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Management Options for Malignant Pleural Mesothelioma

Clinical and Cost Considerations

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Contents

Abstract

Malignant pleural mesothelioma (MPM) is a resistant form of lung cancer that is often related to prior asbestos exposure. While surgical resection and radiotherapy techniques have been refined in recent years, neither has been proven to significantly extend patient survival compared with untreated controls. Until the release of pemetrexed in 2004, even combination chemotherapy regimens often resulted in a response rate of <20%. A recent phase III trial documented a 41.3% response rate for cisplatin plus pemetrexed. In the future, new multimodality regimens featuring novel targeted therapies directed against molecular targets,

such as the vascular endothelial growth factor, hold the greatest promise for improved outcomes in MPM. The standard radiographic assessment of response to MPM therapy remains a poor surrogate for clinically relevant endpoints such as median survival. Furthermore, it is not currently known whether aggressive multimodality treatment for MPM will improve survival or quality of life above and beyond symptomatic care. Ongoing clinical trials are comparing chemotherapy and surgery with supportive care in an effort to define the role of different therapies in MPM. MPM treatment is a costly public health issue; after efficacy is proven, additional studies are needed to measure the cost effectiveness of MPM treatment regimens.

Approximately 80% of cases of malignant pleural mesothelioma (MPM) are attributed to asbestos exposure.[1] Less common risk factors for MPM include exposure to the mineral Turkish erionite, use of Thorotrast® [1] (thorium dioxide) contrast media and prior chest injury.[2] As many as 10 million Americans may have been exposed to asbestos during the collapse of the World Trade Center in 2001, and the future effect of this exposure on public health remains unknown.[3] While 2500 new patients will be diagnosed with MPM in the US this year, the incidence stabilised in the early/mid 1990s and is projected to decline over the next several years.[4] In contrast, the number of newly diagnosed European patients is expected to continue to rise until 2020, causing approximately 250 000 deaths in Europeans over the next 35 years,[5] which explains the particular interest in MPM therapy among European oncologists.

The median survival of patients with MPM is often <12 months.[6] MPM was previously regarded as refractory to traditional chemotherapy regimens, and in 2001, the British Thoracic Society recommended chemotherapy for MPM only within the context of clinical trials, given the unclear role of such treatment in the management of MPM.[7] However, new and promising chemotherapy regimens have recently demonstrated significant activity in this disease. In 2004, pemetrexed became the first MPM therapy approved by the US FDA. These positive results have stimulated new research and renewed interest in combination therapies for treatment of MPM. An algorithm for the treatment of MPM is shown in figure 1.

To gather information for this review, both PubMed and OVID were used to search the MEDLINE database for relevant references. 'Mesothelioma' was used as both a keyword and as a subject heading, with an emphasis on review articles, human studies and clinical trials. In addition, selected abstracts, conference proceedings and pertinent references cited in reviewed articles were included.

1. Prognostic Factors

Both the Cancer and Leukemia Group B (CALGB)[8] and the European Organization for the Research and Treatment of Cancer (EORTC)[9] have produced prognostic scoring systems that have been validated for use in patients with MPM. Poor prognostic factors in the CALGB system include white blood cell $\geq 15.6 \times 10^9$/L and an Eastern Cooperative Oncology Group (ECOG) performance status 1 or 2. Similarly, poor predictors in the EORTC system include low WHO performance status, leukocytosis, male sex and sarcomatoid histology.[1] In several surgical case series, the epithelial subtype of MPM has been associated with improved outcomes, but it is not known if epithelial MPM is more sensitive to therapy or inherently less aggressive.[10]

2. Palliation

The most common presenting symptoms of MPM are dyspnoea and chest wall pain.[1] An effec-

1 The use of trade names is for product identification purposes only and does not imply endorsement.

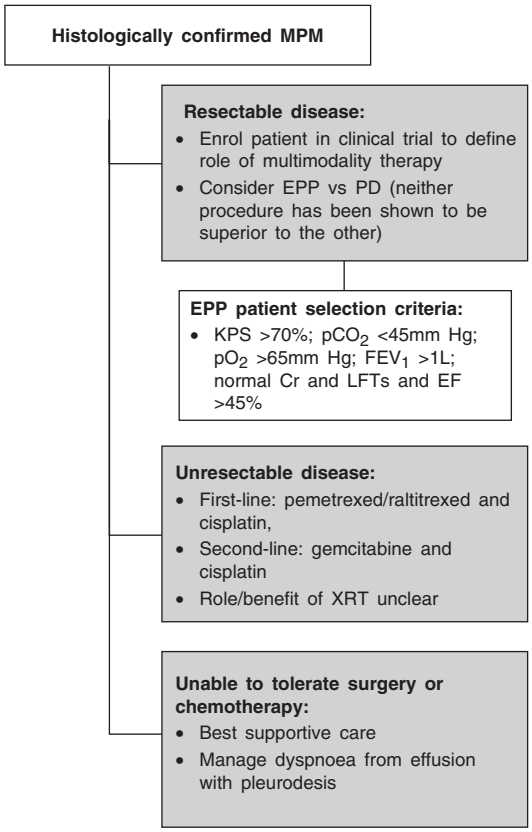

Fig. 1. Recommended management of a patient with malignant pleural mesothelioma (MPM). **Cr** = creatinine; **EF** = ejection fraction; **EPP** = extrapleural pneumonectomy; **FEV_1** = forced expiratory volume in 1 second; **KPS** = Karnovsky performance status; **LFTs** = liver function tests; **pCO_2** = carbon dioxide partial pressure; **PD** = pleurectomy and decortication; **pO_2** = oxygen partial pressure; **XRT** = radiotherapy.

tive palliative care regimen should address visceral, somatic and neuropathic pain, dyspnoea, anorexia and weight loss, and anxiety and depression.[2] Prior to the use of cisplatin and pemetrexed, many patients with advanced-stage MPM were treated with a 'best supportive care' strategy, which prioritises control of tumour-related symptoms over a longer lifespan.

Several different interventions have demonstrated palliative benefit in MPM. After drainage of malignant pleural effusion and consideration of pleurodesis, opioids may be administered for dyspnoea secondary to mesothelioma. Epidural catheters have also been used for pain control.[11] In one study of 52 MPM patients, cervical cordotomy with ligation of spinothalamic tract pain fibres led to improvement in pain control.[12] The procedure was quite successful; 83% of patients were able to reduce their opioid dosage by >50% and 38% were able to discontinue use of opioids.

Radiotherapy appears to reduce chest pain and provide palliative benefit in MPM.[13] Focal irradiation of painful lesions can also reduce the pulmonary toxicity associated with radiation of the entire hemithorax.[13] In a Dutch retrospective series spanning 1979–96, pain was reduced in 50% of patients receiving 4Gy doses of radiation for a median of 69 days (median total dose of 36Gy), compared with 39% palliation in patients receiving smaller fractions of radiation.[14] Palliative radiation is more effective at relieving pain than dyspnoea, superior vena cava syndrome or Horner's syndrome from a Pancoast tumour.[15]

The optimal total dose of a course of palliative radiotherapy for MPM is not clear, since data from small patient series have shown conflicting results.[14] Overall, a dose of at least 40Gy is recommended for palliative radiotherapy, which is similar to the doses used in the treatment of other non-small-cell lung cancers.[15] At the MD Anderson Cancer Center, a standard MPM palliative regimen consists of 45Gy in 15 fractions.[15]

3. Surgery

3.1 Pleurectomy and Decortication

In pleurectomy and decortication, the tumour and associated pleura are removed, leaving the underlying lung parenchyma intact. After resection, the remaining tumour may be eradicated using argon beam coagulation, but local recurrence is almost inevitable. Pleurectomy and decortication is usually reserved for limited disease that does not involve the pleural fissures and is thought to be completely resectable using this technique. In one review of the surgical literature, pleurectomy and decortication was associated with a 1–2% mortality and use of this surgical procedure alone was associated with a me-

dian survival of 9–20 months in patients with MPM.[16]

3.2 Extrapleural Pneumonectomy

Since MPM is almost always confined to a single lung at presentation, unilateral pneumonectomy offers an opportunity for surgical cure. In extrapleural pneumonectomy, the visceral and parietal pleura including the enclosed lung are removed, as well as adjacent portions of the diaphragm and pericardium. Since there is no residual lung parenchyma in the resulting resection cavity, higher doses of postoperative radiation can be delivered without pulmonary toxicity. Unfortunately, despite use of an aggressive combination of extrapleural pneumonectomy, adjuvant chemotherapy and radiotherapy, patient outcomes remain unsatisfying.

Extrapleural pneumonectomy often results in incomplete tumour resection, since vital thoracic structures limit the surgical resection field and surgical margins are often extremely thin.[3] In a surgical series from Brigham and Women's Hospital, 67% of patients treated with extrapleural pneumonectomy, radiotherapy and chemotherapy experienced local recurrence in the ipsilateral hemithorax.[17] Abdominal recurrence was also frequently noted and attributed to post-surgical diaphragmatic defects.

In extrapleural pneumonectomy case series, negative resection margins, three or fewer positive lymph nodes, female sex and epithelial histology confirming epithelial subtype of MPM are positive prognostic signs.[18,19] Sugarbaker et al.,[18] the pioneers of extrapleural pneumonectomy-based multimodality therapy for MPM, have reported a median survival of 19 months after this procedure; however, the series excluded seven patients who died in the perioperative period.[20] In contrast, other groups have reported median survivals of between 9 and 19 months.[16] In a subgroup analysis, Sugarbaker et al.[18] reported a 5-year survival of 45% in patients with limited disease and favourable epithelial-subtype histology (median survival 51 months).

As surgeons have gained more experience and refined the procedure of extrapleural pneumonectomy, the rate of operative complications has declined. Common complications after extrapleural pneumonectomy include venous thromboembolism, including lower extremity deep venous thrombosis and pulmonary embolus, as well as pulmonary oedema.[21] In a series of 328 patients, Sugarbaker et al.[22] reported 3.8% perioperative mortality and 25% morbidity. David Waller's group published data from a series of 74 patients who underwent extrapleural pneumonectomy, in whom the mortality was 6.75% at 30 days, and 63% of patients had major or minor morbidity.[23] The most common postoperative complications were atrial fibrillation in 17.5% of patients, mediastinal shift and 'subacute tamponade' in 10.8%, and pneumonia in 10.8%.

Because of the high morbidity of this procedure, patients must be carefully screened for eligibility for extrapleural pneumonectomy, and only 1–5% of patients are candidates for the procedure at presentation.[24] For example, 20% of patients diagnosed with MPM also have pulmonary fibrosis secondary to asbestos exposure,[25] which limits pulmonary reserve and may preclude pneumonectomy. Furthermore, despite significant risks, extrapleural pneumonectomy has not been shown to lead to improved patient survival; one study found no difference in the overall survival of patients who underwent extrapleural pneumonectomy versus those who did not qualify for extrapleural pneumonectomy, and underwent less radical resection such as pleurectomy and decortication.[26] Since surgery is not a viable treatment option for most patients, future refinement of chemotherapy and radiotherapy regimens offer the greatest hope of improving outcomes in this disease.

3.3 Extrapleural Pneumonectomy and Multimodality Therapy

Recent surgical research has focused on extrapleural pneumonectomy as part of a multimodality treatment regimen. Radiotherapy is designed to reduce the risk of local recurrence after surgical resection, while systemic chemotherapy may limit distant recurrence. In one trial of patients treated with extrapleural pneumonectomy and radiotherapy, 35 of 54 patients experienced distal recurrence, highlighting the need for systemic adjuvant

chemotherapy.[27] In a Swiss surgical trial, 19 patients with completely resectable MPM were treated with 3-monthly cycles of neoadjuvant cisplatin (80 mg/m^2 every 4 weeks) and gemcitabine (1000 mg/m^2 every week for 3 weeks).[20] A partial response rate of 32% was noted. Sixteen of the nineteen patients subsequently underwent extrapleural pneumonectomy, which was often complicated by tumour fibrosis secondary to chemotherapy, and 13 later received postoperative radiotherapy at varying doses. Almost all irradiated patients had local recurrence of disease. An intention-to-treat analysis was employed, and the authors reported a median survival of 23 months. However, the median age of patients included in the study was only 57 years, which is significantly younger than most MPM patients. In 1999, Sugarbaker et al.[18] reported a median survival of 19 months in patients undergoing extrapleural pneumonectomy and postoperative radiotherapy with doxorubicin, cyclophosphamide and cisplatin, or carboplatin and paclitaxel. Despite application of stringent inclusion criteria and careful patient selection, multimodality therapy has not resulted in durable remissions.[11]

In a review of several small published studies, extrapleural pneumonectomy followed by radiotherapy appeared to reduce local progression (but not survival) compared with pleurectomy and decortication followed by radiotherapy.[15] The authors attributed this trend to the higher doses of radiation permitted after extrapleural pneumonectomy, decreased respiratory motion after removal of the diaphragm, or more accurate calculation of treatment volumes after lung removal. The EORTC is currently conducting a phase II trial (protocol #08031) of neoadjuvant cisplatin plus pemetrexed, followed by extrapleural pneumonectomy and adjuvant conformal radiotherapy.[28] The primary outcome will be progression-free survival (PFS) at 90 days. A second separate phase II trial will evaluate carboplatin plus pemetrexed, followed by extrapleural pneumonectomy and radiotherapy.[29]

3.4 The Role of Surgery

To date, no randomised trials have compared surgery to other palliative or treatment modalities in patients with MPM.[7,30] In a nonrandomised trial, there was no significant difference between the median survival of MPM patients who underwent extrapleural pneumonectomy versus those undergoing debulking surgery.[31] Extrapleural pneumonectomy has not been shown to improve survival over pleurectomy and decortication,[19] and neither has been directly compared with supportive care. Extrapleural pneumonectomy and adjuvant chemoradiotherapy appears to prolong survival compared with historical controls, but this treatment has not been compared with chemoradiotherapy alone.[30] In a review of the published literature reporting on surgical treatment of MPM, the absence of randomised trials left the reviewers unable to assess the role of surgery in the treatment of this disease.[30]

Several trials are planned to evaluate the role of radical surgery in the therapy of MPM. The MARS (Mesothelioma and Radical Surgery) trial will randomise patients after chemotherapy (either mitomycin, vinblastine and cisplatin, or cisplatin and gemcitabine) to extrapleural pneumonectomy versus no surgery, and will attempt to measure the effect of extrapleural pneumonectomy on survival and quality of life (QOL).[29]

4. Radiotherapy

While MPM is relatively radiosensitive,[15] there are several limitations to external-beam radiation therapy in the treatment of mesothelioma. The thin, diffuse nature of the tumour complicates the delivery of an effective dose of 60Gy.[32,33] In addition, dosages are limited by the proximity of radiosensitive thoracic structures such as the spinal cord. Furthermore, respiratory motion of up to 3cm makes it difficult to target tumour volume while sparing normal lung parenchyma.[15]

There are no published trials showing that radiotherapy improves survival or QOL in MPM.[34] In fact, a 2006 Cochrane review found no randomised trials comparing radiotherapy with another treatment modality such as surgery, chemotherapy or

best supportive care.[35] A radiotherapy study by Ball and Cruickshank[36] showed no survival benefit and reported dose-limiting radiation toxicity. In a review of chest radiographs of patients who had received between 20 and 71Gy of hemithoracic radiotherapy, 43 of 46 patients had developed grade V/maximal lung injury within 12 months.[37] The three patients who were spared were part of the four-patient group receiving the lowest dose of radiation (20Gy).

In the intensity-modulated radiation therapy (IMRT) technique, radiation is delivered in a 3-dimensional space along the pleural surface in an effort to spare underlying radiation-sensitive lung parenchyma.[38] IMRT is associated with a 6% rate of locoregional progression,[15] and is paired with extrapleural pneumonectomy in an effort to reduce local disease recurrence. Early results were promising; in one series of seven patients treated with extrapleural pneumonectomy followed by IMRT, no local recurrence was noted 13 months after treatment.[39] However, IMRT is not without risks. In a recently published retrospective series of 13 patients treated with 54Gy of IMRT in 1.8Gy fractions after extrapleural pneumonectomy, six patients died from radiation pneumonitis at a median of 30 days after the conclusion of IMRT.[40] The authors speculated that this unexpectedly high rate of toxicity was due to the fact that the entire remaining lung was actually exposed to low levels of spillover radiation during IMRT, and suggested that a mean lung dose as low as 9Gy be adopted.

4.1 Prevention of Tract Metastasis

MPM frequently grows along the needle tracts created during biopsy or thoracentesis, and can form painful nodules under the skin. Small trials have explored the effect of external-beam radiation therapy on preventing tract metastasis, with mixed results.[41-43] While 20 control patients had a tract metastasis rate of 40%, 20 patients treated with three radiotherapy fractions of 7Gy had no tumour formation at the intervention site ($p < 0.001$).[41] The duration of follow-up was not mentioned. In an eight-patient series, a single dose of 15Gy within 30 days of percutaneous procedure prevented seeding of the wound by tumour.[42] In a trial of 58 tract sites (43 patients) randomised to a single treatment of 9 MeV of electron therapy or no treatment within 15 days of intervention, the difference between tract metastasis rates between the two arms was not statistically significant.[43] In a systematic review, Ung et al.[34] found insufficient evidence to recommend prophylactic radiotherapy in this setting.

5. Local Therapies

5.1 Intrapleural Chemotherapy

The location of mesothelioma on the pleural surface makes topical therapy an attractive concept. In conjunction with hyperthermia, intraoperative intrapleural chemotherapy can penetrate tumour cells on the lung surface. In one series of patients undergoing pleurectomy and decortication or simple pleurectomy and intrapleural mitomycin plus hyperthermia, ten patients with stage T1 or T2 disease had a median survival of 41.3 months, while the median survival of seven T3 or T4 patients was only 4.5 months.[44]

In a subsequent trial, 44 patients with resectable MPM underwent pleurectomy and decortication followed by hyperthermic 42°C intrapleural cisplatin lavage (escalating doses from 50 mg/m^2 to 250 mg/m^2) with intravenous sodium thiosulfate (16 g/m^2) for renal protection.[45] The maximum tolerated dose of cisplatin was determined to be 225 mg/m^2. Median survival was 6 months with low-dose cisplatin (50–150 mg/m^2) and 18 months with high-dose cisplatin (175–250 mg/m^2) [$p = 0.0019$]. Twenty-five percent of patients experienced major morbidity, including 11% perioperative mortality. This study employed higher doses of intrapleural cisplatin than had been evaluated in previous studies, but the 76% rate of recurrence in the treated hemithorax emphasised the lack of local control achieved with this regimen.

In a phase II trial of the slowly absorbed liposomal cisplatin analogue *cis*-bisneodecanoato-*trans*-R,*R*-1,2-diaminocyclohexane platinum(II) [L-NDDP], 33 patients with MPM and free-flowing

pleural effusions were treated with thoracentesis and placement of a pleural drain, followed by instillation of L-NDDP (450 mg/m^2 intrapleurally every 3 weeks).[46] After two early treatment-related deaths, the first treatment was delayed for 1 week after drain placement. The primary outcome of pathological remission in subsequent thoracoscopic pleural biopsies was achieved in 42% of patients (95% CI 25, 61), with a median survival of 11.2 months. This endpoint is subject to sampling error and the pathological responses did not correspond to radiographic response rates. The investigators noted that residual tumour could persist in parts of the lung surface isolated from the pleural effusion.[46]

Intrapleural chemotherapy has now been largely supplanted by novel systemic chemotherapies.

5.2 Photodynamic Therapy

In photodynamic therapy, a photosensitiser prodrug is delivered systemically and preferentially concentrated in tumour cells.[11] MPM cells on the pleural surface are then exposed to a specific wavelength of light that converts the photosensitiser to an active compound that can kill tumour cells and obstruct tumour vessels.[47] PDT was initially explored as a means of improving local control of MPM after surgical resection.[48] Foscan® (tetra-[m-hydroxyphenyl]-chlorin) can be activated by 652nm light at up to 150mm of soft tissue depth. When 28 patients were treated with surgical resection and escalating doses of Foscan®, the maximum tolerated dose was found to be 0.1 mg/kg.[48] Half of the patients treated had local control of disease 9 months after therapy and the median survival of the 28 patients enrolled was 10 months. In a second study, a total of 20 MPM patients who were treated with Foscan® photodynamic therapy and either extrapleural pneumonectomy or pleurectomy and decortication had a median PFS of 12.4 months.[49] However, Foscan® therapy was complicated by a systemic capillary leak syndrome.[50]

Activating 630nm light can penetrate 75mm into soft tissue and excite Photofrin® (porfimer sodium) into its active form. However, a phase III trial showed that Photofrin® did not improve survival of patients with MPM when added to debulking surgery and chemotherapy.[51]

The published trials of photodynamic therapy in MPM show no survival benefit, although these trials only enrolled a small number of patients.[52]

6. Chemotherapy

In patients with MPM, single-agent chemotherapy regimens have shown response rates <20%[1] and have not been shown to extend median survival. In attempts to improve on the marginal success of single-agent regimens, several combination chemotherapy regimens have been tested, with response rates often being compared to this benchmark of 20%. In a meta-analysis, combination chemotherapy regimens were shown to produce response rates of 22.6%, as compared with an 11.6% response rate with single-agent regimens ($p < 0.001$).[53] Cisplatin had the highest response rate of the single agents reviewed, with a 23% response. The combination of cisplatin and doxorubicin was the most active doublet, with a response rate of 28.5%.

6.1 Platinum-Containing Regimens

Despite the minimal increase in response with the addition of a second agent, cisplatin doublets are the mainstay of chemotherapy for MPM. The doublet gemcitabine and cisplatin is now considered by many to be second-line therapy for mesothelioma (after pemetrexed and cisplatin).[2] One early 21-patient trial of cisplatin plus gemcitabine by Byrne et al.[54] reported a 48% response rate, but this high rate has not been reproduced in larger subsequent trials.[55,56] In fact, a 25-patient follow-up phase II trial of cisplatin (80 mg/m^2) plus gemcitabine (1250 mg/m^2) administered in 21-day cycles reported a response rate of only 16% (95% CI 1, 31).[56] The investigators suggested that the different radiographic response criteria used by Byrne et al.[54] might have contributed to the dramatically different response rates in the two studies. In another phase II trial of first-line cisplatin (75 mg/m^2 on day 2) plus gemcitabine (1250 mg/m^2 on days 1 and 8), 9 of 35 patients had a partial response (26%; 95% CI

12.5, 43.2), and the median survival was 13 months (95% CI 9.3, 16.7).[57]

The combination has also been studied in the preoperative setting, with 19 patients being enrolled in a study of neoadjuvant cisplatin plus gemcitabine.[20] Eighteen patients received cisplatin 80 mg/m^2 on day 1 and gemcitabine 1000 mg/m^2 on days 1, 8 and 15 of a 28-day cycle for a total of three cycles. Sixteen patients subsequently underwent extrapleural pneumonectomy and 13 underwent adjuvant radiotherapy. The objective response rate to neoadjuvant chemotherapy was 32% and the median overall survival 23 months. Two-thirds of patients who had adjuvant thoracic radiation had in-field recurrence of tumour. While no perioperative deaths were noted, Utkan et al.[58] noted that perioperative morbidity in this study was significant, with 7 of 16 surgical patients experiencing major perioperative complications, including venous thromboembolism, chylothorax and bronchopleural fistula.

Other platinum-containing regimens have also been evaluated for activity against MPM. Between 1986 and 2002, 150 patients with MPM were treated with mitomycin 8 mg/m^2, vinblastine 6 mg/m^2 plus cisplatin 50 mg/m^2 every 3 weeks.[59] No complete responses were noted and the partial response rate was 15.3%. Median survival was 7 months, but 69% of patients reported an improvement in MPM-related symptoms such as dyspnoea, chest pain or cough, hinting at the potential palliative value of this regimen.

Combination chemotherapy with cisplatin plus irinotecan has also been used in MPM. On the basis of preclinical data, 25 untreated patients with MPM were treated with irinotecan alone (125 mg/m^2 weekly for 4 weeks, a colorectal cancer treatment dose) in a phase II trial.[60] No complete or partial responses were noted. Median survival was 9.3 months (95% CI 4.5, 13.2). The trial was stopped early after the investigators observed three toxic deaths, as well as significant rates of diarrhoea and lymphopenia.

A recent report describes the treatment of 49 patients with first-line irinotecan (100 mg/m^2 on days 1 and 15, 28-day cycle), cisplatin (40 mg/m^2 on days 1 and 15) plus mitomycin (6 mg/m^2 on day 1).[61] In this group, 37% of patients had a partial response as defined by modified RECIST (Response Evaluation Criteria in Solid Tumours) criteria and 54% had stable disease. Median PFS was 6.4 months (95% CI 4.5, 7.3), with a median overall survival of 10.8 months (95% CI 7.9, 13.7).

Cisplatin was combined with epirubicin in a phase II trial in which 69 patients with MPM were treated with cisplatin 90 mg/m^2 plus epirubicin 90 mg/m^2 every 3–4 weeks.[62] Twelve partial responses were noted, for an overall response rate of 19.0% (95% CI 9.4, 28.7), and a median survival of 12 months.

In a phase II trial, 26 patients with MPM received vinorelbine (30 mg/m^2 on days 1 and 8) plus oxaliplatin (130 mg/m^2 on day 1) of a 3-week cycle.[63] Median PFS was 4.7 months, and median survival was 8.8 months (95% CI 6.6, 11.0). The overall response rate of 23% was no better than the 24% response rate previously achieved with single-agent vinorelbine.

6.2 Antifolate Compounds

In one study, 72% of MPM samples overexpressed the α-folate receptor, supporting the use of antifolates to treat these tumours.[64] In addition, the methylthioadenosine phosphorylase gene is often deleted in mesothelioma, preventing treated tumour cells from utilising the purine salvage pathway and increasing dependence on *de novo* synthesis of purines.[65]

6.2.1 Pemetrexed

Pemetrexed, a recently-introduced antifolate compound, has shown significant promise in the treatment of mesothelioma. Pemetrexed is preferentially transported into mesothelioma cells via a folate transporter. After entering a cell, pemetrexed is polyglutamated, increasing its affinity for thymidylate synthase and the glycinamide ribonucleotide formyltransferase (GARFT).[65] By inhibiting dihydrofolate reductase, GARFT and thymidylate synthase, pemetrexed inhibits both purine and pyrimidine synthesis.[66]

After promising results from phase I and II pemetrexed trials, a single-blind phase III trial (EMPHACIS; Evaluation of Mesothelioma in a Phase III Study of Alimta with Cisplatin) randomised patients with MPM to up-front pemetrexed 500 mg/m^2 plus cisplatin 75 mg/m^2 every 3 weeks versus cisplatin alone.[67] Use of single-agent cisplatin as a control was subsequently criticised because cisplatin doublets were considered to be the standard of care prior to this trial.[68] While 78% of patients in the EMPHACIS trial had advanced stage III or IV disease, 85% had epithelial subtype or histology,[67] which has been linked to improved survival in extrapleural pneumonectomy patient series.[18] Patients included in this trial also had a relatively low median age of 61 years.[69]

During the conduct of this trial,[67] a study was published[70] linking elevated levels of homocysteine and methylmalonic acid to increased rates of adverse effects from pemetrexed. On the basis of these results, the decision was made mid-trial to administer folic acid and cyanocobalamin (vitamin B_{12}) supplementation to study patients in both arms in an effort to reduce the incidence of neutropenia and leukopenia. Seventy patients received no vitamin supplementation, 47 patients began supplementation after starting chemotherapy and 448 patients were supplemented throughout their entire treatment course. Combination-arm patients received a mean of 4.7 cycles of pemetrexed and cisplatin, while cisplatin-only patients received a mean of 4 cycles of chemotherapy. The median survival of patients in the combination arm was 12.1 months compared with 9.3 months in the cisplatin only arm ($p = 0.02$). In a subgroup analysis of patients who received vitamin supplementation throughout their chemotherapy course, the median survival of combination-arm patients was 13.3 months, compared with 10.0 months for cisplatin-only patients; this difference in median survival was no longer statistically significant ($p = 0.051$).

Notably, the EMPHACIS investigators reported that 37.6% of patients who received cisplatin plus pemetrexed and 47.3% of patients who received cisplatin-only also received at least one other chemotherapy regimen after the conclusion of the trial, which may have affected their survival times.[67] As per protocol, patients in the cisplatin-only arm could not receive subsequent pemetrexed therapy after completion of the trial. The most commonly used post-study chemotherapy regimen was single-agent gemcitabine. Patients who received cisplatin plus pemetrexed and post-study chemotherapy had a median survival of 15.3 months (95% CI 13.3, 18.9), compared with a median survival of 12.2 months (95% CI 9.9, 14.2) for patients receiving cisplatin plus pemetrexed without post-study chemotherapy. Median survival times were 9.8 months (95% CI 8.1, 11.7) for combination-arm patients who did not receive post-study chemotherapy and 6.8 months (95% CI 6.3, 8.7) for cisplatin-only patients without post-study chemotherapy. Even after adjusting for patient prognostic factors and controlling for whether patients initially received cisplatin alone or cisplatin plus pemetrexed, receiving post-study chemotherapy was associated with prolonged survival ($p < 0.001$). It is unclear whether this survival benefit was due to the initial or the subsequent chemotherapy regimens, or whether the interval between finishing the first regimen and starting the second may have affected the statistical analysis.[71]

When the final data from the original phase III trial were reported in 2005, the median survival of patients receiving pemetrexed plus cisplatin was 12.8 months, compared with 9.0 months for patients receiving cisplatin alone.[72] The hazard ratio for death in the combination arm was 0.74 (95% CI 0.60, 0.90; $p = 0.003$). Intention-to-treat analysis was not performed, since eight patient data from eight patients were absent.[64]

QOL data from the phase III trial of cisplatin alone versus cisplatin plus pemetrexed showed statistically significant reductions in pain after three cycles, in dyspnoea after six cycles and in fatigue after six cycles for patients receiving both drugs.[73] The total Lung Cancer Symptom Scale score (modified for mesothelioma) favoured the combination arm after six cycles ($p = 0.004$).

Assessment of radiographic responses in MPM is difficult (see section 7). While the EMPHACIS trial

investigators reported 94 radiographic partial responses in the combination arm, the FDA independently reviewed imaging data from this trial and confirmed only 47 partial responses. Nevertheless, the FDA approved pemetrexed in combination with cisplatin for MPM patients who were not surgical candidates or had unresectable disease. The FDA also recommended that patients begin vitamin supplementation 3 weeks prior to pemetrexed therapy consisting of folic acid 350–1000 μg/day and cyanocobalamin 1000μg intramuscularly every 9 weeks. Dexamethasone was also suggested on days 0, 1 and 2 of chemotherapy to reduce the incidence of pemetrexed-associated rash.[74]

Pemetrexed has also been combined with other platinum-containing compounds for the treatment of MPM. In a phase II trial of front-line therapy, 102 patients were treated with carboplatin (area under the concentration-time curve [AUC] 5 mg • min/mL) and pemetrexed 500 mg/m^2.[75] An overall response rate of 18.6% (95% CI 11.6, 27.5) was reported and two patients had complete responses. Forty-seven percent of patients had stable disease (95% CI 37.1, 57.2). The median time to progression was 6.5 months and the median survival 12.7 months. Ongoing studies using pemetrexed include a three-arm nonrandomised trial of pemetrexed 500 mg/m^2 plus cisplatin 75 mg/m^2 versus pemetrexed plus carboplatin (AUC 5 mg • min/mL) versus pemetrexed alone, and a randomised phase III study of best supportive care alone versus best supportive care plus pemetrexed.[29]

6.2.2 Raltitrexed

Raltitrexed is a thymidylate synthase inhibitor with a lower affinity for GARFT than pemetrexed.[65] Raltitrexed has been approved in Europe and in Canada for the treatment of colorectal cancer but is not yet approved in the US.

A small phase II trial of raltitrexed alone in patients with MPM reported a response rate of 20.8% in 24 patients and a median survival of 7 months, with a wide 95% CI (5.5, 18.7).[76]

In a large phase III trial, chemotherapy-naive patients with MPM were randomised to cisplatin alone (80 mg/m^2 every 3 weeks) or cisplatin plus raltitrexed (3 mg/m^2 every 3 weeks).[77] As in the EMPHACIS trial, cisplatin plus gemcitabine would have been a more relevant comparator than cisplatin alone. Median survival was 11.4 months in the combination arm, compared to 8.8 months in the cisplatin-only arm ($p = 0.048$). These results are comparable with the 2.8-month increase in median survival seen with the addition of pemetrexed to cisplatin.[67] In the raltitrexed arm, there was a trend toward increased PFS, but this difference was not statistically significant.[77] Six percent of patients receiving combination therapy developed grade 3/4 anaemia and 16% developed grade 3/4 neutropenia. While cyanocobalamin and folic acid supplementation is needed to temper haematological toxicity with pemetrexed, the investigators theorised that similar supplementation was unnecessary with raltitrexed because this compound primarily inhibits thymidylate synthase, whereas pemetrexed inhibits several enzymes. Health-related QOL (HRQOL) data were collected during the trial, but no significant difference in global HRQOL was noted between the two treatment arms.[78] Both arms had lower QOL than the general population. Since addition of pemetrexed to cisplatin resulted in a statistically significant survival benefit, whereas addition of raltitrexed did not, a recent systematic review of chemotherapy in MPM concluded that raltitrexed should be reserved for patients in whom pemetrexed has not been approved or is not available.[79]

Oxaliplatin has shown activity in cisplatin-resistant MPM tumour cell lines.[80] Accordingly, raltitrexed 3 mg/m^2 plus oxaliplatin 130 mg/m^2 were administered every 3 weeks to 70 patients (64 with MPM) in a phase II trial.[81] Overall, 20% had a partial response and 46% had stable disease. Interestingly, there was a nonsignificant trend toward longer survival in pretreated patients (median survival 31 weeks; 95% CI 23, 40) compared with chemotherapy-naive patients (median survival 44 weeks, 95% CI 24, 40). In a follow-up phase II trial, 14 previously treated patients were treated with raltitrexed 3 mg/m^2 and oxaliplatin 130 mg/m^2 every 3 weeks.[24] Four patients had stable disease and no complete or partial responses were noted, resulting

in the combination being judged to be inactive against MPM.

6.3 Tyrosine Kinase Inhibitors

The orally available tyrosine kinase inhibitors represent a new class of antitumour therapy. In a CALGB study of 43 patients (42 with MPM), 97% had histological evidence of epidermal growth factor receptor (EGFR) overexpression.[82] These 43 patients were treated with the EGFR inhibitor gefitinib (500 mg/day). Twenty-one patients had stable disease for at least two cycles, with one complete response and one partial response being noted. The 3-month failure-free survival rate in treated patients was 40% (95% CI 25, 56), which was markedly lower than the 60% rate noted in historical treated controls. The authors concluded that gefitinib was not active in MPM.

When 23 patients with MPM were treated with imatinib 400–800 mg/day, no tumour regressions were noted and the investigators concluded that single-agent imatinib was ineffective in the treatment of MPM.[83] In a subsequent trial of 11 patients treated with imatinib 200mg twice daily, four patients had stable disease but the median survival of these patients was only 29.5 weeks.[84]

Patients with MPM have the highest serum vascular endothelial growth factor (VEGF) levels of any solid tumour patients,[85] making the VEGF receptor an attractive therapeutic target. In previous studies, increased VEGF expression has been shown to correlate with increased microvessel density around the tumour and with worse clinical outcomes.[86] Currently, a multicentre randomised phase II trial comparing cisplatin, gemcitabine plus placebo with cisplatin, gemcitabine plus bevacizumab is underway.[85] In a blinded interim analysis of these patients, patients with higher levels of circulating VEGF had shorter median survival times ($p = 0.008$).[86]

6.4 Gene Therapy

Gene therapy has been considered an opportunity to improve outcomes in MPM. A mutant thymidine kinase enzyme from herpes simplex virus (HSV-TK) has been inserted into adenoviral vectors, which allows infected cells to activate the prodrug ganciclovir into a toxic metabolite capable of killing both transfected and neighbouring nontransfected cells. Deletion of key portions of the viral genome impairs the ability of the virus to replicate. In a University of Pennsylvania phase I trial, 26 patients with MPM were treated with adenovirus deficient in viral proteins E1A and E3 that was engineered to express HSV-TK.[87] Only one patient had radiographic evidence of tumour regression after treatment with the adenoviral vector. The median survival of patients receiving $<1.6 \times 10^{13}$ viral particles was 10 months, while the survival of those receiving $>1.6 \times 10^{13}$ particles was 15 months, but this difference was not statistically significant.[87]

A second phase I trial used a 'second-generation' adenovirus unable to produce the E1 and E4 viral proteins.[87] Of the five patients treated in this second trial, two survived for >6 years with relatively asymptomatic recurrence of disease. Fever, hypoxia and abnormal liver function tests were noted in several patients after treatment with the viral vector. The investigators postulated that the few durable clinical responses seen were due to induction of antibodies against unidentified mesothelioma proteins after virus-mediated tumour cell death, rather than to long-term expression of viral transgenes.[87] Subsequently, three patients were treated with 3×10^{13} E1/E4-deficient viral particles, but no lasting clinical responses were noted.

Other gene therapies have also been tested for activity against mesothelioma. In a University of Pennsylvania trial, an adenoviral vector expressing interferon-β was infused into the pleural space of ten patients with pleural tumours.[88] Of the four patients with MPM who were treated with the higher dose of virus, three patients had stable disease at 60 days, one of whom had stable disease for 14 months at last report.

The large T antigen of the simian virus 40 has been implicated in the pathogenesis of mesothelioma, and may prove an effective target for gene therapy.[89] In a German phase II trial, transformed monkey fibroblasts known as Vero cells that secrete

human interleukin-2 were injected into human patients with MPM; the results of this trial are pending.[88]

6.5 Novel Agents

Innovative new compounds continue to be devised and evaluated for activity in MPM. For example, the enzyme ranpirnase digests transfer RNA, and can selectively induce quiescence and cytotoxicity in tumour cells. A phase II study of 105 patients with unresectable MPM treated with ranpirnase 480 μg/m^2 every week reported a median survival of 6 months.[90] While only 4 of 81 had a partial response, 35 of 81 assessable patients had stable disease. Ranpirnase is not myelosuppressive, and <6% of patients experienced grade 3 toxicities such as asthenia, oedema, pain and arthralgia.

In a preliminary phase III trial, 144 MPM patients were randomised to treatment with either ranpirnase 480 μg/m^2 every week plus doxorubicin 60 mg/m^2 or doxorubicin alone.[91] Median survival was 8.4 months in the combination arm and 8.2 months in patients receiving doxorubicin alone. While there was no statistically significant difference in survival between treatment groups, review showed that 38% of the combination patients fell into poor CALGB prognostic groups, while only 17% of doxorubicin-only patients fell into these poor prognostic categories. When all patients in CALGB poor prognostic categories 5 and 6 were excluded, the remaining combination-arm patients had a median survival of 11.6 months and the remaining single-agent patients had a median survival of 9.6 months. A larger phase III trial of ranpirnase 480 μg/m^2 every week plus doxorubicin 60 mg/m^2 versus doxorubicin alone is currently enrolling patients with MPM.

Tetrathiomolybdate binds copper, consequently lowering ceruloplasmin and VEGF levels, and slowing tumour angiogenesis. In a small phase II trial reported in abstract form, 69% of patients with stage I or II MPM treated with tetrathiomolybdate had PFS of at least 24 months.[86,92]

In a phase II study, 27 patients with MPM were treated with oral capecitabine 2500 mg/m^2 daily for 14 days of a 21-day cycle.[55] Median survival was 4.9 months (95% CI 4.0, 10.8) and median PFS 2.4 months (95% CI 1.5, 4.2). Only 1 of the 27 patients had a partial response (4% response rate).

Forty patients with MPM, 36 of whom had the epithelial subtype, were treated with escalating thalidomide doses of 100, 200 or 400 mg/day.[93] Eleven of 40 patients had stable disease for >6 months. The 200 mg/day dosage of thalidomide was considered to be the maximum tolerated dose. Common adverse effects included neuropathy and constipation. The NVALT (Nederlandse Vereniging van Artsen voor Longziekten en Tuberculose; Dutch Society for Lung and Tuberculosis Specialists) trial, which is currently underway, is treating patients who have received pemetrexed plus cisplatin or carboplatin with subsequent thalidomide or placebo.[86]

In a phase I trial, vorinostat (suberoylanilide hydroxamic acid; SAHA), a histone deacetylase inhibitor, induced partial responses in 2 of 13 patients with MPM.[94] A phase III trial of vorinostat is currently recruiting patients with MPM who have failed pemetrexed therapy.

6.6 Role of Chemotherapy

While trials have shown that chemotherapy can improve symptoms associated with MPM such as pain and dyspnoea,[95] published trials of chemotherapy have not included an active symptom control arm.[79] As a result, it is not yet known whether chemotherapy prolongs survival compared with symptomatic care. In the UK, the MS01 trial is underway to compare active symptom control versus mitomycin, vinblastine plus cisplatin versus vinorelbine alone.[69] Because this trial was designed before the full results of the phase III EMPHACIS trial of pemetrexed were released, pemetrexed was not included.

7. The Duke Experience

At Duke University Medical Center, patients with newly diagnosed mesothelioma undergo a staging CT scan using Duke's mesothelioma protocol. Patients with limited disease and epithelial or mixed

histology on biopsy are evaluated for extrapleural pneumonectomy. Cisplatin plus pemetrexed is used as neoadjuvant therapy in selected patients with resectable disease, as well as in patients with unresectable disease. Adjuvant radiotherapy is delivered using intensity-modulated radiotherapy protocols. This centre will soon be enrolling MPM patients in a phase II trial of first-line cisplatin, pemetrexed plus the VEGF receptor inhibitor bevacizumab; PFS will be the primary outcome and overall survival a secondary outcome (Garst JL, personal communication, 2006 and D'Amico TA, personal communication, 2006).

8. Assessment of Response

The selection and reproducible measurement of a clinically relevant primary outcome remains a central issue in clinical trials of new chemotherapeutic agents. Since cancer research funds are limited, if a particular agent does not show significant response at the tested dose and schedule, investigators are likely to abandon that agent outright, rather than allocate the significant time and expense required to refine the treatment schedule in subsequent trials.

The majority of the literature pertaining to the treatment of MPM consists of single-arm phase II trials designed to measure the percentage of patients who meet radiographic criteria for complete or partial response. Muers et al.[69] have questioned the validity of response rate as a primary outcome in these trials, stating that "response rates do not necessarily reflect symptom relief, which is more important for patients with an incurable disease".

Mesothelioma tends to grow along the pleural space instead of forming discrete spherical tumours. This unusual growth pattern complicates accurate measurement of tumour volume and thus complicates the assessment of response to therapy. Interobserver variability in the assessment of response is high. When independent reviewers and the FDA retrospectively assessed the radiological response data from the phase III trial of pemetrexed plus cisplatin versus cisplatin alone,[67] their results differed widely from the response rates published in the trial.

Over the past 25 years, several sets of radiographic response criteria have been proposed. Indeed, different trials cited in this review used different standards to define response, complicating direct comparison of results from different trials. The WHO tumour response criteria[96] are more applicable to spherical tumour lesions than to the 2-dimensional spreading growth pattern of MPM. In 2000, the RECIST criteria defined radiographic response as a ≥30% reduction in the sum of the longest diameter of each individual tumour lesion.[97]

In 2004, Byrne and Nowak[98] proposed a modified RECIST system, whereby tumour thickness is measured perpendicular to the chest wall or mediastinal structure twice at each of three transverse levels, and a ≥30% reduction in the sum of these six measurements is defined as a partial response. When these authors applied these modified RECIST criteria to serial CT scans of 73 patients with MPM, they showed a statistically significant difference in both median survival and in change in forced vital capacity between patients who met the new response criteria and those who did not. As a result, these authors suggested that tumour response as determined by these modified RECIST criteria served as a valid surrogate endpoint for patient benefit.

Because response rate may underestimate the efficacy of cytostatic/noncytotoxic agents, changes in tumour metabolic activity, tumour markers or activity of growth factor pathways may therefore be more appropriate evaluation criteria for these therapies.[99] Francart et al.[100] analysed several European MPM trials, most of which used WHO response criteria. On the basis of response rates, these investigators concluded that the only regimen with 'significant clinical activity' was the combination of cisplatin and raltitrexed. However, it is important to note that this European review did not include trials of pemetrexed. The median PFS rate of patients in the cisplatin plus raltitrexed combination arm was 72% at 3 months, 67% at 4 months and 43% at 6 months. These investigators advocated use of PFS rate as a more clinically relevant endpoint in MPM trials.

9. Cost

The expenses associated with the diagnosis, treatment and palliation of patients with MPM are nothing short of staggering. The total cost of mesothelioma to the US economy over the next 40 years is expected to exceed $US200 billion,[33] and more than $US300 billion in economic costs to the Western world is expected in 'coming decades'.[2] The treatment preferences of each individual patient must take precedence over cost considerations. As with many cancers with poor prognoses, patients with MPM should be considered for participation in clinical trials and research budgets can underwrite the cost of care for these patients.

A healthcare consulting firm and Eli Lilly, the manufacturer of pemetrexed, jointly studied the costs of cisplatin plus pemetrexed therapy in Australia.[101] When pemetrexed was added to cisplatin alone, the mean incremental cost-effectiveness ratio per year of life saved was $US57 285 (converted from Australian dollars). According to calculations by the Scottish Medicines Consortium, a course of pemetrexed plus cisplatin would cost the equivalent of $US14 760 (2007 values) more than a course of cisplatin alone, which amounts to $US64 080 per quality-adjusted life year (QALY).[102] As a reference point, $US50 000 per QALY is often quoted as the cost to Medicare of haemodialysis and associated care for a single patient.

Future trials comparing chemotherapy to best supportive care will help delineate if chemotherapy improves outcomes and if the additional cost is excessive.

10. Conclusion

Research into new therapeutic options for MPM is complicated by the nature of the disease itself. MPM is a relatively rare condition that affects older patients with multiple co-morbidities. In addition, MPM grows by spreading along the pleural surface, which complicates the radiographic measurement of tumour volume and the assessment of response to therapy. At this point, it is not known whether aggressive multimodality therapy for MPM, including radical surgical resection, will improve patient survival or QOL compared with symptom control measures. Since most patients have significant co-morbidities and present with advanced disease, curative surgery is usually not a viable treatment option. As a result, novel chemotherapies and radiotherapy techniques offer the greatest hope of improving outcomes in this disease. Pemetrexed, the first drug FDA-approved for use in the treatment of MPM, has only recently become available. Trials currently underway should help define the role of both surgical and medical therapies for this deadly disease.

As the worldwide incidence of MPM continues to rise, the health care and societal costs of MPM patients will run into the hundreds of billions of dollars. After the efficacy of chemotherapy and multimodality therapies for MPM are established, further study is needed to establish the cost effectiveness of these treatments.

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