

Systemic Treatments for Mesothelioma: Standard and Novel

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Opinion statement

Systemic therapy is the only treatment option for the majority of mesothelioma patients, for whom age, co-morbid medical illnesses, non-epithelial histology, and locally advanced disease often preclude surgery. For many years, chemotherapy had a minimal impact on the natural history of this cancer, engendering considerable nihilism. Countless drugs were evaluated, most of which achieved response rates below 20% and median survival of <1 year. Several factors have hampered the evaluation of systemic regimens in patients with mesothelioma. The disease is uncommon, affecting only about 2500 Americans annually. Thus, most clinical trials are small, and randomized studies are challenging to accrue. There is significant heterogeneity within the patient populations of these small trials, for several reasons. Since all of the staging systems for mesothelioma are surgically based, it is almost impossible to accurately determine the stage of a patient who has not been resected. Patients with very early stage disease may be lumped together with far more advanced patients in the same study. The disease itself is heterogenous, with many different prognostic factors, most notably three pathologic subtypes—epithelial, sarcomatoid, and biphasic—that have different natural histories, and varying responses to treatment. Finally, response assessment is problematic, since pleural-based lesions are difficult to measure accurately and reproducibly. Assessment criteria often vary between trials, making some cross-trial comparisons difficult to interpret. Despite these limitations, in recent years, there has been a surge of optimism regarding systemic treatment of this disease. Several cytotoxic agents have been shown to generate reproducible responses, improve quality of life, or prolong survival in mesothelioma. Drugs with single-agent activity include pemetrexed, raltitrexed, vinorelbine, and vinflunine. The addition of cisplatin to pemetrexed or raltitrexed to cisplatin prolongs survival. The addition of cisplatin to pemetrexed, raltitrexed, gemcitabine, irinotecan, or vinorelbine improves response rate. The combination of pemetrexed plus cisplatin is considered the benchmark front-line regimen for this disease, based on a phase III trial in 456 patients that yielded a response rate of 41% and a median survival of 12.1 months. Vitamin supplementation with folic acid is essential to decrease toxicity, though recent data suggests that there may be an optimum dose of folic acid that should be administered; higher doses may diminish the effectiveness of pemetrexed. There are also several unresolved questions about the duration and timing of treatment with pemetrexed that are the subject of planned clinical trials. It is essential to recognize

that the improvements observed with the pemetrexed/cisplatin combination, though real, are still modest. Other active drugs or drug combinations may be more appropriate for specific individuals, and further research is still needed to improve upon these results. Since the majority of mesotheliomas in the United States occur in the elderly, non-cisplatin-containing pemetrexed combinations may be more appropriate for some patients. Now that effective agents have been developed for initial treatment, several classical cytotoxic drugs and many novel agents are being evaluated in the second-line setting. These include drugs targeted against the epidermal growth factor, platelet-derived growth factor, vascular endothelial growth factor, src kinase, histone deacetylase, the proteasome, and mesothelin. Given the progress made in recent years, there is reason to believe that more effective treatments will continue to be developed.

Introduction

It was exactly 20 years ago that the *Journal of Clinical Oncology* published an article entitled “Malignant mesothelioma, a disease unaffected by current therapeutic maneuvers” [1]. That title aptly sums up the profound sense of nihilism toward treatment for mesothelioma that existed for many years. At that time, chemotherapy truly had a minimal impact on the natural history of this cancer. Countless drugs were evaluated. Given the rarity of mesothelioma, most trials were small, assessment criteria varied, and few agents demonstrated meaningful activity.

Response rates were all under 20% and patients rarely survived more than a year [2].

We have made a great deal of progress against this disease in the ensuing years. New chemotherapy drugs have now been shown to improve survival and quality of life for patients with mesothelioma. This review discusses the current treatment options for mesothelioma, focusing on the most recent studies, as well as on many of the novel agents undergoing assessment in clinical trials.

Cytotoxic chemotherapy before pemetrexed

- The anthracyclines were once considered the “gold-standard” drugs for mesothelioma. Before computed tomography was routinely used, response rates of up to 44% were reported for doxorubicin [2, 3]. However, in the largest retrospective series, the Eastern Cooperative Oncology Group documented a response rate of only 14% in 51 patients [4]. The data are similar for epirubicin [3]. Several liposomal formulations and cardiac protectants have been evaluated to decrease anthracycline-induced cardiac toxicity, but these are even less effective [3, 5, 6].
- Three recent trials have combined epirubicin with either cisplatin or gemcitabine. The European Lung Cancer Working Party (ELCWP) observed a 19% response rate and a median survival of 13.3 months in a phase II trial of epirubicin and cisplatin in 69 patients [7]. The North Central Cancer Treatment Group evaluated 2 dose levels of the combination of epirubicin and gemcitabine and reported response rates of 13% and 7%, respectively, for the high-dose and low-dose regimens. Moderately severe toxicity was observed in both treatment groups [8]. Similarly, Italian researchers reported a 14% response rate and a median survival of 55 weeks for epirubicin/gemcitabine in a 26-patient study [9]. None of these combinations are significantly better than the more recent gemcitabine- or antifolate-based regimens, thus, none are being pursued further.
- A meta-analysis of clinical trials from 1965 to 2001 determined that cisplatin was the most active single agent in mesothelioma [10•]. Carboplatin has similar activity [10•]. Oxaliplatin has been studied in combination with raltitrexed, vinorelbine, and gemcitabine, but has

not been evaluated as a single agent in this disease [3]. The platinum analog ZD0473 demonstrated no activity in a phase II trial in 41 previously treated mesothelioma patients [11].

- Although paclitaxel, docetaxel, and irinotecan inhibit mesothelioma growth in preclinical models, these drugs have no single-agent activity in mesothelioma patients [2, 3, 12]. Phase II studies of irinotecan plus cisplatin with or without mitomycin C suggest that irinotecan may have activity in combination with cisplatin [3, 13].

The antifolates

- The antifolates are the most active class of cytotoxic drugs for mesothelioma. In a 60-patient trial, high-dose methotrexate yielded a 37% response rate and a median survival of 11 months [14]. The Cancer and Leukemia Group B (CALGB) reported a response rate of 25% and significant toxicity in a phase II trial of edatrexate; both response and toxicity were decreased by the addition of leucovorin [15]. More recently, the novel antifolate pralatrexate demonstrated activity in preclinical models, but not in a phase II trial in mesothelioma patients [16].
- The only FDA-approved agent for mesothelioma is pemetrexed, an antifolate which principally targets thymidylate synthase, as well as dihydrofolate reductase and glycinamide ribonucleotide formyltransferase. Pemetrexed may be more active in mesothelioma than in other cancers because of a high capacity cell membrane transporter in mesothelioma which is highly specific for pemetrexed [17].
- The activity of single-agent pemetrexed is similar to many other drugs in this disease. A 64-patient phase II trial of pemetrexed demonstrated a partial response rate of 14%, a median time to progression of 4.7 months, and a median overall survival of 10.7 months [18]. Pemetrexed was approved by the Food and Drug Administration (FDA) based on a 456 patient, single-blind, placebo-controlled, phase III study. Patients were randomized to pemetrexed, 500 mg/m² every 21 days and cisplatin 75 mg/m², or placebo and cisplatin [19••]. The response rate for the combination was significantly greater than for single-agent cisplatin (41% vs 17%; $P < 0.001$). Pemetrexed/cisplatin-treated patients had a median survival of 12.1 months, compared with 9.3 months for patients treated with cisplatin alone ($P = 0.020$). Time to progression was also superior (5.7 vs 3.9 months, $P = 0.001$). In addition, treatment with this combination resulted in a significant improvement in pulmonary function, quality of life, and symptoms such as pain and dyspnea.
- After the first 117 patients enrolled in this study, all patients were supplemented with dietary doses of folate and vitamin B₁₂. Vitamin supplementation improved response rates and survival in both treatment arms, and reduced the incidence of serious toxicity. In preclinical models, there is a very significant decrease in pemetrexed activity as the extracellular folate level increases above the physiologic range. This suggests that it may be appropriate to limit folate supplementation to no more than 400 µg, the amount found in a multivitamin, rather than the 1000 µg that is more frequently prescribed [20•].
- In the United States, mesothelioma is a disease of the older patient, with a median age of onset of 74 years [21]. Since elderly mesothelioma patients with co-morbid illnesses may not be able to tolerate cisplatin, the better-tolerated carboplatin is frequently substituted; the two regimens have comparable activity. A similar time to progression (6.5 months) and overall survival (12.7 months) was observed in a

102-patient phase II trial of pemetrexed plus carboplatin as in the phase III trial of pemetrexed-cisplatin [22]. A 76-patient phase II study reported a time to progression of 8.0 months, a median survival of 14 months, and a response rate of 25% using the same regimen [23]. A retrospective subset analysis of these two trials reported similar outcomes with pemetrexed-carboplatin in elderly patients compared with younger individuals, with the exception of greater hematologic toxicity in the older patients [24].

- There are several unresolved questions regarding timing and duration of pemetrexed treatment. Some epithelial mesothelioma patients may have prolonged stable disease for months or even years without chemotherapy. It is not known whether these patients should be treated at diagnosis, at symptom progression, or at radiographic progression. In a very small pilot study from the Royal Marsden Hospital, there was a trend toward a longer time to symptomatic progression and overall survival in those patients who received chemotherapy at diagnosis rather than at symptom progression [25]; however, these results need to be validated in a larger study with a more active chemotherapy regimen than was employed in that study. We also do not know the optimum length of treatment. Most patients receive between 4 and 8 cycles of pemetrexed with cis- or carboplatin, few can tolerate more. Should they stop treatment at that point, or continue with single-agent pemetrexed? A small, non-randomized Dutch feasibility study of pemetrexed maintenance demonstrated that maintenance is well tolerated, and that responses can occur after six cycles of treatment [26]. The CALGB is currently designing a larger, randomized study to more definitively address this question.
- Pemetrexed is not the only antifolate which has activity in mesothelioma. The European Organization for the Research and Treatment of Cancer and the National Cancer Institute of Canada performed a 250-patient, randomized phase III trial of raltitrexed-cisplatin vs cisplatin. No vitamin supplementation was given. The combination achieved a response rate of 24% and a median survival of 11.2 months, compared with 14% and 8.8 months for cisplatin. The *P* values were of borderline significance, likely because the study was underpowered [27].

Other active cytotoxic agents

- Although gemcitabine has limited single-agent activity in this disease, response rates ranging from 12% to 48% have been reported for the gemcitabine/cisplatin combination [28–30]. These differences in activity likely reflect the heterogeneity in patient selection and inconsistency in response assessment between trials, rather than the slightly different schedules of these regimens. As an example, in the initial study, Byrne and colleagues administered gemcitabine 1000 mg/m² on days 1, 8, and 15, and cisplatin 100 mg/m² on day 1 of a 28-day schedule to 21 patients. They reported a partial response rate of 48%, a median survival of 9.4 months, and symptom improvement in 90% of responding patients [29]. These investigators then employed an identical regimen in a 52-patient multicenter study, and noted a partial response rate of 33% and a median survival of 11.2 months [28].
- Other gemcitabine doublets with activity in mesothelioma include gemcitabine plus carboplatin, which achieved a 26% response rate and a median survival of 15.1 months in a 50-patient trial [28], and gemcitabine plus oxaliplatin, which produced a response rate of 40% and a median survival of 13 months in a 25-patient study [31]. The

- combination of gemcitabine plus pemetrexed is no more active than either agent alone, but has greater toxicity [32].
- Vinorelbine has one of the highest response rates of any single-agent against mesothelioma, and recent phase III data suggest that it may improve survival over best supportive care. A phase II trial of vinorelbine, 30 mg/m² weekly, in 29 patients reported partial responses in 24%, stable disease in 55%, and a median survival of 10.6 months. Quality of life improved in 41% of patients, and pulmonary symptoms were better in 48% [33]. In a 63-patient trial in the second-line setting, a response rate of 16% and a median survival of 9.6 months were achieved [34]. The combination of vinorelbine with cisplatin yielded a response rate of 29.6% and a median survival of 16.8 months [35].
 - The phase III MS01 trial, from the Medical Research Council and British Thoracic Society, randomized 409 newly diagnosed mesothelioma patients to active symptom control (ASC) alone or with chemotherapy (vinorelbine or mitomycin–vinblastine–cisplatin, MVP). Pooled survival data for the two chemotherapy arms achieved borderline significance in favor of chemotherapy (7.6 vs 8.5 months, $P = 0.32$) compared with ASC. When analyzed by the type of chemotherapy given, ASC and MVP resulted in similar survival (7.6 and 7.8 months, respectively), while the patients who received vinorelbine lived a median of 9.4 months (HR 0.81, $P = 0.11$). Although the study was not powered to detect a difference between chemotherapy arms, one may infer that the addition of inactive chemotherapy (MVP) does not improve survival or quality of life in mesothelioma patients, while the addition of an active drug, such as vinorelbine, may do so [36••].
 - Vinorelbine is not the only vinca alkaloid which has activity in mesothelioma. The novel vinca alkaloid, vinflunine, achieved a response rate of 13.8% and a median survival of 10.8 months [37]. Despite this activity, the drug is not being developed further for mesothelioma.

Novel agents

- Given the relative rarity of mesothelioma, a surprising number of novel agents have been evaluated, including drugs targeted against the epidermal growth factor, platelet derived growth factor, vascular endothelial growth factor, src kinase, histone deacetylase, the proteasome, and mesothelin.
- Despite preclinical data that suggested activity, the initial studies of targeted agents were underwhelming. Although EGFR is highly over-expressed in mesothelioma, and although the EGFR tyrosine kinase inhibitor gefitinib inhibits mesothelioma *in vitro*, minimal activity was observed in two phase II trials of gefitinib and in one trial of erlotinib [38–40]. This may be explained, in part, by the rarity of EGFR mutations in mesothelioma [41]. Similarly, preclinical data suggested a key role for platelet-derived growth factor (PDGF) in mesothelioma, yet imatinib, a selective inhibitor of the PDGF receptor tyrosine kinase, failed to achieve any responses in 4 phase II trials [42].
- Vascular endothelial growth factor signaling may have an important role in the biology of mesothelioma. High serum VEGF, a negative prognostic factor in this disease, is inversely correlated with survival. Phase II studies of SU5416, vatalanib, thalidomide, and sorafenib have demonstrated only modest single agent activity, comparable to

other single agents in this disease [42]. Vatalanib, an inhibitor of PDGFR- β and all VEGFR tyrosine kinases, yielded an 11% response rate, a 66% rate of stable disease, and a 10-month median survival in a phase II CALGB trial [43]. Stable disease for longer than 6 months was achieved in 27.5% of the 40 patients in a phase II Dutch study of thalidomide [42]. On the basis of these data, the phase III NVALT 5 trial evaluates maintenance thalidomide after the completion of pemetrexed-based chemotherapy. The CALGB studied sorafenib, an inhibitor of VEGFR2, PDGFR- β , and raf kinase, in both chemo-naïve and previously treated patients. As a likely result of patient selection, median survival in the chemo-naïve patients was 5.2 months, compared with 14.3 months for the patients who were previously treated [44]. An ongoing study of sunitinib in previously treated patients showed a 15% response rate by conventional CT scan, and a 30% response rate by FDG-PET [45].

- The University of Chicago performed a double-blind, placebo-controlled randomized phase II trial in 108 patients to evaluate the addition of the anti-VEGF monoclonal antibody bevacizumab to gemcitabine plus cisplatin [46]. Progression-free survival, the primary endpoint, was 6.9 months for the bevacizumab arm and 6.0 months for placebo (HR 0.93, $P = 0.88$). Median overall survival, for bevacizumab and placebo, respectively, was 15.6 and 14.7 months ($P = 0.91$). Higher baseline plasma VEGF levels correlated with shorter progression-free survival ($P = 0.02$) and overall survival ($P = 0.0066$). Bevacizumab-treated patients with low baseline VEGF levels had a longer overall survival. Several studies of bevacizumab in combination with pemetrexed and platinum are ongoing.
- Src is very frequently expressed and activated in mesothelioma. Src kinase activity is associated with advanced stage in mesothelioma and may contribute to invasiveness and metastatic spread. Dasatinib, a potent inhibitor of src family kinases, inhibits migration and invasion of mesothelioma in preclinical models [47]. The CALGB is currently testing dasatinib in previously treated patients.
- Suberoylanilide hydroxamic acid (SAHA), an oral inhibitor of class I and II histone deacetylases, is a potent inhibitor of mesothelioma growth *in vitro*. It is interesting that SAHA represses the gene for thymidylate synthase, the principal target of pemetrexed. In a phase I trial of SAHA, there were two partial responses in the 13 mesothelioma patients enrolled [48]. All patients with at least stable disease had a decrease in dyspnea or pain. These data formed the basis of the ongoing double-blind, placebo-controlled, randomized phase III international trial in 660 previously treated patients. The primary endpoint is overall survival.
- In preclinical mesothelioma models, the proteasome inhibitor bortezomib inhibits constitutive activation of NF κ B and enhances the cytotoxicity of cisplatin and pemetrexed [49, 50]. Bortezomib, both as a single agent and in combination with cisplatin, is being evaluated in two European mesothelioma trials.
- Over 90% of mesotheliomas express mesothelin, a cell surface glycoprotein found on normal mesothelial cells of the pleura, peritoneum, and pericardium. Several agents with activity in preclinical models are being developed to target mesothelin: a recombinant immunotoxin, (SS1P), a humanized monoclonal antibody (MORAb-009), and an attenuated listeria vector that encodes human mesothelin (CRS-207). SS1P and Morab-009 have completed phase I evaluation. Preclinical models have demonstrated significant synergy of

these agents with cytotoxic chemotherapy, and trials that combine these drugs with pemetrexed and cisplatin are in development [51•–54].

- In conclusion, it is clear that mesothelioma is no longer a disease that inspires nihilism. Chemotherapy improves survival, response, and quality of life in mesothelioma patients. Many novel agents are being investigated, and further progress is eagerly awaited.

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