

MESOTHELIOMA UPDATE

Aggressive management under debate

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The incidence of mesothelioma in Canada has been steadily increasing since the 1970s. The number of new cases diagnosed in 2007 was 514, up from 276 in 1992.¹ From 1960 to 1968, there only 99 cases of mesothelioma in Canada.²

The main goal of treatment for malignant pleural mesothelioma (MPM) is disease control. Aggressive management involving radical surgery, chemotherapy and radiotherapy is feasible in suitable candidates,³ but long-term survivorship may be a function of patient selection.⁴

AGGRESSIVE MANAGEMENT: ROLE OF RADICAL SURGERY

The results of the Mesothelioma and Radical Surgery (MARS) trial have raised questions about the role of extrapleural pneumonectomy (EPP).⁵ Intended to address the feasibility of performing a randomized trial of radical surgery, a total of 50 subjects were assigned to either EPP or no EPP. Based on an intention-to-treat analysis, the no-EPP group had a better outcome, with a median survival of 19.5 vs 14.4 months, a difference primarily due to perioperative complications, leading the MARS trialists to caution against EPP. Proponents of EPP have criticized this conclusion given the small size of the trial and because survival was not the primary endpoint.

The next study planned by the MARS trialists eschews EPP in favour of pleurectomy.⁶ A large retrospective review of surgery at major American centres demonstrated no major differences in outcomes between EPP and pleurectomy.⁷ However, with the goal of surgery to achieve maximal cytoreduction, the latest strategy of the MARS trialists has also been criticized,⁸ and the definition of what qualifies as a pleurectomy for MPM is under debate.

The MARS trial highlights another important management issue. Enrollment occurred at 12 centres in the United Kingdom over a 3-year period. Screening logs were not mandatory, and only 261 patients were accounted for in this manner. Of all those diagnosed with MPM, 112 were registered for the trial, and

over half were not randomized due to a variety of factors, such as disease progression and the decision by patients to withdraw. Regardless of the exact denominator, the 50 patients randomized to EPP or no EPP undoubtedly represent a small fraction of the patients diagnosed with MPM.

In Ontario, there are at least 2 major thoracic surgery centres that routinely perform radical surgery for MPM. A recent review of practice in the province indicates that approximately 10% of patients are managed aggressively⁹ (probably representing the upper limit of the MPM population in whom radical surgery might be performed). In many other communities, there is a lack of expertise and/or interest in performing radical surgery for MPM.

MANAGEMENT WITH CHEMOTHERAPY

Chemotherapy is associated with a modest survival benefit in fit patients with MPM.¹⁰ The combination of cisplatin + pemetrexed is standard, although reimbursement issues may affect access to pemetrexed. Retrospective reviews suggest comparable survival outcomes using gemcitabine or raltitrexed in place of pemetrexed.^{9,11} Similarly, carboplatin can substitute for cisplatin. Vinorelbine and pemetrexed have demonstrated activity as single agents, and may be alternatives for individuals with platinum-analog contraindications.

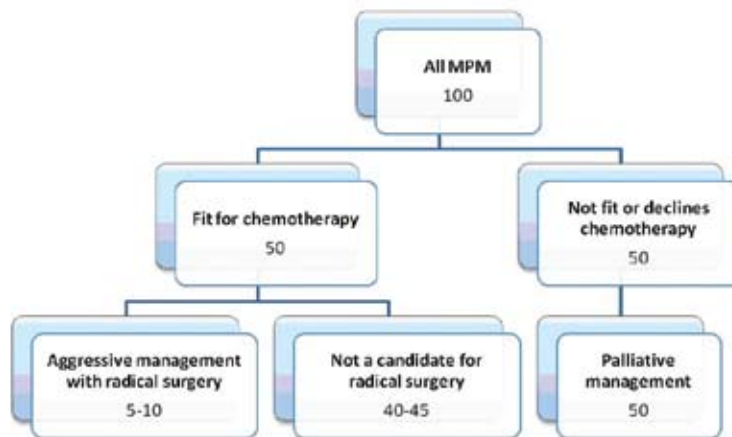
In individuals with a long progression-free interval, retreatment may be considered.¹² However, there is little data to support second-line systemic therapy. A trial of single-agent pemetrexed as salvage therapy following a platinum-based doublet failed to demonstrate any benefit.¹³ Recently, a large placebo-controlled trial of the histone deacetylase inhibitor, vorinostat, in the second-line setting has also reported negative results.¹⁴

There remains hope that novel targeted agents will prove useful in treating MPM despite the finding that epidermal growth factor tyrosine kinase inhibitors, specifically gefitinib and erlotinib, and angiogenesis inhibitors, such as bevacizumab and sunitinib, have demonstrated little activity.¹⁰



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FIGURE 1. MPM, with proportion (%) of patients suitable for each treatment category



PALLIATIVE TREATMENT

While 10% of patients are candidates for aggressive management, only about 50% are suitable for chemotherapy. For the rest, the focus is entirely on palliative measures (see Figure 1). Radiotherapy is used primarily for control of chest pain.¹⁵

Essential elements of active symptom management include:¹⁶ regular specialist followup; structured assessments for physical, psychologic and social issues; rapid access to other specialty services, such as pain management and social work; and parallel nursing support. With the benefit of early integration of palliative care into management of advanced non-small cell lung cancer, it is likely that there would be a comparable advantage in MPM.

REFERENCES

1. Canadian Cancer Society's Steering Committee on Cancer Statistics. Canadian Cancer Statistics 2011. Toronto, ON, 2011.
2. McDonald AD, Magner D, Eyssen G. Primary malignant mesothelial tumors in Canada, 1960-1968. A pathologic review by the Mesothelioma Panel of the Canadian Tumor Reference Centre. *Cancer* 1973. 31:869-76.
3. de Perrot M, Feld R, Cho BC et al. Trimodality therapy with induction chemotherapy followed by extrapleural pneumonectomy and adjuvant high-dose hemithoracic radiation for malignant pleural mesothelioma. *J Clin Oncol* 2009. 27:1413-18
4. Hasani A, Alvarez JM, Wyatt JM et al. Outcome for patients with malignant pleural mesothelioma referred for Trimodality therapy in Western Australia. *J Thorac Oncol* 2009.4:1010-16.
5. Treasure T, Lang-Lazdunski L, Waller D et al. Extra-pleural pneumonectomy versus no extra-pleural pneumonectomy for patients with malignant pleural mesothelioma: clinical outcomes of the Mesothelioma and Radical Surgery (MARS) randomised feasibility study. *Lancet Oncol* 2011.12:763-72.
6. Treasure T. Surgery for mesothelioma: MARS landing and future missions. *Eur J Cardiothorac Surg* 2010. 37:509-10.
7. Flores RM, Pass HI, Seshan VE et al. Extrapleural pneumonectomy versus pleurectomy/decortication in the surgical management of malignant pleural mesothelioma: results in 663 patients. *J Thorac Cardiovasc Surg* 2008.135:620-6, e621-3.
8. Rusch VW. The Mars trial: resolution of the surgical controversies in mesothelioma? *J Thorac Oncol* 2009. 4:1189-91.
9. Hasani A, Sun B, Liu G et al. Systemic therapy usage and outcomes for patients diagnosed with malignant pleural mesothelioma (MPM) between 2005 and 2010 in Ontario, Canada. *J Clin Oncol* 2011;29 suppl:abstr 7085.
10. Tsao AS, Wistuba I, Roth JA et al. Malignant pleural mesothelioma. *J Clin Oncol* 2009. 27:2081-90.
11. Lee CW, Murray N, Anderson H et al. Outcomes with first-line platinum-based combination chemotherapy for malignant pleural mesothelioma: a review of practice in British Columbia. *Lung Cancer* 2009;64: 308-13.
12. Ceresoli GL, Zucali PA, De Vincenzo F et al. Retreatment with pemetrexed-based chemotherapy in patients with malignant pleural mesothelioma. *Lung Cancer* 201. 72:73-7.
13. Jassem J, Ramlau R, Santoro A et al. Phase III trial of pemetrexed plus best supportive care compared with best supportive care in previously treated patients with advanced malignant pleural mesothelioma. *J Clin Oncol* 2008; 26:1698-1704.
14. Krug L. VANTAGE 014: Vorinostat in patients with advanced malignant pleural mesothelioma (MPM) previously treated with pemetrexed and either cisplatin or carboplatin therapy: a phase III, randomized, double-blind, placebo-controlled trial. ESMO 36. Stockholm, Sweden, 2011
15. Ung YC, Yu E, Falkson C et al. The role of radiation therapy in malignant pleural mesothelioma: a systematic review. *Radiother Oncol* 2006; 80:13-8.
16. BTS statement on malignant mesothelioma in the UK, 2007. *Thorax* 2007; 62 Suppl 2:ii1-ii19.

Disclosure:

Dr. Lee has served on ad boards for Lilly oncology.