staging by imaging is certainly required, but it is not sufficient. Prognostic scoring systems have been proposed as a method for evaluating single patient prognosis and for stratification of risks in MPM clinical trials (14). Because of scarce reproducibility, however, the use of scoring systems so far has been disappointing in clinical practice. Mori *et al.* noted that in their series, the low N-ERC level group, which showed significantly longer overall survival, included 4 stable disease patients and 5 progressive disease patients, possibly due to difficulties in evaluating by imaging tumor reduction (10).

While the N-ERC index seems promising in preliminary studies, it should also be investigated in diverse clinical scenarios as translational research projects (15). It should be tested for early diagnosis in subjects at risk for MPM, such as workers exposed to asbestos, and for differential diagnosis in patients with recurrent undetermined pleural effusion. Moreover, the N-ERC index could be used to stratify MPM patient sub-groups for new therapeutic trials, as recently proposed also for disease-specific genetic mutations (16).

In conclusion, the N-ERC index may be used as a new prognostic factor in the design of MPM clinical trials, and in the implementation of translational research projects.

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