Malignant pleural mesothelioma: new guidelines make us stronger for defeating this disease

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Malignant Pleural Mesothelioma: new guidelines make us stronger for hitting this disease.

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Malignant pleural mesothelioma (MPM) remains a rare thoracic malignancy with an incidence in Europe of 1.83 cases per 100.000 individuals annually.[1] Asbestos exposure is the most common cause of this disease. In Europe, the regulations of individual countries resulted in partial or total asbestos bans in the 1980's and 1990's, with a complete ban Europe-wide on all types of asbestos since 2005.[2] Although globally, asbestos use has been banned in many countries (with 67 countries worldwide having a total ban since 2019),[2] mining to export asbestos continues, especially in developing economies, perpetuating the global incidence of exposure.[3] These different timeframes for asbestos bans, combined with a latency period of approximately four decades between exposure and MPM presentation, as well as the domestic usage of asbestos, together explain why the incidence rate of MPM is not homogeneous geographically and continues to rise in many countries.[2, 3] MPM has been considered an orphan thoracic malignancy with no significant improvement in the 5-year overall survival (OS) rate over several decades.[4] However, the implementation of immune checkpoint inhibitors (ICI) into the therapeutic strategy of patients with unresectable MPM has shed a new ray of hope for this orphan disease, especially in the first-line setting.[5]

The Multidisciplinary Tumor Boards (MTB) represent a focal point for the patient trajectory, and even in cancers with high incidence such as breast or colon cancer, multidisciplinary case discussion may alter the treatment recommendation in up to one-third of cases.[6] For rare cancers, the MTB carries even more relevance as clinical expertise is more likely to be limited, and evidence-based decision-making is difficult to pursue.[7–9] In this scenario, cancer care guidelines providing recommendations about diagnosis, treatment and follow-up based on the best evidence available at the time they are elaborated, represent the guiding light for rare malignancies.[10–12]. As new data are continually being published, it is essential that the guidelines be updated and revised over time as frequently as is relevant, to reflect new data and clinical information that may add to, or alter clinical practice.

In the current issue of *Annals of Oncology*, Popat et al. report the European Society Medical Oncology (ESMO) Clinical Practice Guidelines for diagnosis, treatment and follow-up of patients with MPM. [13] These guidelines provide key recommendations for managing patients with MPM based on the foundation of good

practice and the most recent scientific evidence. These guidelines describe optimal diagnostic methods, pathological evaluation, and the role of surgery and radiotherapy as a part of multimodality therapy. Moreover, they provide updated recommendations regarding new systemic treatments, notably ICI in unresectable MPM, as well as the role of maintenance therapy, and personalized treatment approaches. Importantly, all recommendations are accompanied by both the level of evidence and the ESMO-Magnitude of Clinical Benefit Scale (MCBS), helping clinicians judge the value of these recommended therapies in a standardized way.

In the time elapsed since the last ESMO MPM guidelines, published in 2015,[10] and despite the low incidence of MPM, several challenging therapeutic controversies have been clarified. These include prophylactic radiotherapy of tracts after diagnostic or therapeutic pleural procedures to prevent chest wall metastases is no longer recommended, while talc poudrage via thoracoscopy remains the surgical procedure of choice for pleurodesis over video-assisted thoracoscopic (VATS) partial pleurectomy. Although surgery (mainly extended pleurectomy decortication) as part of multimodality treatment is recommended in selected patients in highly experienced centers, the guideline stresses that the true survival advantage for patients undergoing surgery is unclear, due to a potential bias related to a highly selected population. We can hope that the role of surgery in MPM will become clearer after completion of the ongoing MARS-2 clinical trial (NCT02040272).

For systemic treatments, the dual-immunotherapy combination of nivolumab plus ipilimumab (evaluated in the phase III CheckMate 743 trial) alongside platinum–pemetrexed and bevacizumab (evaluated in the phase III MAPS trial) represent new standard-of-care options in the first-line setting for patients with unresectable MPM. This is clinically remarkable as, for the first time since 2003, two strategies have significantly improved the OS compared with the standard therapy of platinum-pemetrexed chemotherapy. Importantly, 23% of the patients with unresectable MPM treated with this dual-immunotherapy combination were alive at three years, whereas only 15% were alive with chemotherapy, suggesting that similar to other thoracic malignancies, ICI administration could improve long-term survival in this population. In daily practice, most patients who develop MPM are aged over 75 years,[2] some with comorbidities or frailty. Therefore, exploring

chemo-sparing strategies is relevant in this population. However, subgroup analysis of the CheckMate 743 trial raised questions of the benefit of this strategy in sub-populations such as elderly patients and females.[5] Indeed, several challenges regarding the use of ICI in this disease are expected to fuel scientific and clinical debate. One topic is the best upfront immunotherapy approach - ICI-ICI versus ICI plus chemotherapy, based on recent promising data.[14, 15] As the magnitude of the survival benefit of the dual nivolumab-ipilimumab combination seems to be greater in the non-epithelioid subtype than in epithelioid disease (HR 0.46, 95% CI 0.31-0.68 and HR 0.86, 95% CI 0.69-1.08, respectively),[5] an histology-tailored immunotherapeutic approach could revolutionize our view of unresectable MPM. In the second-line setting, ICIs have improved OS compared with best supportive care but not with chemotherapy. Moreover, in light of the expected wide adoption of immunotherapy combinations in the first-line setting, in the near future ICI would only remain a potential option in a few patients with platinum-relapsed immune-naïve MPM.

Finally, the possibility of a personalized therapeutic approach is a pending challenge in MPM. Currently, there are no predictive biomarkers routinely evaluated for patient selection. However, as translational biomarker studies have revealed potential molecular targets, ongoing master protocols are providing a platform for molecular stratification of MPM to test individualized approaches, such as the phase 2 Mesothelioma Stratified Therapy (MiST) umbrella trial (NCT03654833).[16] Therefore, besides the meaningful improvements in the therapeutic strategy of MPM as reported in the current ESMO guidelines, clinical trial recruitment and translational biomarker studies should be prioritized to improve the understanding of this challenging disease and, ultimately, patients' outcome.

One of the aims of guidelines is to give care recommendations according to scientific evidence. However, sometimes evidence and recommendations are not aligned with daily clinical practice, especially when guidelines are addressed to different countries in the same continent. Despite upfront bevacizumab plus platinum-pemetrexed improving OS in patients with unresectable MPM, to date, bevacizumab has not been submitted for regulatory approval, limiting the applicability of this strategy in most European countries. This is of relevance in a disease with limited therapeutic options. Likewise, drug-access inequalities in Europe [17] are a

limitation for specific recommendations that are endorsed in the current guidelines. As an example, the European Medicines Agency (EMA) approved the dual-immunotherapy combination of nivolumab plus ipilimumab in the first-line setting for patients with unresectable MPM on April 22nd 2021,[5] and this recommendation is included in the current MPM guidelines with a level of evidence IA and ESMO-MCBS score 3. However, currently only a limited number of European countries have individually approved this strategy to make it available. The inclusion of this recommendation in a European guideline that assesses the clinical benefit and the level of evidence of each treatment should be regarded as an opportunity to facilitate the decision-making on the value of anticancer therapies by National Health Authorities, reducing inequity of access to high-value but high-cost cancer treatments.

MPM is mainly considered a work-related illness attributed to occupational asbestos exposure with higher incidence in men.[2] In Europe's Beating Cancer Plan, the Commission plans to present a legislative proposal in 2022 to further reduce workers' exposure to asbestos.[18] Such policies would ultimately lead to the reduction of MPM in males, while women may not obtain the same benefit. It is of note that the incidence of MPM in females has been stable over time despite asbestos bans, reflecting the role of other sources of asbestos exposure in women, such as environmental and familial. Therefore, if we want to further reduce the incidence of this deadly form of cancer with a well-established causal relationship, the next step will be to shift the focus of research and legislation to other sources of asbestos, in order to target all potential avenues of exposure.[2]

There is no doubt that the publication of an updated guideline in a rare thoracic malignancy like MPM is a relevant achievement. A new road has now been traced thanks to new therapies that improve patients' survival, increasing the hopes and providing light in a previously dark tunnel.

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