Treatment of Malignant Mesothelioma With Methotrexate and Vinblastine, With or Without Platinum Chemotherapy*

Karen J. Hunt, MD; Gary Longton, MS; Margaret A. Williams, BA; and Robert B. Livingston, MD

**Study objective:** To determine the efficacy of methotrexate, vinblastine, and platinum chemotherapy in patients with diffuse unresectable malignant mesothelioma.

**Design:** Patients with histologically confirmed malignant mesothelioma were evaluated for treatment with methotrexate, vinblastine, and cisplatin chemotherapy. If the patient had preexisting hearing loss or neuropathy, or was significantly disabled (e.g., spending greater than half of the day in bed or a chair), cisplatin therapy was withheld.

**Setting:** All patients were initially evaluated at the University of Washington Medical Center and received chemotherapy at the University of Washington or in the community.

**Interventions:** Between 1990 and 1994, 17 patients received this chemotherapy. Ten patients received cisplatin, 100 mg/m² IV on day 1, methotrexate, 30 mg/m² IV on days 8, 15, and 22, and vinblastine, 3 mg/m² IV on days 8, 15, and 22, in 28-day cycles. One patient had carboplatin substituted for cisplatin due to preexisting hearing loss. Six patients received weekly methotrexate and vinblastine at the same doses without platinum.

**Measurements and results:** Nine of the 17 (53%; 95% confidence interval [CI], 28 to 77%) patients responded, including two complete remissions, two partial remissions, and five regressions. Median time to progression is 8 months. The median survival time for all patients is 14 months. Projected 2-year survival is 35% (95% CI, 12 to 60%).

**Conclusions:** Although the number of the patients in this study is small, the response rate and projected 2-year survival of 35% are better than those typically reported for unresectable malignant mesothelioma. Further investigation is warranted in confirmatory trials.

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**Key words:** carboplatin; chemotherapy; cisplatin; mesothelioma; methotrexate; vinblastine

**Abbreviations:** CI=confidence interval

Unresectable malignant mesothelioma is a uniformly fatal disease for which treatment is largely ineffective. Reported median survival times for patients who have unresectable mesothelioma are in the 6- to 12-month range. Phase 2 chemotherapy regimens tested in this disease have shown little benefit over supportive care alone, with response rates commonly less than 20%.

Since 1990, we have been treating patients with unresectable malignant mesothelioma with a combination of methotrexate and vinblastine, with or without cisplatin. This particular regimen was chosen because this combination had not been tested in mesothelioma (to our knowledge), and because of reports of the efficacy of weekly methotrexate and vinblastine in desmoid tumors and retroperitoneal fibromatosis. We combined these drugs with cisplatin, an agent with response rates in mesothelioma between 13% and 36% when used as a single agent.11-13

**Materials and Methods**

This is a retrospective analysis of patients with malignant mesothelioma seen at the University of Washington Medical Center between 1990 and 1994, and treated with methotrexate and vinblastine, with or without platinum chemotherapy. All had histologically confirmed malignant mesothelioma, and all were deemed to have unresectable disease because of local invasion or poor overall condition. Patients were offered this chemotherapy program providing they had a creatinine concentration within normal limits, a granulocyte count of 1,500/mm³ or more, a bilirubin level of 2 mg/dL or less, a platelet count of more than 100,000/mm³, and a Karnofsky performance status of 50% or greater (i.e., they were at least capable of self-care and were spending no more than 50% of the day in a chair or bed). Cisplatin was not employed in patients who had significant hearing loss, peripheral neuropathy, or borderline performance status.

Patients who were eligible for cisplatin received this drug at 100 mg/m² IV on day 1, with precisplatin and postcisplatin hydration and antiemetics. Patients treated at the University of Washington.
received dexamethasone and ondansetron as the primary antiemetic. They then received methotrexate at a dose of 30 mg/m² IV, and vinblastine at 3 mg/m² IV, on days 8, 15, and 22, in 28-day cycles. For patients with large pleural effusions, the starting dose of methotrexate was 15 mg/m², and was escalated up to 30 mg/m² providing no mucositis or cytopenias occurred. One patient with preexisting hearing loss received carboplatin in substitution for cisplatin at a dose of 235 mg/m². Patients who were not eligible for platinum therapy received methotrexate and vinblastine alone on a weekly basis at the same doses. Doses were modified for hematologic, allergic, and neurologic toxic reactions.

The criteria for response were as follows. Complete response was defined as complete disappearance of all measurable or evaluable lesions without appearance of new lesions, of at least 4 weeks' duration. Partial response was defined as at least a 50% decrease from baseline in the sum of the products of perpendicular diameters of all measurable lesions, without appearance of new lesions, of at least 4 weeks' duration. Regression was defined as a definite decrease from baseline in assessable tumor size for lesions not bidimensionally measurable (not including pleural effusions) agreed on by two independent investigators, without appearance of new lesions for at least 8 weeks. Stable disease was defined as a less than 50% reduction or less than 25% increase from baseline in the sum of the products of the perpendicular diameters of all measurable lesions, or the absence of clear-cut change in assessable tumor size, without appearance of new lesions for at least 8 weeks. Progressive disease was defined as a more than 25% increase from maximal regression in the sum of the products of the perpendicular diameters of all measurable lesions, or a definite increase in assessable tumor size.

Response was assessed by measurements of pulmonary masses or pleural thickening; effusions were not used in assessment of response. Assessment by chest CT and chest radiograph was done at the discretion of the treating physician. Fifteen patients had CT scans repeated in 4- to 16-week intervals (median, every 9 weeks), with chest radiographs done between CT scans in most cases. One patient, who had stable disease on this regimen, was followed up with monthly chest radiographs and every-5-month chest CT scans. The patient with peritoneal mesothelioma was documented to have progressive disease after two cycles of chemotherapy by clinical examination.

Kaplan-Meier curves were used for the display of survival and time to progression. Confidence limits for Kaplan-Meier estimates used Greenwood's formula.

RESULTS

From 1990 until 1994, 19 patients with histologically confirmed malignant mesothelioma were treated with chemotherapy at our institution. Seventeen patients received methotrexate, vinblastine, plus or minus cisplatin or carboplatin as first-line treatment of their unresectable disease. The other two patients received alternative chemotherapy regimens and are not included in this analysis.

Table 1 shows the patient characteristics. Fourteen of the 17 patients were male. The median age was 66 years (range, 45 to 72 years), with only four patients younger than 50 years. Sixteen had pleural mesothelioma, and one had peritoneal mesothelioma. Ten had epithelial histologic features, six mixed, and one sarcomatoid. All had unresectable disease, most commonly due to invasion of the chest wall, ribs, or mediastinum. Two patients had decortication and intrapleural cisplatin as primary therapy, then developed recurrent, inoperable disease that was then treated with this chemotherapy. The remainder of the patients had no prior chemotherapy.

In regards to known unfavorable prognostic factors in mesothelioma,6,8,15,16 seven patients had thrombocytosis, 11 had 6 months or less of symptoms before diagnosis, and 9 patients had chest pain; 1 additional patient, who had peritoneal mesothelioma, had abdominal pain. Weight loss was documented in only nine patients, with a median weight loss of 4.5 kg.

Median follow-up for all patients was 12 months (range, 4.6 to 44 months). The ten patients who were treated with cisplatin, methotrexate, and vinblastine received a median of 5 monthly cycles of chemotherapy (range, 3 to 20+ months). The six patients who received only methotrexate and vinblastine received a median of 5 months (range, 3 to 12 months) of treatment, and the one patient receiving carboplatin, methotrexate, and vinblastine continues to receive therapy after receiving 8 months of treatment.

Response

All patients were evaluable for response. Four patients had bidimensionally measurable disease; of these, two had a partial remission. Of the 13 patients

<table>
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<th>Characteristic</th>
<th>Patients</th>
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<td>Age, yr</td>
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<tr>
<td>Median</td>
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<tr>
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<td>Duration of symptoms</td>
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<td>Yes</td>
<td>9</td>
</tr>
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with evaluable disease, 2 had a complete remission and 5 had regressions. Overall response rate is 9 of 17 patients, or 53% (95% confidence interval [CI], 28 to 77%). Eight of the nine responders received three-drug therapy. The median time to progression (Fig 1) is 8 months (range, 4 to 20 months). Seven patients had stable disease, for a median duration of 5 months (range, 4 to 15 months). The median survival time of all patients is 14 months (Fig 2). Projected 2-year survival is 35% (95% CI, 12 to 60%).

Toxicity

Toxicity of the this regimen was as expected from these chemotherapy agents. There were no treatment-related deaths. One patient had vomiting requiring hospitalization (grade 4 toxicity), and three other patients had six to ten episodes of vomiting in a 24-h period (grade 3 toxicity). Myelosuppression was mild to moderate: three patients developed a neutrophil nadir of between 500 and 900/mm³, and one patient had a platelet count nadir of 49,000/mm³. The myelosuppression lasted 2 weeks and resolved after holding the methotrexate and vinblastine for 1 week, then reducing the doses upon hematologic recovery. Other toxic reactions included one episode of methotrexate-induced pneumonitis and one of methotrexate-induced hepatitis, both of which were reversed by discontinuation of this drug therapy. Six patients developed moderate paresthesias and three developed tinnitus, necessitating discontinuation of cisplatin therapy in two patients and of vinblastine therapy in one.

Discussion

This particular regimen was chosen because of reports of the efficacy of weekly methotrexate and vinblastine in desmoid tumors and retroperitoneal fibromatosis. Although desmoid tumors are histologically distinct from mesothelioma and technically benign, they share a similar pattern of locally aggressive, infiltrating spread. Methotrexate and vinblastine have a reported response rate in desmoid tumors of 72%.9,10 We combined these drugs with cisplatin, an agent with modest activity11-13 in patients who we believed could tolerate the drug.

Although the number of patients in this analysis is small, we are encouraged by the results. The 53% response rate and projected 2-year survival of 35% for these patients with unresectable mesothelioma are better than those typically reported in phase 2 trials of chemotherapy, although we acknowledge that these results could be due to patient selection factors. The 18 to 77% CI for response overlaps with the response rates seen with single-agent cisplatin (13 to 36%). The
of good prognostic factors, since most of our patients were older than 50 years, had chest pain as a predominant symptom, and had a less than 6-month duration of symptoms. Most (ten) of our patients had epithelial mesothelioma, which can have a relatively indolent course. Responses to treatment, however, were seen in patients having either epithelial (six of ten) or mixed (three of six) histologic type; the one patient with sarcomatoid mesothelioma had stable disease. Toxic reactions were moderate overall, as expected from these drugs.

Regression by comparison of serial CT scans was used as a measure of response in this analysis, as has been done in many phase 2 reports of mesothelioma response to treatment. Because mesothelioma typically infiltrates the pleura or peritoneum without producing a bidimensionally measurable mass, assessment can be difficult. We considered our patients to have had a regression if two different investigators agreed that there was a definite decrease in the tumor’s size and no new lesions appeared for 8 weeks. In non-small cell lung cancer, regression carries the same prognostic implications as partial remission.\textsuperscript{17}

Although the small number of patients and the retrospective nature of this study make it difficult to draw valid comparisons of subsets, we observed a differential response rate for patients receiving three-drug therapy compared with those receiving methotrexate and vinblastine alone. Of the 11 patients who received platinum, methotrexate, and vinblastine, 1 had a complete remission, 2 had partial remissions, and 5 had regressions (8 of 11 patients). Of the six receiving methotrexate and vinblastine alone, there was only one responder (a patient who had a complete remission). This differential response rate for the three-drug combination may be due to a synergistic effect among the three drugs or perhaps due to the platinum compound alone. Further investigation of the three-drug regimen is warranted in confirmatory trials.

\textbf{REFERENCES}