Malignant Pleural Effusion in Malignant Pleural Mesothelioma
An Innocent Bystander?
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Malignant pleural mesothelioma (MPM) is a disease that portends a poor prognosis with a median survival that ranges from 8 to 14 months after diagnosis (5-year survival rate: 5.5%).1 Malignant pleural effusion (MPE) is the most common first presentation of MPM; >95% of individuals with MPM will experience a pleural effusion during their lifetime.2 At present, there is no cure for MPM; numerous therapeutic approaches have been attempted with modest results.1 Like other forms of malignant pleural disease, management of MPE related to MPM is directed towards palliation of symptoms.3

The clinical course of MPE does not always take a direct path in relation to the predicted survival, and fluid reaccumulation can vary during an individual’s limited life span. It is important to note that individuals with MPE related to MPM are a distinct group of patients with regards to treating their MPE. The condition can be diagnostically challenging; survival rates differ, and individuals are potentially at greater risk of having trapped lung. Definitive management of MPE related to MPM often needs to cater for all these factors.

Current prognostic scores for MPE (such as from Brims et al,4 LENT score,5 and PROMISE score6) use independent baseline variables that reflect systemic and inflammatory factors (eg, serum lymphocyte to neutrophil ratio, performance status, tumor type, MPM subtype, weight loss, age, previous chemotherapy or radiotherapy, hemoglobin, serum WBC count, serum albumin, serum C-reactive protein) rather than those specific to the effusion (apart from pleural fluid lactate dehydrogenase alone in the LENT score) to predict survival. More recently, Mishra et al7 showed a correlation between breathlessness and survival in patients with MPE. Duration of exposure to pleural effusion in patients with MPM that affects survival has not been studied thus far. There is in vitro evidence to suggest that the MPE may contain properties that enhance tumor cell growth and may impact survival8; hence, a symptomatic approach to the management of pleural effusions in this population may be a missed opportunity in prolonging survival in patients with MPM.

In this issue of CHEST, the question posed by Asciak et al9 about whether pleural fluid exposure influences survival in individuals with MPM is an interesting one and potentially could shift the management paradigm of MPE related to MPM. This is a large study that involved 761 patients who were diagnosed with MPM over a 10-year period (2008 to 2018) from three tertiary pleural units in the United Kingdom. The median overall survival of the study population was 278 days. Duration of pleural fluid exposure showed no association with survival once adjusted for other variables known to affect survival in these group (hazard ratio, 1.0; 95% CI, 1.0-1.0). Strikingly however, there were differences in survival seen between pleurodesis groups, with a median survival of 473 days for patients who underwent complete pleurodesis, 378 days for patients with partial pleurodesis, and 258 days for patients with no pleurodesis (P = .008). These included spontaneous pleurodesis related to indwelling pleural catheters or secondary to bedside or surgical chemical pleurodesis.

With respect to the primary outcome of the study, the authors9 caution that no safe conclusion can be drawn reliably on whether the size and duration of effusion is truly insignificant because of the retrospective nature of the trial. The dataset available could not determine the length of exposure to pleural effusion before the diagnosis of MPM. Chest radiographs opportunistically obtained during encounters of care were the primary mode of imaging used to calculate effusion presence and
achieved a successful pleurodesis. These findings that showed a survival benefit in patients with MPE who achieved a successful pleurodesis reported that 13 of 15 studies demonstrated improved survival in favor of successful pleurodesis. A similar observation also was made in a study that examined outcomes exclusively in MPM. The authors of the article raise two possibilities for the apparent survival benefit seen in patients who achieve pleurodesis. The first is that more advanced, bulky tumor may prevent full apposition of the pleural surfaces and prevent pleurodesis. The second and potentially more important mechanism is that talc may have antitumor properties. Talc has been shown in vitro to have an apoptotic effect on MPM and lung adenocarcinoma cells while sparing normal pleural mesothelial cells. One proposed mechanism for the observed antitumor effect is the induction of endostatin from healthy pleural mesothelial cells, which impairs the angiogenesis required for continued tumor growth. Talc was the sclerosing agent used in most studies that reported improved survival with pleurodesis success; it was instilled via an intercostal catheter in slurry form or poudrage via video-assisted thoracoscopic surgery.

It should be noted that the observation of improved survival in patients whose condition achieves successful pleurodesis is subject to bias. The selection of patients for talc pleurodesis in the first instance is skewed towards those with a better performance status. This would be even more significant in patients who received talc poudrage via a video-assisted thoracoscopic surgery procedure; however, this data were not assessed in this trial.

A particularly sobering observation is that, even though patients were divided by time epochs to prevent confounding by developments in medical treatments, there was no survival difference seen, even with a comparison of the earliest epoch with the latest. This is in stark comparison with advanced non-small cell lung cancer, where advances over the past decade have seen a significant improvement in patient survival. The authors also found no significant differences in chemotherapy response when comparing the effect of the size of the MPE in patients who had MPE at the start of chemotherapy. However, little can be drawn from this at this stage, given the retrospective design limitation. The article by Asciak et al adds value to the current literature and forms a platform for future prospective research.

References