Newer Issues in Mesothelioma Chemotherapy

Nicholas Vogelzang, MD, and Harvey I. Pass, MD†*

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During the last 20 years, a multitude of cytotoxic drugs have been tested in malignant pleural mesothelioma (MPM), both as single agents and within combination regimens. Of the single-agent drugs, the most commonly effective drugs are cisplatin, methotrexate, and trimetrexate. The antimetabolites, particularly anti-folates, have the highest response rates, whereas platinum compounds and anthracyclines have a slightly lower response rate.[1] From these earlier small phase II trials enrolling a limited number of poorly staged patients, it became clear that there was a limited advantage to using combination chemotherapy compared with single agents for MPM. More recently, however, the combination of an antimetabolite and a platinum derivative has emerged as the standard of treatment for patients with MPM,[2] although, once again, the use of doublets of cytotoxic drugs was mainly supported by the results of phase II studies. Among the most commonly used doublets, alimta and cisplatinum,[2] cisplatin (or carboplatin) and gemcitabine,[3,4] or raltitrexed and oxaliplatin[5,6] have emerged as the most promising in a first-line setting.

PROGNOSTIC FACTORS AND RESPONSE CRITERIA

Parallel with these studies, novel methods for the measurement of response in MPM to chemotherapy have been developed, and poor-risk prognostic categories have been further stratified for therapy of the disease. Applying Response Evaluation Criteria in Solid Tumors (RECIST) criteria[7] for defining radiologic response of solid tumors to MPM proved difficult and required modification. The new modified RECIST criteria for the assessment of response in MPM[8] measure the tumor thickness perpendicular to the chest wall or mediastinum in up to three involved areas of pleural rind. Each rind can be measured at up to three separate points provided that at least one measurement is greater than 1.5 cm. Pleural thicknesses should be measured at the same position, at the same level, and by the same observer at reassessment. The modified RECIST criteria have been used in the major trials of chemotherapy of MPM since their development, including the phase III randomized trial.

Concomitant with advances in imaging assessment, there has been a realization that certain individuals with MPM do poorly with therapy, and the search for prognostic factors that can aid in stratifying such groups has matured. The Cancer and Leukemia Group B[9] has reported that the key prognostic factors in MPM include performance status, age, hemoglobin, white blood cell count, chest pain, and weight loss, and that these may be useful in predicting outcomes for chemotherapy-treated patients. As performance status, age, and white blood cell count increase, survival decreases. Prospective validation of these prognostic groupings and, in particular, the worst prognostic CALGB cohorts has been reported.[10]

THE INFLUENCE OF PEMETREXED

The standard therapy for MPM began to change in 1999 after a key publication from a phase I study showing that the combination of pemetrexed plus cisplatin had clinical activity in patients with various solid tumors, including confirmed partial responses in five of the 11 patients with MPM.[11] Pemetrexed is a novel multi-targeted anitfolate that inhibits glycinamide ribonucleotide formyl transferase and leads to purine depletion and also inhibits dihydrofolate reductase (similar to methotrexate) and thymidylate synthase, causing pyrimidine depletion.[12] The combination of purine and pyrimidine depletion by a single drug is unique among antineoplastic agents. The promising phase I clinical data of pemetrexed and cisplatin led to the design of a second phase I study in which carboplatin was combined with pemetrexed in patients with MPM. This combination regimen resulted in an overall response rate of 32%, and 70% of the patients noted an improvement in symptoms.[13] Single-agent pemetrexed was associated with the best survival time (10.7 months) reported to that date and with a moderate response rate of 14%.[14] While these trials were being conducted, it became clear that drug-related death was associated with severe gastrointestinal toxicity and severe neutropenia. Investigation of the phenomenon revealed that an increased homocysteine level at baseline, along with an increased methylmalonic acid level, was highly correlated with severe toxicity, suggesting that they could be relatively folic acid- and/or vitamin B12-deficient and, thus, also at increased risk of severe toxicity.[15] Dietary supplementation with low-dose folic acid (350 to 1000 μg) and vitamin B12 (1000 μg) intramuscular injections was shown to markedly improve the tolerability of pemetrexed while maintaining clinical activity.

*Department of Medical Oncology, Nevada Cancer Institute, Las Vegas, Nevada; †Department of Cardiothoracic Surgery, Division of Thoracic Surgery, New York University School Medicine, New York, New York
Address correspondence to: Nicholas Vogelzang, MD, Nevada Cancer Institute, One Breakthrough Way, 10441 West Twain Avenue, Las Vegas, NV 89135. E-mail: Harvey.pass@med.nyu.edu

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THE PHASE III TRIAL

Based on the encouraging results of phase I trials with pemetrexed and cisplatin among patients with MPM, a large, randomized, single-blind phase III study was conducted to compare the combination of pemetrexed with cisplatin versus cisplatin alone in patients with MPM.[2] The trial randomized 456 eligible patients to pemetrexed 500 mg/m^2 IV bolus over 10 minutes plus cisplatin 75 mg/m^2 administered every 3 weeks (n = 226) or to single-agent cisplatin 75 mg/m^2 plus saline (to preserve blinding) administered every 3 weeks (n = 222). A statistically significant longer median survival time was observed in all patients receiving the combination therapy versus those receiving cisplatin alone (12.1 versus 9.3 months) (hazard ratio [HR] = 0.77; P = 0.020). One-year survival rates were also higher in the pemetrexed/cisplatin group (50.3 versus 38.0%). Median time to progressive disease was significantly longer for patients in the pemetrexed/cisplatin arm compared with those in the cisplatin-only arm (5.7 versus 3.9 months) (HR = 0.68, P = 0.001). Tumor response rates (as measured by an average 30% reduction in the thickness of the pleural rind measured at up to nine points on the computed tomographic scan) were 41.3% in the combination arm versus 16.7% in the cisplatin-alone arm (Fisher's exact $P < 0.001$). Time to disease progression, pulmonary function, and quality of life also improved in a statistically significant manner among pemetrexed/cisplatin-treated patients.

Serious adverse events were more common with pemetrexed/cisplatin than with cisplatin alone (22.5 versus 7.2%); however, supplementation with folic acid and vitamin B12 resulted in consistent declines in toxicity. In fact, toxicity analysis revealed that pemetrexed plus cisplatin treatment with folic acid and vitamin B12 supplementation provided a superior risk-benefit ratio for patients with MPM without changes in efficacy. Median survival times for patients who received supplementation at any time throughout the median of six cycles of treatment were 13.2 months for patients treated with pemetrexed/cisplatin and 9.4 months for patients treated with cisplatin alone (HR = 0.71, log-rank P = 0.022).

This phase III trial has led to a number of other follow-up trials of the Alimta cisplatin combination. The most notable of these trials is a multicenter phase II trial of induction Alimta and cisplatin followed by extrapleural pneumonectomy and postoperative hemithorax radiotherapy. This trial should be completed in late 2005.

OTHER RECENT PHASE III CHEMOTHERAPY TRIALS FOR MPM

A phase III trial with raltitrexed, another thymidine synthase inhibitor, was conducted in combination with cisplatin and compared with cisplatin alone in patients with malignant pleural mesothelioma.[6] Two hundred fifty patients were randomized, and among the 213 patients with measurable disease, the response rate was 13.6% for cisplatin alone versus 23.6% for the combination (P = 0.056. No difference in quality of life was observed. Median overall and 1-year survival favored the combination and were 8.8 months (95% CI, 7.8–10.8) versus 11.4 months (95% CI, 10.1–15) and 40% versus 46%, respectively (P = 0.048).

NEW AGENTS FOR THERAPY OF MESOTHELIOMA

Ranpirnase is an antineoplastic ribonuclease that has antitumor activity in mesothelioma.[16] In a multicenter trial of ranpirnase among 105 patients, four of the 81 patients with evaluable disease had a PR, two had a minor response, and 35 had stabilization of previously progressive disease. For the entire group, the median survival duration was 6 months, and the 1- and 2-year survival rates were 34% and 22%, respectively.[17] This actually compares favorably to the CALGB data for the 1- and 2-year survival rates in "good risk" groups 1 to 4 (27% and 12%, respectively). Ranpirnase is presently being tested in a phase III trial in MPM comparing doxorubicin plus ranpirnase versus doxorubicin alone, and the study accrual goal is 240 patients.

The rationale for inhibition of angiogenic mechanisms in MPM is quite strong because vascular endothelial growth factor, vascular endothelial growth factor C, and their receptors are overexpressed in MPM tissue, cell lines, and pleural effusions, as well as in some nonmalignant mesothelial specimens and effusions.[18] At least three angiogenesis inhibitors, SU5416 (a tyrosine kinase activity of the vascular endothelial growth factor receptor flk-1), bevacizumab (Avastin, Genentech, South San Francisco, CA), and thalidomide, have been or are in clinical trials for the treatment of MPM. SU5416 has been abandoned for the treatment of MPM. Bevacizumab, a recombinant human anti-monoclonal antibody that blocks the binding of vascular endothelial growth factor to its receptors, is being evaluated in a double-blind, placebo-controlled, randomized phase II trial.[19] This trial includes patients with both pleural and peritoneal mesothelioma and compares cisplatin/gemcitabine with or without bevacizumab chemotherapy and should be presented at the ASCO conference in 2006.

Other targeted agents, including epidermal growth factor receptor pathway inhibitors (erlotonib), platelet-derived growth factor receptor pathway (gleevec), and proteasome/ubiquitin pathway (bortezomib), are presently in trials or preparing to be tested for the treatment of MPM.

CONCLUSION

There are new agents with improved efficacy for cytotoxic therapy for malignant mesothelioma. Combinations of these agents are associated now with very tolerable toxicity profiles. Future studies either combining cytotoxics with targeted agents or using targeted agents alone after chemotherapy may further enhance progression-free and overall survival in these patients.

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