Commentary (Vogelzang/Manno): Update on Malignant Mesothelioma

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In their historical review of the topic of malignant mesothelioma, Drs. Antman, Hassan, Eisner, and colleagues point out that the natural history of malignant pleural mesothelioma has not changed "over the past 2 decades." We disagree and suggest that it was altered with the discovery that the combination of pemetrexed (Alimta) and cisplatin is active in this setting.[1] Subsequently, the largest phase III trial ever conducted in pleural mesothelioma showed that median survival improved by nearly 4 months for pemetrexed/cisplatin recipients, compared to treatment with cisplatin alone (13 vs 9 months, P < .001). Based on these data, the US Food and Drug Administration approved pemetrexed, cisplatin, and supplementation with vitamin B12 and folic acid for the treatment of pleural mesothelioma, and this regimen is now the standard of care.[2]

**Other Chemotherapy Doublets**
A somewhat confirmatory phase III trial was reported in 2004 by the European Organization for Research and Treatment of Cancer (EORTC), comparing cisplatin plus raltitrexed, a thymidilate synthase inhibitor (available only in Europe) to cisplatin alone. Although this trial showed a trend in favor of survival for the doublet, it did not reach statistical significance.[3] Importantly, the survival in the single-agent cisplatin control arms of the two studies were identical (9 months) and consistent with multiple other phase II studies. Other randomized trials continue to be conducted in this uncommon disease. Most recently, at the 2005 meeting of the American Society of Clinical Oncology (ASCO), Kindler et al reported on the randomized phase II trial of gemcitabine (Gemzar) and cisplatin, with or without bevacizumab (Avastin).[4] That trial demonstrated a median survival of 16 months (for the composite group; individual arms were not reported). These three trials together confirm that doublet chemotherapy is substantially superior to single-agent chemotherapy, is the standard of care, and has altered the natural history of mesothelioma. Future trials in chemotherapy-naive patients will require large phase II trials (probably with novel doublet or triplet regimens) showing median survivals that clearly exceed the current standard of 13 to 16 months. How best to conduct such next-generation trials will be the subject of considerable discussion among pharmaceutical firms, cooperative groups, and mesothelioma experts. Given the documented activity of doublet cisplatin-based chemotherapy, we believe that the next pressing clinical trial question to answer is the role of adjuvant or neoadjuvant chemotherapy in the treatment of mesothelioma. The vast majority of patients with malignant pleural mesothelioma die of their disease even with aggressive surgical therapy. The 10% to 20% of patients cured with extrapleural pneumonectomy are generally those with T1/T2, node-negative disease and epithelial histology.

**Extrapleural Pneumonectomy**
The role of extrapleural pneumonectomy in the management of malignant pleural mesothelioma has recently been the subject of a systematic literature review and summary of evidence.[5] Maziak et al reviewed the published literature on this subject from 1995 to 2004 and noted that there were no phase II or III trials comparing pleurectomy with extrapleural pneumonectomy. There were 4 temporally comparative studies, 7 noncomparative prospective studies, and 16 retrospective case series. The group concluded that "the role of surgery in the management of malignant pleural mesothelioma cannot be precisely defined, as the lack of randomized controlled clinical trials makes it impossible to determine whether the use of [extrapleural pneumonectomy] or [pleurectomy] improves survival or effectively palliates the symptoms of the disease." Recent prospective data
from Weder et al,[6] Sugarbaker et al,[7] and Yajnik et al[8] suggest that extrapleural pneumonectomy in combination with chemotherapy and postoperative radiation therapy in carefully selected individuals leads to a 10% to 20% no evidence of disease (NED) rate at 5 years and a median survival of fully resected patients of approximately 24 months. Surgical morbidity and mortality has substantially decreased over the past decade. **Staging Considerations**

Unfortunately, most patients have either clinical T3 or T4 disease at the time of diagnosis. T3 disease is defined as involvement of all pleural surfaces plus the endothoracic fascia, mediastinal fat, or a solitary resectable focus in the chest wall or pericardium. T4 disease is defined as involvement of all pleural surfaces plus diffuse multifocal chest wall invasion, transdiaphragmatic spread, contralateral pleural involvement, or involvement of the myocardium, spine, or mediastinal structures. Clearly, some of these categories of T4 disease are in fact M1 disease, thus calling into question the validity of the staging system. Furthermore, we have seen the progressive refinement of noninvasive staging methods. Computed tomography (CT) and magnetic resonance imaging (MRI) show improved detection of disease involving the diaphragm, endo thoracic fascia, chest wall invasion, and transdiaphragmatic spread. Positron-emission tomography (PET) scanning and particularly PET/CT scanning may be superior to both CT and MRI for defining mediastinal lymph node involvement and for defining occult extrathoracic disease.[9] Thus, these T3/T4 patients should be readily identified preoperatively and could be entered into trials of adjuvant or neoadjuvant chemotherapy. **Adjuvant Chemotherapy**

Since the role of chemotherapy has been well established in colon cancer, breast cancer, and non-small-cell lung cancer, we believe there is likely to be a beneficial role of adjuvant chemotherapy in malignant pleural mesothelioma; however, the magnitude of the effect is likely to be small. The first report on a potential role of adju vant chemotherapy in mesothelioma was made in 1999 by Sugarbaker et al, who studied 183 patients treated with extrapleural pneumonectomy, the majority of whom also received postoperative chemotherapy.[10] Median survival was 19 months. In 2000, Taverna et al treated 12 extrapleural pneumonectomy patients, of which 10 received postoperative cisplatin and cyclophosphamide. The median survival was 13 months.[11] Pass et al reported on a phase II trial of tetrathiomolybdate after cytoreductive surgery for malignant pleural mesothelioma in 28 patients. He noted a median survival of 14 months for T3/ stage III patients; the median survival for stage I/II patients has not yet been reached. The 2-year survival rate was 69% for stage I/II patients and 14% for stage III patients.[12] These promising data have led the Cancer and Leukemia Group B to develop a trial of adjuvant pemetrexed and cisplatin. **Neoadjuvant Chemotherapy**

An alternative approach is to consider neoadjuvant therapy before surgical resection of mesothelioma. This approach has been explored in four studies, the first by Weder et al, in which 19 patients received preoperative gemcitabine and cisplatin for an objective response rate of 32%. Extrapleural pneumonectomy was successfully completed in 16 patients, and postoperative radiotherapy was given to 13 patients. Although there were no pathologic complete responders, two patients remained NED at the time of the report in 2004.[6] A more recent report by Stahel et al included data on 61 patients again receiving gemcitabine and cisplatin, and again no pathologic complete responses were seen.[13] Extrapleural pneumonectomy was completed successfully in 45 patients, but only 37 were fully resectable. The overall median survival was 18.5 months, and the extrapleural pneumonectomy patients who were completely resectable had a median survival of 26 months. Flores reported on nine patients treated with gemcitabine and cisplatin neoadjuvantly, and no pathologic complete responses were seen.[14] Lastly, Krug et al are prospectively conducting a 77-patient trial of neo-adjuvant pemetrexed and cisplatin followed by extrapleural pneumonectomy and hemithoracic radiation therapy. They reported the preliminary results in 35 patients at the ASCO 2005 meeting.[15] Of these 35 patients, 18 (51%) were clinical stage III, 14 (40%) were clinical stage II, and only 1 was clinical stage IB. The majority of patients (68%) had epithelial mesothelioma. Among the 25 patients evaluable for response, there were no complete responses but there were 10 partial responses, for a 40% response rate (consistent with that seen in the Vogelzang et al study).[2] Clinical benefit (defined as partial or stable disease) occurred in 96% of patients; only one patient had progressive disease. Extrapleural pneumonectomy was successfully performed in 80% of patients. **Conclusions**

In conclusion, pemetrexed/cisplatin is the new standard of care for patients with unresectable malignant pleural mesothelioma. Its role in peritoneal mesothelioma seems equally promising.[16] It is likely that gemcitabine/ cisplatin is an equally efficacious regimen, but phase III trials of this combination in mesothelioma have not been performed. We have seen increasing interest in using adjuvant and neoadjuvant therapy for pleural malignant mesothelioma, as evidenced by a rapid
escalation in the number of phase II reports. Whether therapy should be given neoadjuvantly or adjuvantly remains unclear, but preliminary data show no pathologic complete responses with neoadjuvant therapy. Phase III trials will be very difficult to complete due to the low number of patients available, the large number of patients needed, and continued investigator biases. Meanwhile, carefully designed phase II trials of adjuvant and neoadjuvant chemotherapy with translational end points are warranted.

Disclosures:
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References: