Palliative care in mesothelioma: Are current services RESPECT-able enough?

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Malignant pleural mesothelioma (MPM) remains a devastating disease with a poor prognosis; median survival ranges from just 8 to 14 months from diagnosis.[1] The incidence is the highest in the UK and Australia and while this is expected to peak by 2020, the global incidence is predicted to increase for several decades particularly in emerging economies. Treatment options remain limited. Chemotherapy using third-generation antifolate agents is the only treatment modality that has been shown to improve survival in MPM.[2] Standard first-line treatment is combination pemetrexed and cisplatin (or carboplatin), however response rates to these regimens are low. An evaluation of over 1700 patients who received pemetrexed with either cisplatin or carboplatin demonstrated response rates of 26.3% and 21.7%, respectively.[3] Surgical management is controversial with a lack of robust randomised trial data. Novel treatments are however on the horizon. The genomic era has led to the early development of precision therapies, and as with several other cancers, immunotherapy may hold promise.[4]

Alongside a paucity of current effective treatments, patients with MPM are also subject to a high symptom burden. In a study of 495 patients,[5] 92% reported three or more symptoms at diagnosis with fatigue (94%), dyspnoea (89%), chest pain (85%), appetite loss (87%) and cough (75%) being the most common. The psychological burden of a diagnosis of MPM can be equally distressing with patients reporting feelings of uncertainty and lack of control.[6] Carers of patients with MPM similarly report an emotional and physical toll.[7] Arguably, MPM is therefore the archetypal disease necessitating effective palliative care, defined by the WHO as 'an approach that improves the quality of life of patients and their families facing life-threatening illness, through the prevention and relief of suffering by early identification and impeccable assessment and treatment of pain and other problems, physical, psychosocial and spiritual'. Indeed, the 2018 British Thoracic Society Guideline for the investigation and management of MPM recommends the early involvement of specialist palliative care (SPC) services.[8] This recommendation is however highlighted as a 'good practice point', reflecting the limited availability of studies directly investigating the role of early SPC in MPM to date.

It is timely therefore that Brims *et al*[9] report on the findings of the RESPECT-Meso trial that aimed to provide objective evidence to address if early SPC intervention positively impacts patients with MPM, an area often neglected in large-scale clinical studies. The study design comprised a multicentre, randomised group controlled trial of 174 patients (and 145 main carers) across 19 sites in the UK and a single site in Western Australia. The intervention group received early review by SPC within 3 weeks and every 4 weeks thereafter for at least 24 weeks, until death, or end of trial, alongside standard care. The control group received all standard, appropriate, routinely provided treatment for MPM including specialist multidisciplinary team (MDT) discussion and a dedicated specialist thoracic cancer nurse at all centres. Patients within the control group could also be referred to SPC services at any time if deemed clinically appropriate. The primary endpoint measured was change in patients' health-related quality of life (HRQoL) at 12 weeks as measured by the global health status subscale of the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Core 30. As highlighted by the authors, 21.8% of patients did not complete all three SPC visits within 12 weeks while 17.2% of patients within the control arm were referred to and received SPC input, increasing to 34.5% at 24 weeks—such a dilution of effect is perhaps inevitable in a pragmatic, real world study. The authors have however used robust statistical methods, accounting for analysis of multiple potential confounding factors and subgroups. The results of the trial however reveal no statistically significant benefit of the intervention to patients for the primary endpoint measured. Additionally, no significant benefit for the secondary endpoints of patient HRQoL at 24 weeks, mood at 12 and 24 weeks and overall survival was identified. A positive impact on secondary endpoints related to carer mood and satisfaction with end-of-life care however was noted.

These results appear contradictory to similar studies examining the impact of early SPC in other cancers, including thoracic malignancies. In a pivotal study of 151 patients with newly diagnosed metastatic non-small cell lung cancer[10] early SPC intervention was associated with significantly improved HRQoL and mood at 12 weeks and an improvement in median overall survival compared with standard care. In a further study of 191 patients with advanced thoracic malignancies (including MPM) and 159 patients with advanced gastrointestinal malignancies,[11] early SPC intervention was associated with a positive impact on HRQoL for the group as a whole at 24 weeks, and for patients with thoracic malignancies at 12 weeks alongside a positive impact on mood. A 2014 study of early SPC in 461 patients with stage III/IV solid malignancies including lung cancer identified a significant improvement in HRQoL at 4 months in the intervention arm.[12] The ENABLE II study randomised 322 patients with advanced solid malignancies to psychosocial intervention conducted by advanced practice nurses with SPC training or usual care.[13] Once again, an improved HRQoL and mood was seen in the intervention arm. Conversely, the follow-up ENABLE III study compared early versus delayed SPC referral in 207 patients with advanced cancer revealing no significant difference in symptoms reported by patients between the groups.[14] Patient survival at 1 year was greater in the early SPC group, however overall survival by log-rank analysis was not significantly different. Brims *et al*[9] highlight a recent Cochrane review[15] including these studies that concludes early SPC input in advanced solid malignancies may slightly increase patient HRQoL and symptoms but effects on mood and survival are uncertain. Notably, the Cochrane review[15] grades this evidence as either low or very low for these variables and therefore the results of the well-designed RESPECT-Meso trial (Randomised controlled trial of regular early specialist palliative care on quality of life in malignant pleural mesothelioma),[9] while contradictory, cannot be interpreted as completely inconsistent with existing evidence. Two main factors appear to contribute to the negative results, as highlighted by the authors. First, the inclusion

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criteria for the RESPECT-Meso trial[9] included patients with a good performance status (ie, ambulatory), and it may be that the benefits of early SPC are more marked for more debilitated patients. Including such patients however would have likely led to significant numbers not completing the trial and the study being underpowered. Second, this trial exclusively assessed patients diagnosed with MPM in the UK and Australia. With a high symptom burden and poor prognosis, it seems unlikely that patients with MPM would benefit less from early SPC than other advanced solid malignancies. Both the UK and Australia however operate public healthcare systems, and end of life care has been a policy priority for successive governments in both countries.[16] Existing services available to patients newly diagnosed with MPM in the UK and Australia include a formal MDT approach to management and dedicated specialist cancer nurses, both of whom will often refer to SPC if needed, as reflected by the 34.5% of patients in the control arm that had been referred by 24 weeks. Optimistically, it may be that existing services in the UK and Australia already meet the holistic needs of patients with MPM. This however is in the context of additional informal care provided by carers who bear a significant amount of the cost of end-of-life care for cancer.[17] If current demographic and cancer trends continue however, a greater demand for care and a decrease in the supply of informal care could lead to an increased role for early SPC, and such a trial might yield different results in the future. Despite their significant role, few studies report on the needs of carers, and it is commendable therefore that the RESPECT-Meso trial[9] includes carer-related secondary endpoints.

Despite the negative results reported by Brims *et al*,[9] nihilism for the role of early SPC in MPM would be inappropriate. Rather, early referral to SPC does not appear to be warranted for patients with a good performance status treated at centres with MDT and specialist nurse input with additional access to SPC as indicated. The role of early SPC outside this setting in MPM remains unclear, yet the integrated approach to cancer care established in the UK and Australia may mean these patients also receive additional SPC input in an appropriate and timely manner, as indicated by the high proportion of the control arm receiving such care. In their admirable goal of providing objective evidence for the role of early SPC in MPM, perhaps Brims *et al*[9] have highlighted that existing palliative care services available to patients with MPM in the UK and Australia are currently respectable enough.

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