



Medical management of mesothelioma

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Summary

Mesothelioma is a malignant tumour of pleura and other serosal tissues. It arises many years after asbestos exposure. There is currently no highly effective therapy and the median survival is approximately 10–12 months from diagnosis. Most patients cannot be treated surgically due to the advanced stage of the disease at diagnosis or are unfit for radical surgery. New antifolate drugs (pemetrexed or raltitrexed) in combination with platinum are associated with longer median survival than platinum alone, an increase which averages about three months. Radiation therapy is limited by its toxicity to the underlying lung, but newer field and dose planning methods are under investigation. Mesothelioma presents major challenges for the palliative management of dyspnoea, pain, and cancer cachexia syndrome.

Key words: antifolate, cisplatin, pemetrexed.

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Introduction

Mesothelioma is an aggressive tumour of serosal surfaces, most commonly the pleura, associated with exposure to asbestos often many years previously. In Australian men the age standardised incidence of mesothelioma rose from 2.3 new cases per 100 000 population in 1982 to 5.4 in 2007. The peak incidence is predicted to occur within the next decade and the 2011 Australian caseload is estimated to be 990 new cases. Mesothelioma is resistant to classical anticancer treatments with a median survival from diagnosis of approximately 10–12 months. Highly effective therapy for the disease remains elusive.

Surgical treatment

The role of surgery alone in mesothelioma is debatable. Non-randomised studies of radical trimodality treatment (extrapleural pneumonectomy, chemotherapy and radiotherapy) report median survival rates of 9.4 to 27.5 months. Extended survival is more likely in those with complete resections, epithelial histology, and without involvement of extrapleural nodes. This management

approach may be suitable for highly selected patients with good functional status who have Stage 1 or 2 epithelioid tumour subtypes and can be treated in a centre with specific surgical expertise, but it is generally unsuitable for the majority of patients.

Key trials underpinning current 'standard' chemotherapy

Establishing a 'standard' active chemotherapy for mesothelioma has been difficult. There are few randomised trials, they involve small numbers of patients and the response to treatment is difficult to measure. There is difficulty comparing trial results because patients have different stages of disease and different histopathology subtypes. Response rates greater than 15% (based on tumour dimensions) have been reported for several single drugs including gemcitabine, platinum, vinorelbine, several anthracyclines (such as doxorubicin), and several antifolate drugs (such as pemetrexed).¹ Platinum-containing combinations generally produced higher response rates than single drug therapy, for example cisplatin plus gemcitabine response rates ranged from 15% to 48% in three non-randomised trials. However, there are few direct randomised comparisons of single drugs versus combinations.

There is only one randomised trial of chemotherapy versus no chemotherapy. This multicentre trial was initially designed with two older chemotherapy regimens – either four cycles of mitomycin, vinblastine and cisplatin or weekly vinorelbine for 12 weeks. Because of slow recruitment of patients these regimens were combined in a *post hoc* analysis of the primary outcome of overall survival and compared with active symptom control. A total of 409 patients were randomised. The median survival with chemotherapy (8.5 months) was not significantly different from that with active symptom control (7.6 months), and there was no evidence of a difference in quality of life.² Active symptom control was as recommended by the British Thoracic Society at the time and did not include chemotherapy, however 15% of patients in the active symptom control arm and 14% of those in the chemotherapy arms received chemotherapy other than the protocol chemotherapy. The relative lack of effectiveness of platinum based chemotherapy may have been affected by the limited dose and duration of treatment in this trial.

Antifolate combinations

A randomised single-blind study of 456 patients found an

improved response rate (41% vs 16.7%) and a longer median survival in those treated with cisplatin plus pemetrexed (12.1 months) versus cisplatin alone (9.3 months). Both haematological (grade 3/4) and non-laboratory toxicity were significantly more frequent in the combination arm than in the cisplatin only arm (anaemia 5% vs 0%, neutropenia 28% vs 2.3%, thrombocytopenia 6% vs 0%, vomiting 13% vs 3%, diarrhoea 4% vs 0%, dehydration 4% vs 0.5%, and stomatitis 4% vs 0%). Supplements of vitamin B₁₂ and folic acid reduced the haematologic toxicity of pemetrexed/cisplatin including rates of febrile neutropenia and infection, and non-haematological toxicity including nausea and vomiting without reducing the efficacy of the combination.³ Superior pain, dyspnoea, and fatigue scores, as well as stabilisation of global quality of life and activity level scores were subsequently reported for patients on the combination arm of this study. A similarly designed study of platinum with raltitrexed (a specific inhibitor of thymidilate synthase) also showed a similar survival advantage for the combination compared with cisplatin alone, as well as no deterioration in health related quality of life over time in either arm.⁴

Although there is no published randomised study of single drug platinum versus no chemotherapy, it is assumed that platinum alone is either active or at least not detrimental. These studies showing a survival benefit and improved quality of life for patients treated with antifolates plus platinum over platinum alone, underpin the Australian approval of pemetrexed in combination with platinum as first-line chemotherapy for mesothelioma. Further experience with antifolates in mesothelioma was gained in expanded access programs in the USA and Europe. These non-randomised studies report that median survival for patients given platinum with pemetrexed is longer than with pemetrexed alone in both first- and second-line settings. However, there is a possible bias that fitter patients may have been selected for combination chemotherapy rather than pemetrexed alone.⁵

Combination regimen

For patients with good performance status and adequate end-organ function, the standard treatment in Australia is pemetrexed 500 mg/m² as a 10-minute intravenous infusion followed by cisplatin 75 mg/m² over two hours on day one of 21-day cycles. Pharmaceutical costs are approximately \$19 000 for six cycles of treatment. Patients must take folic acid 350–1000 microgram daily (usually 500 microgram) and be given vitamin B₁₂ 1000 microgram intramuscularly seven days before the start of treatment repeated nine-weekly during treatment to reduce haematological and non-haematological toxicity. Dexamethasone is given for three days starting the day before pemetrexed therapy to reduce the risk of skin rash.

A single small randomised study of chemotherapy given immediately after diagnosis or delayed until symptoms progressed showed that the duration of controlled symptoms

and survival were longer in patients receiving immediate treatment.⁶ Although the difference of four months in median survival was not statistically significant, it suggests that there is no advantage in delaying treatment.

There is a lack of data concerning optimal duration of treatment – patients in the single-blind study received 1–12 cycles, with a median of six.³ Treatment is usually given for a total of six cycles or ceased earlier if the patient develops progressive disease or unacceptable toxicity. Carboplatin may be substituted for cisplatin in patients with mild to moderately impaired renal function (response rates were similar to the cisplatin-based combination).⁷ The International Expanded Access program also included carboplatin.⁸ Platinum drugs and pemetrexed are contraindicated in severe renal insufficiency.

Second-line and maintenance treatment

To date there is one randomised study of treatment after failure of first-line chemotherapy. Second-line treatment with pemetrexed was associated with prolonged progression-free survival compared with best supportive care (median 3.6 months vs 1.5 months),⁹ however few patients had received pemetrexed in their first-line chemotherapy. Although there was no significant increase in the primary endpoint of overall survival in the pemetrexed arm, this may have been affected by the higher proportion of patients in the best supportive care arm who received post-discontinuation chemotherapy (including pemetrexed in some cases). Several phase II studies have been reported, but do not support recommendation of a particular treatment. For maintenance treatment, a randomised phase II trial is studying pemetrexed versus observation in patients with stable disease after first-line treatment.

Clinical trials of targeted treatments

The presence of growth factor receptors in mesothelioma has prompted research into targeted therapies.

Epithelial growth factor receptor tyrosine kinase inhibitors

Epithelial growth factor receptor (EGFR) is often overexpressed in mesothelioma. However, phase II trials of the EGFR tyrosine kinase inhibitors erlotinib and gefitinib have not reported objective responses.

Vascular endothelial growth factor inhibitors

Vascular endothelial growth factor (VEGF) is an autocrine growth factor which induces new blood vessel formation. High concentrations of VEGF are associated with a poorer prognosis in mesothelioma. In phase II trials the antiangiogenic drugs bevacizumab, sorafenib and sunitinib have been relatively well tolerated, but have produced generally low response rates.¹⁰ There was no advantage when bevacizumab was added to cisplatin and gemcitabine.¹¹ A randomised phase II/III trial

(IFCT-GFPC-0701) of cisplatin and pemetrexed with or without bevacizumab as first-line treatment reported superior outcomes for the bevacizumab arm¹² and so recruitment will continue to complete the phase III trial.

Histone deacetylase inhibitors

Histone deacetylase inhibitors, such as sodium valproate, activate transcription of genes involved in apoptosis, cell proliferation and angiogenesis. Trials of sodium valproate in patients with progressive disease found some biological activity. Numerous newer drugs in this class are in testing including a phase III trial of vorinostat.

Ranpirnase

Ranpirnase is a ribonuclease which disrupts protein translation. It showed disease modifying activity by stabilising progressive disease, but a phase III trial of adding ranpirnase to adriamycin showed no overall survival advantage.

Proteasome inhibitors

The transcription factor NF- κ B regulates proteins associated with evasion of apoptosis. Proteasome inhibitors interfere with degradation of inhibitor- κ B, and so restore apoptosis. Two phase II studies of bortezomib are in progress.

Mammalian target of rapamycin inhibitors

Loss of a tumour suppressor in mesothelioma activates the mammalian target of rapamycin (mTOR), a serine threonine kinase. This enzyme is highly expressed in mesothelioma, providing a rationale for evaluation of mTOR inhibitors such as rapamycin itself (sirolimus) and analogues temsirolimus and everolimus (currently in phase II trial).

Imatinib

Signalling by platelet derived growth factor receptor promotes mesothelioma growth. Imatinib mesylate, an inhibitor of the enzyme associated with this receptor, was ineffective as a single drug, but increased tumour xenograft uptake of other anticancer drugs by its effect on tumour endothelium. There is now a phase II trial of gemcitabine plus imatinib.

Vascular disrupting drugs

These drugs target the established tumour vasculature causing tumour ischaemia and necrosis. They include small molecules of two classes – flavonoids and tubulin binding drugs. A trial of a tubulin binding drug BNC105P in mesothelioma is registered with the Australasian Lung Cancer Trials Group and is currently enrolling patients in multiple centres (the B2P2M2 trial).

Thalidomide

Thalidomide has anti-angiogenesis and other complex antitumour activity. There is a collaborative Dutch and

Australian trial which is studying pemetrexed-based chemotherapy with or without maintenance thalidomide.

Novel first-line drugs

Mesothelin is a cytoplasmic membrane glycoprotein involved in cell adhesion and is proposed as a diagnostic and treatment response biomarker for mesothelioma. An anti-mesothelin monoclonal antibody Morab-009 (amatuximab) is in phase II trial. Also being studied are an anti-mesothelin antibody conjugated with pseudomonas exotoxin A, and a mesothelin vaccine designed to elicit an antibody dependent cytotoxicity response against mesothelin expressing tumour cells.

Palliative management

Effective palliative management of mesothelioma often requires multiple interventions to alleviate symptoms of dyspnoea due to recurrent pleural effusion or lung encasement, pain due to parietal pleural irritation or intercostal nerve compression or invasion, and anorexia cachexia syndrome. An excellent review of palliative care for mesothelioma¹³ and randomised trials of palliative interventions are available to guide the management of common problems, including several studies of pleural drain site irradiation,¹⁴ pleurodesis versus partial pleurectomy, and thoracoscopic versus closed pleurodesis. New methods for managing repetitive drainage of recurring effusions in ambulatory patients using tunnelled pleural catheter systems are also available.

Regular medical follow-up with assessment of physical, psychological and social problems and action to address these is fundamental to effective management. Patients with thoracic pain due to mesothelioma require treatment with sustained release opioids and other analgesics with regular review of dosage, effectiveness, and pre-emptive management of adverse effects, particularly nausea, vomiting and constipation. Several studies report effective pain relief in over 50% of patients treated with radiation therapy.¹⁵ When pain is not readily relieved referral to a specialist pain management service is advisable. Advanced pain relief measures, including adjuvant treatment for neuropathic pain, nerve blocks, neurolytic procedures and epidural delivery of opioids and anaesthetics, can provide effective pain management. Glucocorticoids may be beneficial for anorexia and cachexia.

Recognition and management of depression is essential and an important element of good palliative care is identification of various sources of social and psychological stress, which can include those encountered in applying for compensation. Fortunately for Australians occupationally exposed to asbestos, this process has been simplified by previous litigation. Engagement of specialist oncology and palliative care services, medical social worker, psychologist and other specialists is frequently needed to help patients cope with symptoms of mesothelioma.

Future

The goal of establishing highly effective therapy for mesothelioma remains elusive, but multiple promising avenues towards this goal are opening. Personalised therapeutic approaches under investigation in mesothelioma include use of the ERCC1 gene as a predictor of poor response to platinum therapies and elevated thymidilate synthase as a predictor of reduced pemetrexed activity. One study found varying levels of *in vitro* chemoresistance in 168 cell lines generated from resected tumours.¹⁶ If this information predicts clinical response, it may help in future to identify the most effective treatment with the least amount of toxicity for an individual patient.

Conclusion

There is no cure for malignant mesothelioma. Radical treatments remain unproven by randomised controlled clinical trial, and only a minority of patients are eligible for such therapy. Although platinum with antifolate chemotherapy is effective in prolonging survival and improves quality of life, it is not without toxicity and is not curative. Effective palliation for symptomatic disease requires an active pre-emptive approach. Vigorous research efforts are still required to discover effective treatment or secondary prevention strategies for a disease with an increasing worldwide incidence.

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Conflict of interest: none declared

Self-test questions

The following statements are either true or false (answers on page 159)

5. Patients treated with pemetrexed and cisplatin need regular injections of vitamin B₁₂.
6. Compared to cisplatin alone, cisplatin with pemetrexed increases the median survival of patients with mesothelioma by 12 months.