

Role of Conservative (Palliative) Care-only in the Management of Advanced Malignant Pleural Mesothelioma

ANTONIN LEVY¹, AVI ASSOULINE^{2,3}, SOFIA RIVERA⁴, CYRUS CHARGARI⁵ and PATRICIA TAI⁶

¹Department of Radiation Oncology, Gustave Roussy Institute, Paris XI University, Villejuif, France;

²Department of Radiation Oncology, Porte de Saint Cloud Clinical Centre, Boulogne-Billancourt, France;

³Department of Radiation Oncology, Pitié Salpêtrière Hospital, Paris, France;

⁴Department of Radiation Oncology, Saint-Louis Hospital, Paris, France;

⁵Department of Radiation Oncology, Val de Grâce Hospital, Paris, France;

⁶Department of Radiation Oncology, Allan Blair Cancer Center, University of Saskatchewan, Regina, Canada

Abstract. *Despite new aggressive therapeutical options for advanced malignant pleural mesothelioma (MPM), benefits to survival remain limited. Moreover, deleterious effects of high-dose chemotherapy and aggressive surgery are well-known. Outcomes of untreated patients are usually not reported, and whether a treatment can be delayed or avoided is still an open question. We discuss here two clinical cases and with conservative (palliative) management alone for advanced MPM.*

Malignant pleural mesothelioma (MPM) is a neoplasm with a notoriously poor prognosis. The median survival reported for untreated patients ranges from 6-9 months, with 5-year survivors being fewer than 5% (1, 2). No treatment has demonstrated statistically significant improvements in survival (3), although there have been encouraging reports on extrapleural pleuropneumectomy (EPP) and pemetrexed (4, 5). EPP consists of an en-bloc removal of the lung, visceral and parietal pleura, hemi-pericardium and diaphragm. It is followed by pericardial and diaphragmatic reconstruction with prosthetic material. The first large experience was from Sugarbaker, with 183 patients over nearly two decades, with adjuvant platinum-based chemotherapy and radiotherapy. The 5-year survival was 15% and the median survival was 19 months. Interestingly, the results of the Mesothelioma and Radical Surgery (MARS) trial have questioned the value of EPP (6). This study investigated the feasibility of performing a randomized prospective study of radical surgery. Thus, 50 patients underwent EPP or not EPP.

Correspondence to: Patricia Tai, Department of Radiation Oncology, Allan Blair Cancer Center, 4101 Dewdney Avenue, Regina, Saskatchewan, S4T 7T1, Canada. Fax: +1 3067662845, e-mail: Patricia.Tai@saskcancer.ca

Key Words: Mesothelioma, conservative surgery.

A better outcome was reported in the no-EPP group, with a median survival of 19.5 vs. 14.4 months. This difference was mainly due to perioperative complications of radical surgery. These conclusions were debated because of the small size of the trial and because survival was not the primary endpoint (7). In light of the controversy on aggressive treatment for MPM, we feed the debate regarding the advantages of aggressive treatments and report two cases of patients who might not have benefited from aggressive treatment.

Case Report

Case 1. A 67-year-old man presented in early October 2009 with worsening shortness of breath of three months duration. He had a history of tobacco consumption and possible asbestos exposure. Total body computed-tomography (CT) showed a massive left-sided pleural effusion with affected abdominal lymph nodes. Thoracoscopy revealed diffuse pleural nodules and the biopsy was positive for epithelioid mesothelioma. The pleural effusion was drained. The patient declined chemotherapy. Because of the lack of chest symptoms at that time, the large treatment volume and risk of radiation pneumonitis, chest radiotherapy was not given. The patient was re-admitted seven months later with a seizure and the brain CT showed a right temporal ill-defined hypodensity with suspected associated minimal peripheral enhancement. Magnetic resonance imaging (MRI) showed abnormal areas of T2 hyperintensity in the right temporal lobe, with peripheral rim enhancement and surrounding vasogenic oedema. The biopsy revealed, glioblastoma multiforme of WHO grade 4/4 which was glial fibrillary acidic protein-positive and radiotherapy to partial brain was given. Chemotherapy (temozolomide) was refused and the patient died from brain glioblastoma in early November 2010, five months after completion of radiotherapy to the brain and 13 months after the diagnosis of mesothelioma.

Case 2. A 63-year-old female smoker was referred after 7 years of recurrent pneumonia with productive cough resistant to antibiotics. On examination, the patient had stridor and spasmodic coughing. CT scan of the chest in January 2011 revealed a large soft tissue mass in the posterior mediastinum, with extension from the aortic arch inferiorly to the left atrium. Additionally, there were soft tissue nodules inferior to the mass within the posterior mediastinum, a prominent cardiophrenic angle node, pleural plaques and a small right-sided pleural effusion. A percutaneous biopsy under CT guidance of the subcarinal node was arranged and pathology concluded a diagnosis of epithelioid mesothelioma. Chemotherapy (cisplatin and pemetrexed) was given, with stable disease, in May 2011. Palliative radiotherapy (30 Gy in 10 fractions over two weeks) was delivered to the residual mediastinal lymph nodes. At six months after diagnosis, this patient needed oxygen and the CT report in August 2011 described increased pleural densities with a reduced lung volume. Due to the extent of the progressive disease, not easily encompassed by re-irradiation, the previous lung dose, and poor general condition, the patient was given supportive care only. She died in December 2011, 11 months after diagnosis of MPM

Discussion

Usually, MPM is classified into three broad histological subtypes: epithelioid (60%), sarcomatoid (20%), and biphasic (mixed, 20%). The epithelioid variant is the most common and is usually described as having a better outcome. On the other hand, according to the European Organisation for Research and Treatment of Cancer (EORTC) (8) and the Cancer and Leukaemia Group B (CALGB) (9), sarcomatous or mixed-histology MPM have poorer prognosis. It is also suggested that the histological subtype could be a finer independent prognostic factor in patients receiving best supportive care only. In 101 conservatively-treated patients, Merrit *et al.* reported that the median survival was 8.7, 8.6 and 2.7 months in epithelial, mixed and sarcomatous types, respectively ($p=0.0016$) (10). Moreover, Ak *et al.* showed that patients with an epithelial subtype of MPM had a good prognosis, even if they did not receive any treatment, while histological subtype was not related to the prognosis in patients undergoing chemotherapy (11). Prognostic factors defined by the EORTC and CALGB include Eastern Cooperative Oncology Group (ECOG) performance status score (PS), age, gender, chest pain, pleural effusion, fever of unknown origin, stage of disease, histology, and biological parameters (white blood cell and platelet count) (8, 9). Although neither of these patients belonged to the subgroup of MPM with an unfavourable outcome, clinicians pondered what was the best course of action. Although their expected median survival was only about a year, the first case survived longer than that period, prior to any specific treatment.

When there is no or only limited resection of disease, delivery of high-dose radiotherapy to the entire hemithorax in the setting of an intact lung is not the standard of care (12). Even with advanced technology (intensity-modulated radiotherapy), ionizing radiation to a large lung volume could result in significant toxicity, including radiation-induced pulmonary fibrosis, radiation pneumonitis, and bronchopleural fistula, without any survival benefit (13). It is unclear if case 2 actually benefited from palliative radiotherapy, or if alteration of her pulmonary function was in fact a side-effect of therapy. Due to the large volume required for re-irradiation, the patient received supportive care only.

For patients with advanced MPM, who are not candidates for locoregional therapy, combination of chemotherapy is the standard of care. In the randomized phase III trial reported by Vogelzang *et al.*, the median time to progression was 1.8 months longer in the pemetrexed/cisplatin-treated arm (*hazard ratio*=0.77; $p<0.01$). This short-term survival benefit was also associated with high-grade hematological and gastrointestinal toxicities, despite supplementation with folic acid and vitamin B12 during therapy (5). Moreover, while toxicities may be increased for elderly patients (2, 9), the median age of patients with MPM typically ranges from 62 (in clinical trials) to 74 years (routine practice). As a matter of fact, Chapman *et al.* described that for 37% (54/146) patients declared suitable for chemotherapy, 52% declined (similarly to our case 1) this option and eventually only 18% of the total number of patients were randomized into chemotherapy trials (2).

Molecularly targeted agents are currently being evaluated for MPM. Unfortunately, while therapeutic benefits were observed in non-small cell lung cancer, (14) new clinical trials are still required to establish whether these high-cost agents will have a role in MPM management. Indeed, epidermal growth factor receptor and vascular endothelial growth factor pathway proteins are expressed in MPM. Nevertheless, in a phase II trial with previously untreated patients receiving the inhibitor erlotinib, no objective responses were observed (15). Monoclonal antibody to vascular endothelial growth factor bevacizumab, was also tested in combination with gemcitabine and cisplatin in a randomized phase II trial, but the addition of bevacizumab did not improve overall survival compared to chemotherapy alone (16).

Overtreatment of patients often occurs because doctors engage in defensive medicine, and can be justified by fear of malpractice suits, particularly for young patients. Of course, chemotherapy and high-tech irradiation have become standard practice in most developed countries. In the setting of an economic crisis that will impact on public health, these expansive practices with a limited benefit should be questioned. The quality-adjusted life-years (QALYs) gained

are particularly doubtful in elderly patients. Financial constraints should force practitioners and policy makers to carefully analyze the true clinical benefit of treatment modalities, particularly in the palliative setting. Reasonable quality of life may be achieved with symptomatic care and it justifies thorough evaluation of the potential advantage of a planned specific-therapy for patients with advanced MPM.

Conflict of Interest Statement

The Authors declare no financial support and no funds received.

References

- 1 Van Mererbeeck JP, Scherpereel A, Surmont VF and Baas P: Malignant pleural mesothelioma: the standard of care and challenges for future management. *Crit Rev Oncol Hematol* 78: 92-111, 2011.
- 2 Chapman A, Mulrennan S, Ladd B and Muers MF: Population based epidemiology and prognosis of mesothelioma in Leeds, UK. *Thorax* 63: 435-439, 2008.
- 3 Montanaro F, Rosato R, Gangemi M, Roberti S, Ricceri F, Merler E, Gennaro V, Romanelli A, Chellini E, Pascucci C, Musti M, Nicita C, Barbieri PG, Marinaccio A, Magnani C and Mirabelli D: Survival of pleural malignant mesothelioma in Italy: a population-based study. *Int J Cancer* 124: 201-207, 2009.
- 4 Sugarbaker DJ, Flores RM, Jaklitsch MT, Richards WG, Strauss GM, Corson JM, DeCamp MM Jr., Swanson SJ, Bueno R, Lukanich JM, Baldini EH and Mentzer SJ: Resection margins, extrapleural nodal status, and cell type determine postoperative long-term survival in trimodality therapy of malignant pleural mesothelioma: results in 183 patients: *J Thorac Cardiovasc Surg* 117: 54-63, 1999.
- 5 Vogelzang NJ, Rusthoven JJ, Symanowski J, Denham C, Kaukel E, Ruffie P, Gatzemeier U, Boyer M, Emri S, Manegold C, Niyikiza C and Paoletti P: Phase III study of pemetrexed in combination with cisplatin versus cisplatin alone in patients with malignant pleural mesothelioma. *J Clin Oncol* 21: 2636-2644, 2003.
- 6 Treasure T, Lang-Lazdunski L, Waller D, Bliss JM, Tan C, Entwisle J, Snee M, O'Brien M, Thomas G, Senan S, O'Byrne K, Kilburn LS, Spicer J, Landau D, Edwards J, Coombes G, Darlison L and Peto J: 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* 12: 763-772, 2011.
- 7 Lee CW: Mesothelioma update. Aggressive management under debate. *Oncol Exchange* 10: S11-12, 2011.
- 8 Fennell DA, Parmar A, Shamash J, Evans MT, Sheaff MT, Sylvester R, Dhaliwal K, Gower N, Steele J and Rudd R: Statistical validation of the EORTC prognostic model for malignant pleural mesothelioma based on three consecutive phase II trials. *J Clin Oncol* 23: 184-189, 2005.
- 9 Herndon JE, Green MR, Chahinian AP, Corson JM, Suzuki Y, and Vogelzang NJ: Factors predictive of survival among 337 patients with mesothelioma treated between 1984 and 1994 by the Cancer and Leukemia Group B. *Chest* 113: 723-731, 1998.
- 10 Merritt N, Blewett CJ, Miller JD, Bennett WF, Young JE and Urschel JD: Survival after conservative (palliative) management of pleural malignant mesothelioma. *J Surg Oncol* 78: 171-174, 2001.
- 11 Ak G, Metintas S, Metintas M, Yildirim H, Erginel S, Kurt E, Alatas F and Cadirci O: Prognostic factors according to the treatment schedule in malignant pleural mesothelioma. *J Thorac Oncol* 4: 1425-1430, 2009.
- 12 National Comprehensive Cancer Network Clinical Practice Guidelines in Oncology 2.2012 www.nccn.org, last accessed 10 April 2011.
- 13 Kristensen CA, Nøttrup TJ, Berthelsen AK, Kjaer-Kristoffersen F, Ravn J, Sørensen JB and Engelholm SA: Pulmonary toxicity following IMRT after extrapleural pneumonectomy for malignant pleural mesothelioma. *Radiother Oncol* 92: 96-99, 2009.
- 14 Besse B, Ropert S and Soria JC: Targeted therapies in lung cancer. *Ann Oncol* 18S: 135-142, 2007.
- 15 Garland LL, Rankin C, Gandara DR, Rivkin SE, Scott KM, Nagle RB, Klein-Szanto AJ, Testa JR, Altomare DA and Borden EC: Phase II study of erlotinib in patients with malignant pleural mesothelioma: a Southwest Oncology Group Study. *J Clin Oncol* 25: 2406, 2007.
- 16 Kindler HL, Karrison TG, Gandara DR, Lu C, Krug LM, Stevenson JP, Jänne PA, Quinn DI, Koczywas MN, Brahmer JR, Albain KS, Taber DA, Armato SG 3rd, Vogelzang NJ, Chen HX, Stadler WM and Vokes EE: Multicenter, Double-Blind, Placebo-Controlled, Randomized Phase II Trial of Gemcitabine/Cisplatin Plus Bevacizumab or Placebo in Patients With Malignant Mesothelioma. *J Clin Oncol*. 2012 Jun 4. [Epub ahead of print].

Received April 13, 2012

Revised July 2, 2012

Accepted July 3, 2012