Malignant pleural mesothelioma continues to be a challenging clinical problem. While traditionally, chemotherapy has been thought to be of only modest benefit to patients with this disease, novel antineoplastic agents and combination regimens incorporating these agents are gradually changing this perception. Early attempts at treatment and palliation with single agents such as doxorubicin met with low response rates and little clinical benefit. However, the recently reported clinical benefits of pemetrexed and raltitrexed in combination with cisplatin are changing the perception about the ability of chemotherapy to affect the natural history of the disease. Other combinations, including cisplatin and gemcitabine, have also shown encouraging response rates and clinical activity. Single-agent therapy with vinorelbine may provide useful palliation with low toxicity. Targeted agents developed through increased understanding of the biology of the disease, used alone or as part of multimodal therapy, may provide major clinical gains in the next few years.

Key words: cancer, chemotherapy, mesothelioma, novel agents

Introduction

Malignant mesothelioma is generally viewed as a treatment-resistant tumor with a very poor prognosis, regardless of the stage at diagnosis. Until recently, chemotherapy had not been shown to alter the natural course of the disease. The role of surgery is uncertain for most patients, though selected series have shown long-term survival in a small number of cases [1]. Radiation has minimal impact on survival, but has a limited role in palliation [2].

There are approximately 2500 new cases of malignant mesothelioma annually in the United States, mostly malignant pleural mesothelioma (MPM), and they are usually diagnosed in the fifth to seventh decades of life, with a median survival of 4–18 months, and strong male predominance [3]. Projections for Europe indicate a doubling of the number of new cases until 2018 [4]. The situation in the developing world is also of concern because asbestos-derived products are still widely used and marketed there [5].

Development of MPM is strongly associated with asbestos exposure, with 77% of patients previously exposed to this single risk factor [6]. Of the two major forms of asbestos that exist, the rod-shaped amphiboles (actinolyte, amosite, anthophyllite, crocidolite and tremolite) are more carcinogenic, while the curly chrysotile form is less carcinogenic [7, 8]. Chrysotile is frequently contaminated with amphibole asbestos and should therefore be considered a hazardous substance. The pathway by which asbestos fibers reach the pleural space appears to be similar to the trapping of other particles, such as coal dust, resulting in the production of parietal pleural black spots [9]. The mean latent period between the initial exposure to asbestos and the development of MPM is 48.7 years (range 14–72 years), depending on the type and intensity of exposure and other risk factors [10].

Several studies have implicated simian virus 40 (SV 40) as an important risk factor in the development of MPM and have suggested that asbestos and SV 40 are cocarcinogens, with one potentiating the effect of the other [11], but have yet to prove the tumor initiation role of SV 40. Retrospective data indicate that the presence of SV 40 infection also may be a poor prognostic factor in the biphasic or sarcomatous subtypes of MPM [12].

The etiology of MPM is starting to be understood at the molecular level. Deletions of chromosome regions 1p, 3p, 9p and 6q, as well as loss of chromosome 22, are all commonly found in MPM. These regions contain putative tumor suppressor genes that may be important in the progression of malignancy, including the neurofibromatosis 2 (NF2) tumor suppressor gene (chromosome 22), p16INK4A and p14ARF (9p21) [13]. The importance of core-apoptosis failure in the resistance to treatment of MPM has been reviewed recently [14]. Detailed understanding of how and why mesothelioma
apoptosis mechanisms fail will have fundamental relevance for oncology in general.

Several staging systems for MPM have been proposed; however, none has been universally accepted. The major problem is that staging can only be defined accurately following cytoreductive surgery: a procedure only performed on a minority of patients. The International Mesothelioma Interest Group (IMIG) proposed a TNM (tumor–node–metastasis)-type staging system based on a retrospective analysis of the impact of T and N status on survival [15]. In addition, two prognostic scoring systems [by the Cancer and Leukemia Group B (CALGB) and the European Organization for Research and Treatment of Cancer (EORTC)] have been developed for MPM based on data collected from patients entered into large cooperative group trials [16, 17]. The combination of a new staging system and standardized prognostic scoring systems allows for the selection of patients for appropriate clinical trials and for some degree of comparison of patient populations in separate trials of novel therapies [18].

Chemotherapy of malignant mesothelioma

Most of the studies using either single agents or combination regimens have been small, unrandomized phase 2 trials. Patients are usually heterogeneous between studies with regard to stage and prognostic factors. This makes comparisons between studies difficult and potentially misleading. Tumor response is also difficult to measure radiologically. Standardized criteria improved the consistency of reported response rates (compared with older studies), but these criteria require the presence of bidimensionally measurable tumor, even though MPM is most often only measurable in one dimension because it grows contiguously along the pleural surface. Adoption of unidimensional measurement standards as outlined by the Response Evaluation Criteria In Solid Tumors (RECIST) guidelines should make tumor response in MPM studies more meaningful in the future [19, 20].

Single agents

Most available chemotherapy drugs have been tested in malignant mesothelioma as single agents. In general, single-agent response rates are under 20%, and no survival advantage for single-agent chemotherapy has ever been clearly demonstrated. Doxorubicin is one of the most studied single-agent treatments for MPM. However, in a large retrospective series by the Eastern Cooperative Oncology Group, the response rate of single-agent doxorubicin was reported to be only 14%, with a median survival of 7.3 months [21]. Other anthracycline analogues and formulations of epirubicin and liposomal doxorubicin have been tested and dose escalations have been studied. These approaches have generally yielded disappointing response rates under 10–20% [22–24].

Platinum analogues have been studied both as single agents and in combined regimens for MPM. Cisplatin demonstrated an overall response rate of 14% at a dose of 100 mg/m² given every 21 days in patients with diffuse malignant mesothelioma [25], and it was included as the control arm of two large phase III trials studying novel agents: one evaluating pemetrexed in combination with cisplatin [26], and another evaluating raltitrexed in combination with cisplatin [27]. These trials are discussed in detail below. At higher doses (e.g. 80 mg/m² weekly), cisplatin achieved a response rate of 36% [28], with significant discontinuations (34%) due to toxic effects. Carboplatin, an analogue of cisplatin that is better tolerated and easier to administer, produces response rates similar to conventional doses of cisplatin (7–16%) in phase II studies [29, 30].

The alpha-folate receptor gene is overexpressed in up to 72% of MPM tumors, suggesting a possible link to the pathogenesis of the disease [31]. This finding may explain the activity of some antifolates in MPM. In a phase II trial of 60 MPM patients, high-dose methotrexate produced a response rate of 37% and a median survival of 11 months [32]. The treatment was remarkably well tolerated in light of the known effects of pleural fluid collections on methotrexate pharmacokinetics. In a CALGB phase II study of 58 patients, weekly edatrexate with or without leucovorin demonstrated an objective response rate of 15%, but an unacceptable level of toxicity [33]. Raltitrexed, a thymidylate synthase inhibitor, is currently being evaluated in combination with oxaliplatin and cisplatin (discussed below) in two phase III trials [27, 34]. Unlike most newer antifolates tested in MPM, 5-FU only showed minimal activity [35]. Similarly, the oral derivative of 5-FU, capecitabine, had little useful clinical benefit [36]. A single-agent study of pemetrexed in 64 chemonaive MPM patients has recently been reported and is discussed below.

Vinorelbine is the only vinca alkaloid with proven single-agent activity in MPM. Treatment of 29 assessable MPM patients (ECOG performance status 0–2) with weekly vinorelbine 30 mg/m² gave a partial response rate (50% unidimensional reduction in transthoracic thickness of tumor) of 24%, and an improvement in general physical symptoms in 41% of patients. Stable disease (neither 25% increase or 50% decrease in transthoracic tumor thickness measure unidimensionally) was reported in 55% of patients. Median survival was an encouraging 10.6 months and serious toxicity was low [37]. This schedule is now under evaluation in a phase III trial in the UK (discussed below).

Gemcitabine has limited activity as a single agent in MPM [38] and taxanes are not active in MPM [39]. Other agents, including mitomycin C, cyclophosphamide and temozolomide, have also been studied as single agents in mesothelioma, with generally poor results [40–42].

Combination chemotherapy

The majority of combination chemotherapy regimens that have been studied for MPM are anthracycline- and/or platinum-based. These regimens generally produce response rates of 20% or less, and median survival remains in the range of 6–12 months. In addition to these regimens, several newer agents have been tested in combination regimens, with variable results (Table 1).
Table 1. Response rates with selected chemotherapy regimens for malignant mesothelioma

<table>
<thead>
<tr>
<th>Regimen</th>
<th>Response rate (%)</th>
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<tbody>
<tr>
<td>Doxorubicin + cyclophosphamide [73]</td>
<td>12</td>
</tr>
<tr>
<td>Doxorubicin + cisplatin [74]</td>
<td>25</td>
</tr>
<tr>
<td>Gemcitabine + cisplatin [46, 47]</td>
<td>16–48</td>
</tr>
<tr>
<td>Pemetrexed + cisplatin [26]</td>
<td>41</td>
</tr>
<tr>
<td>Raltitrexed + cisplatin [27]</td>
<td>23</td>
</tr>
<tr>
<td>Oxaliplatin + raltitrexed [43]</td>
<td>30–35</td>
</tr>
<tr>
<td>Oxaliplatin + gemcitabine [44]</td>
<td>40</td>
</tr>
<tr>
<td>Oxaliplatin + vinorelbine [45]</td>
<td>23</td>
</tr>
<tr>
<td>Vinorelbine (weekly) [37]</td>
<td>24</td>
</tr>
<tr>
<td>CPT-11 + docetaxel [49]</td>
<td>0</td>
</tr>
<tr>
<td>CPT-11 + cisplatin [50]</td>
<td>27</td>
</tr>
<tr>
<td>Methotrexate + leucovorin + alpha-interferon + gamma-interferon [52]</td>
<td>29</td>
</tr>
</tbody>
</table>

Oxaliplatin is a platinum analogue that has been studied in several combination regimens for MPM and is currently approved by the Food and Drug Administration and European Medicine Evaluation Agency for colon cancer. The combination of oxaliplatin and raltitrexed was evaluated in a phase II study of both chemonaive and previously treated patients [43]. The overall response rate was 20%, and median survival from start of treatment for the chemonaive and previously treated groups was 31 and 44 weeks, respectively. Oxaliplatin is also active when combined with gemcitabine, with a response rate of 40% reported for the combination [44]. When used with vinorelbine in a phase II trial, however, oxaliplatin significantly increased toxicity and did not seem to offer any additional advantage in response rate over vinorelbine alone [45].

Although gemcitabine has limited activity as a single agent, it has shown promising activity in MPM when combined with cisplatin. In one trial, a response rate of 48% was reported in MPM patients, with symptom improvement in 90% of radiologically responding patients and 33% of unresponsive patients [46]. Grade 3 leukopenia was recorded in 38% of patients and median survival was 9.5 months. Other trials of this combination have shown lower response rates of 16% [47]. Gemcitabine is currently being studied in MPM in combination with epirubicin in a trial through the North Central Cancer Treatment group [48].

Irinotecan (CPT-11) is a topoisomerase I inhibitor with activity in several tumor types including colon cancer and lung cancer. When used in combination with docetaxel in 15 patients with IMIG stage III–IV MPM, it failed to produce an objective response, with 15% of the patients exhibiting minor responses (between 25% and 50% reduction in transthoracic tumor thickness, ie not 50% shrinkage) [49]. Toxicity was severe, with almost 50% of patients developing neutropenic fever and 40% developing WHO grade 3–4 diarrhoea. Irinotecan with cisplatin may be an effective combination, however, as it produced a response rate of 40%, with tolerable toxic effects, in a 15-patient Japanese pilot phase II trial [50]. Another phase II trial evaluated irinotecan, cisplatin and mitomycin administered every 14 days [51]. The response rate, in an intention-to-treat analysis, was 41% and toxicity was moderate.

A study of high-dose methotrexate (with leucovorin rescue) in combination with alpha-interferon and gamma-interferon in 26 patients with localized MPM demonstrated a response rate of 29% and a median survival of 17 months [52]. One-year and 2-year survival rates were 62% and 31%, respectively. The treatment was surprisingly well tolerated, with only two patients requiring dose reductions and one patient discontinuing treatment secondary to toxicity.

Palliative care

With all currently available therapies, response rates remain low and the goal of treatment must be optimal palliation. Two major symptoms, dyspnea and chest wall pain, remain the focus of palliative efforts in patients with advanced malignant mesothelioma. Because of the poor aeration of the lung, fatigue becomes debilitating with little help from supplemental oxygen [53]. Evidence of the palliative benefit of chemotherapy is available for vinorelbine, pemetrexed/cisplatin and the combination of mitomycin, vinblastine and cisplatin [26, 37, 54]. The role of chemotherapy in the palliative treatment of MPM is the subject of an ongoing clinical trial sponsored by The British Thoracic Society and Cancer Research UK (Study ID No. MS-01) [55]. This trial is comparing chemotherapy with ‘active symptom control’, which can include palliative surgery and radiotherapy. Although chemotherapy, when applied judiciously, may help control some symptoms, adequate pain control and attention to respiratory function form the basis of effective palliation in MPM.

Randomized trials and newer approaches in mesothelioma

Several novel approaches to the treatment of MPM, incorporating new chemotherapeutic, biologic, and targeted therapies, are coming into clinical practice (Table 2). Phase 3 randomized
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Table 2. Novel therapeutic approaches to malignant mesothelioma

<table>
<thead>
<tr>
<th>Agent</th>
<th>Putative biological target</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pemetrexed</td>
<td>Multitargeted antifolate</td>
</tr>
<tr>
<td>Ranpirnase</td>
<td>Ribonuclease inhibitor</td>
</tr>
<tr>
<td>SS1(dsFv)-PE38</td>
<td>Pseudomonas exotoxin conjugated immunotoxin</td>
</tr>
<tr>
<td>Bevacizumab (rhuMAbVEGF)</td>
<td>VEGF targeted monoclonal antibody</td>
</tr>
<tr>
<td>SU5416</td>
<td>Selective VEGF receptor kinase inhibitor</td>
</tr>
<tr>
<td>Thalidomide</td>
<td>Multiple mechanisms/VEGF inhibitor</td>
</tr>
<tr>
<td>ZD 1839</td>
<td>EGFR inhibitor</td>
</tr>
<tr>
<td>STI-571</td>
<td>PDGF, c-kit, Bcr-abl inhibitor</td>
</tr>
</tbody>
</table>

EGFR, epidermal growth factor receptors; VEGF, vascular endothelial growth factor; PDGF, platelet-derived growth factor.
trials have also become feasible and have completed recruitment.

The antifolate pemetrexed, administered at 500–600 mg/m² as a single 10 min infusion during a 3 week cycle, inhibits several enzymes important in folate metabolism including glycinamide ribonucleotide formyl transferase (GARFT) [56]. In common with methotrexate, renal function is an important consideration in patients treated with pemetrexed. In a phase I single-agent study, patients with calculated creatinine clearance of 40 ml/min and above tolerated treatment with pemetrexed [57].

During the pemetrexed development program severe, unpredictable toxic effects were observed, including grade 4 neutropenia with and without infection, grade 3/4 diarrhea with or without neutropenia, grade 4 thrombocytopenia, grade 3/4 mucositis, and drug-related death. Analysis of patient characteristics and these toxic effects showed an association between elevated homocysteine (a sensitive marker of folate status) and increased toxicity. Because of these observations, supplemental folic acid (350–1000 mg, commencing 1–2 weeks before treatment and finishing 3 weeks post-treatment) and vitamin B₁₂ (1 mg every 9 weeks) were administered and significantly reduced the incidence and severity of hematological and nonhematological toxic effects—without apparently negatively impacting efficacy.

Sixty-four patients with MPM were enrolled into a phase II trial of pemetrexed measuring response, time to event and toxicity [58]. Nine out of 64 patients (14%) experienced a partial response (50% reduction in sum of two bidimensionally measured lesions or 30% reduction in unidimensionally measured lesions), with seven out of nine responses (78%) seen in vitamin-supplemented patients. Median survival was 10.7, 13.0 and 8.0 months for all patients, supplemented patients, and nonsupplemented patients, respectively. Myelosuppression was the most common toxicity. Grade 3–4 neutropenia occurred in 52% of nonsupplemented patients and 9% of supplemented patients. Vitamin-supplemented patients tolerated treatment better and received a median of six cycles of treatment, while nonsupplemented patients received a median of only two cycles.

Recently a large phase III trial of pemetrexed and cisplatin versus cisplatin has been reported [26]. Four hundred and forty-eight chemonaive patients with MPM received treatment (226 pemetrexed/cisplatin, 222 cisplatin). Pemetrexed/cisplatin treated patients received six cycles of treatment, while cisplatin patients received four cycles. Because of the evidence early in the study of toxicity related to reduced folic acid and vitamin B₁₂, all patients subsequently received folic acid and vitamin B₁₂ supplementation. This resulted in three patient subgroups: not supplemented (completed treatment before the protocol change), partially supplemented (started treatment before the change and completed treatment after the change), and fully supplemented (began treatment after the change).

According to the final results, the pemetrexed/cisplatin treatment was more effective than the cisplatin treatment in terms of median survival (12.1 months versus 9.3 months; \( P=0.020 \)), median time to progressive disease (\( \geq 25\% \) increase in unidimensionally measured lesions or \( \geq 50\% \) increase in bidimensionally measured lesions). Or the appearance of new lesions or death from mesothelioma (5.7 months versus 3.9 months), and response rate (41% versus 17%; \( P<0.0001 \)) using criteria that allowed for both bi- and unidimensional disease [26]. Pemetrexed/cisplatin also appeared to be more effective than cisplatin alone in the subgroup of fully supplemented patients, although the median overall survival times (13.3 versus 10 months) were not clearly statistically significant (\( P=0.051 \)). Time to progressive disease was 6.1 versus 3.9 months (\( P=0.008 \)), and the response rate was 45.4% versus 19.6% (\( P<0.001 \)). A similar treatment effect was seen when the fully supplemented and partially supplemented subgroups were combined. It must be highlighted that the data presented were not compiled by a true intention-to-treat analysis because data from eight patients were omitted from the final analysis of end points.

Toxicity was more common in the pemetrexed/cisplatin arm, with grade 3/4 neutropenia (28%) and leukopenia (18%) being the most common toxic effects. Pulmonary function tests (PFT) and clinical benefit measures were also collected in this study. Pemetrexed/cisplatin showed improvement in both PFT and major disease-related symptoms such as dyspnea and pain. Overall, pemetrexed appears to be a promising new option in the treatment of MPM. These data are encouraging but further experience will show whether pemetrexed offers a new level of activity compared with other cytotoxics [59].

The European Organization for the Research and Treatment of Cancer (EORTC) and the National Cancer Institute of Cancer (NCIC) have reported results of another phase III trial [27]. These data are currently available in abstract form only. Two hundred and fifty patients were randomized to receive cisplatin 80 mg/m² (control arm) or cisplatin 80 mg/m² plus raltitrexed 3 mg/m² (the experimental arm). Chemotherapy was administered every 3 weeks. The patient characteristics were comparable with the University of Chicago study of pemetrexed and cisplatin, although patients with a performance status of 2 were included in the EORTC trial. Overall 13% of patients had a performance status of 2.

The median overall survival in patients treated with raltitrexed and cisplatin was 11.2 months [95% confidence interval (CI): 10.0–13.9 months] compared with 8.8 months in the cisplatin-only group (95% CI: 7.7–11.4 months). The 1 year survival rates were 45% for patients treated with raltitrexed and cisplatin and 40% for patients treated with cisplatin only (\( P=0.06 \)). The investigators attempted to increase the cohort numbers to achieve a clear result but were unable to do so for regulatory reasons. The conclusion was that the combination of cisplatin and raltitrexed appeared to offer an improved overall and 1 year survival in this representative group of mesothelioma patients.

These new data are interesting in light of the previous data from the pemetrexed and cisplatin trial. Both trials included a cisplatin/antifolate combination compared with single-agent cisplatin and both trials showed that the combination
Chemotherapy was more effective at inducing radiological responses than cisplatin alone. In the case of the EORTC/NCIC study, the result was just outside the range of conventional statistical significance and in the University of Chicago study, the result (which was not based on a full intention-to-treat analysis) was reported as being fractionally inside the range of statistical significance.

The median survival of patients treated with an antifolate and cisplatin was approximately 12 months in both studies. The EORTC/NCIC trial patients had marginally shorter survival, possibly explained by the proportion of poorer performance status patients included. Based on these data, the combination of cisplatin and either pemetrexed or raltitrexed can reasonably be offered to patients as a first-line option in mesothelioma. For fit patients a clinical trial remains the first-line treatment approach [59].

Ranpirnase (also known as Onconase), a ribonuclease extracted from leopard frog eggs, has been studied extensively in mesothelioma. In a phase II trial of 105 patients with unresectable malignant mesothelioma, ranpirnase demonstrated a response rate of only 5%, but it produced stable disease in 43% of patients [60]. Overall survival was 6 months in the intent-to-treat population but 8.3 months in a subset of patients with a good prognosis defined by CALGB criteria. In a randomized phase III trial, ranpirnase showed an improvement in survival by 2 months over doxorubicin (11.3 versus 9.1 months) in patients with a CALGB prognostic score of 1–4 [61]. However, overall quality of life in the ranpirnase-treated group was inferior to that of patients treated with doxorubicin, and survival analysis in the intent-to-treat population was hampered by an imbalance between groups of patients with a poor prognosis. A phase III randomized trial comparing doxorubicin to a combination of ranpirnase and doxorubicin is ongoing.

Various cytokines have been studied in malignant mesothelioma and have shown some activity. In a small phase 2 trial of intrapleural interleukin-2 (IL-2) in 15 patients with malignant pleural effusions, one patient showed a complete response (complete disappearance of all previously recorded tumor masses or thickening) and six showed partial responses [62]. A follow-up study of intrapleural IL-2 in 22 patients with MPM demonstrated one complete response, 11 partial responses, and a median survival of 18 months [63]. In a phase II trial of 37 patients with advanced MPM, a combination of alpha-2b interferon with cisplatin and doxorubicin showed a response rate of 29% and a median survival of 9.3 months [64]. The combination appeared to have antitumor activity but was limited by toxicity, particularly myelosuppression and fatigue.

Some of the best-known novel anticancer agents have recently been tested in mesothelioma. Most notably, ZD 1839 (gefitinib), an inhibitor of the epidermal growth factor receptor (EGFR), showed no significant activity as monotherapy in EGFR-positive chemonaive malignant mesothelioma [65]. STI-571 (imatinib mesylate), an inhibitor of the platelet derived growth factor (PDGF) receptor, was ineffective and not well tolerated as a single agent in patients with pleural mesothelioma [66].

**Future directions**

SV 40 virus has been identified as a possible cause of human cancer, in particular MPM [11]. This fact has been applied to the production of a potential therapeutic vaccine for malignant mesothelioma. By cloning a modified, nontransforming SV 40 T antigen gene into a vaccinia vector, a candidate vaccine was produced and tested preclinically in animal models of malignant mesothelioma with positive results [67]. A phase I trial is under way and merits special attention due to the prognostic correlation between SV 40 and MPM.

SS1(dsFv)-PE38 is an immunotoxin produced by the fusion of pseudomonas exotoxin P38 to a high affinity, disulfide-stabilized antibody to mesothelin. The fused protein retains cytotoxic activity and only targets cells expressing mesothelin [68], such as mesothelioma, epithelial carcinomas of ovary and peritoneum, and squamous cancers of cervix and upper aerodigestive tract (i.e. esophagus, head and neck cancers). SS1(dsFv)-PE38 is currently being studied in phase I/II trials in advanced mesothelin expressing tumors.

Vascular endothelial growth factor (VEGF) is an autocrine growth factor important in the pathogenesis of malignant mesothelioma [69]. Three potential inhibitors of VEGF are being investigated for activity against MPM [70]. Bevacizumab (rhuMAbVEGF), a recombinant humanized anti-VEGF monoclonal antibody, is being investigated in a large multicenter, randomized phase II trial. Patients all receive gemicitabine/cisplatin and are randomized to receive bevacizumab or placebo [71]. SU5416 directly inhibits the VEGF receptor through inhibition of its kinase activity. Preliminary results from a small phase 2 study showed some activity [72]. Thalidomide is also thought to be a VEGF inhibitor. Data will be available on its efficacy against mesothelioma in the near future.

**Conclusions**

Chemotherapy for MPM, although still far from ideal, is starting to have a clinical impact. The recent phase III trials of cisplatin with an antifolate (either pemetrexed or raltitrexed) have demonstrated improved survival for those patients treated with an antifolate and cisplatin when compared with single-agent cisplatin. There were also improvements seen in disease-related symptoms. The combination of gemcitabine with cisplatin may also produce clinical benefit in a proportion of patients. Weekly vinorelbine offers useful palliation with low toxicity—especially in less fit individuals. Biological agents, vaccines and immunotoxins, are also being tested in MPM with phase II trials now open to recruitment. Initial results have encouraged optimism for the development of effective therapies.

**References**


