Malignant pleural mesothelioma: new treatments, new hopes?

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Malignant pleural mesothelioma (MPM) is a rare and aggressive tumour type arising from the mesothelial surface of the pleural space. MPM is difficult to treat and commonly associated with asbestos exposure, which is its main risk factor [1]. In Europe, the incidence is about 20 per million, with large inter-country variation [2]. As a ban on the use of asbestos was proposed quite recently in most countries, and the median latency between asbestos exposure and MPM onset is about 40 years, incidence rates in some European nations are still rising, with peak incidences expected around 2020 and beyond. Moreover, asbestos continues to be used in many developing and emerging countries of the world, suggesting a potential mesothelioma epidemic in the future. The clinical signs are usually late and nonspecific. Chest computed tomography scanning, a key imaging procedure in MPM, usually shows unilateral pleural effusion, sometimes combined with pleural thickening [1, 3].

The treatment of MPM is quite elusive and relies mostly on palliative treatment by standard first-line chemotherapy (cisplatin/pemetrexed) and best supportive care, with median overall survival of ∼13 months [1, 3–5]. A recent phase III randomised trial recruiting 448 unresectable MPM patients found significantly longer survival (median 18.8 months; adjusted hazard ratio 0.76; p=0.012) when bevacizumab (anti-vascular endothelial growth factor antibodies) was added to cisplatin/pemetrexed, compared with chemotherapy alone [6]. This triple treatment had acceptable toxicity, making it a new treatment paradigm for this cancer. Therapeutic options beyond first-line treatment are at present highly limited, with a disease control rate of ⩽30% [1, 7, 8], leading to patients being recommended to join as many clinical trials as possible. Preliminary results with targeted therapies and immunotherapy (*e.g.* anti-PD-1 (anti-programmed death-1) or anti-PD-L1 (anti-programmed death ligand-1) antibodies, and drugs targeting mesothelin) are very exciting but need confirmation by large randomised trials [9]. In fact, the first results with anti-CTLA4 (anti-cytotoxic T-lymphocyte-associated protein 4) antibodies (tremelimumab) as second/third-line treatment of MPM were recently not confirmed by a larger randomised trial (n=571), when compared with placebo [10]. Early data from a phase Ib basket trial with anti-PD-1 (pembrolizumab) in the same setting showed a promising RR of 28% and disease control rate of 76% in PD-L1-positive MPM [11]. Other trials with immune checkpoint inhibitors are underway.

Surgery plays an important role in the diagnosis and staging of MPM but it is more controversial in the treatment of this cancer, although it may sometimes be proposed with a curative intent instead of medical treatment, or combined with (neo)adjuvant chemotherapy and/or radiotherapy as part of a multimodal treatment. To obtain macroscopic complete resection of MPM, two main procedures are discussed:

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extrapleural pneumonectomy (EPP) and pleurectomy/decortication (P/D). If including resection of pericardium and diaphragm involved by the tumour, this is termed "extended" P/D [2, 12, 13]. Modalities of this multimodal treatment of MPM patients, including EPP or P/D, are not yet well defined. Therefore, surgery of MPM must be performed by highly experienced multidisciplinary teams in dedicated centres, and is not recommended outside clinical trials [1]. Most recent trials, such as the European Organisation for Research and Treatment of Cancer trial [14] and the highly controversial Mesothelioma and Radical Surgery trial [15], as well as meta-analyses, plead for stopping EPP and continuing P/D only in clinical trials to find the best multimodal treatment for potentially resectable MPM patients who are fit for surgery [2]. Cao *et al.* [12] reported median overall survival ranges of 13–29 months for extended P/D and 12–22 months for EPP, which can be compared with median overall survival of 19 months in patients less selected than surgical patients, treated only by cisplatin/pemetrexed/bevacizumab [6]! Moreover, morbidity and mortality rates are also higher with EPP than with P/D but are decreased in experienced teams for MPM, and patients in the different studies were highly heterogeneously selected and treated.

However, two groups have recently published promising data from large single-centre series. Friedberg *et al.* [16] found an exciting median overall survival of 3 years (7.3 years in N0 patients) in a series of 90 patients treated by extended P/D, intrapleural photodynamic therapy and adjuvant chemotherapy. de Perrot *et al.* [17] in Toronto (ON, Canada) reported median overall survival of 36 months (51 months in epithelioïd subtypes compared with 10 months in biphasic subtypes; p=0.001) in patients treated with accelerated hemithoracic intensity-modulated radiation therapy (IMRT) followed by EPP. Both these experienced groups had an operative mortality rate of 3% or below. Moreover, the switch from induction chemotherapy to induction IMRT in the Toronto group was associated with resection in older patients with more advanced tumours, fewer transfusion requirements, and comparable post-operative morbidity and 90-day mortality [18].

A crucial issue remains: what are the parameters to select good candidates for surgery and multimodal treatment? Operability is usually based on the same criteria as in lung cancer patients [1]. Current best resectability criteria include epithelioïd histological subtype (the most frequent MPM subtype) and tumour staging, although these are still being discussed. A new TNM classification for MPM has recently been proposed by experts from the International Association for the Study of Lung Cancer, to be integrated into the eighth TNM classification of the American Joint Committee on Cancer/Union for International Cancer Control staging system, based on the series of a series of 2460 eligible cases [19–21]. Despite there being a majority of surgical cases in this database, in contrast with there being more usually a large majority of patients having only medical treatment, this initiative is highly interesting and pertinent. The main proposed changes for the T classification are to merge T1a and T1b stages into a unique T1 stage based on the absence of prognostic value of the tumour involvement of the visceral pleura only, a very tricky criterion to assess clinically. The N staging is simplified, merging the previous N1 and N2 stages of similar outcome into the new N1 stage; N3 stage (contralateral intrathoracic or supraclavicular lymph nodes) becomes the new N2 stage. There is no change for the M stage with rare M1 tumours in the series.

Evaluation of tumour volume based on three measurements of pleural thickness seems to have a high prognostic value whatever the tumour stage is. However, it will not be part of the next TNM classification. In fact, assessment of MPM by volumetric computed tomography was found not only to help in assessing the response to treatment [22] but also to have prognostic value. If this tool is found to be practical and reproducible, it could improve clinical MPM classification in the future, as suggested by a first study in six North American centres [23].

In this issue of the *European Respiratory Journal*, de Perrot *et al.* [24] report on their assessment of tumour thickness from 65 patients included in their trial evaluating EPP after radiotherapy, which they conducted in order to improve selection of candidates for MPM multimodal treatment. Total tumour thickness was determined by measurements of maximal thickness on nine predefined sectors on the chest wall, mediastinum and diaphragm. They found that total tumour thickness was an independent predictor of overall survival (p=0.02) and disease-free survival (p=0.01) after radical treatment for MPM. Interestingly, in this multivariate analysis, total tumour thickness was an outcome predictor independently of other retained parameters: epithelioïd histological subtype (p<0.0001) and nodal disease status (pN2; p=0.03). Thus, in addition to histology and TNM stage, tumour thickness, correlated with tumour volume and maximum standardised uptake value in this study, could improve patient selection for multimodal treatment including EPP or P/D.

However, these suggested parameters need to be prospectively validated in trials assessing the value of multimodal treatment in MPM patients, in a similar way to what is presently undertaken with biomarkers for targeted therapies and immunotherapy. Moreover, MPM thickness measurement may be very difficult, with sometimes very thin and/or inhomogeneous pleural thickness, which could also be mixed up with non-tumoural pleural abnormalities or atelectasis.

A better knowledge of the disease pathogenesis [25] and the development of these new exciting drugs and strategies, in parallel with the potential capability to target the best patients for each therapy, open promising perspectives in the management of MPM. An ongoing European task force (European Respiratory Society/European Society of Thoracic Surgeons/European Association for Cardio-Thoracic Surgery/European Society for Radiotherapy and Oncology/European Lung Foundation) has the goal of proposing an update of previous guidelines on MPM management [1] by the end of 2017, based on a systematic review of the literature. All these elements put together may finally bring hope for MPM patients and clinicians after a long dark age.

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