Cisplatin, Mitomycin, and Interferon-α2a Combination Chemoimmunotherapy in the Treatment of Diffuse Malignant Pleural Mesothelioma*

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Study objective: **To investigate the therapeutic activity and toxicity of combination chemoimmunotherapy with cisplatin, mitomycin, and interferon (IFN)-α2a, by comparing the responses in a group of patients with diffuse malignant pleural mesothelioma (DMPM) to the responses in a control group of DMPM patients given supportive care alone.**
Design: **Patients with histopathologically confirmed DMPM were evaluated for treatment with chemoimmunotherapy.**
Setting: **After the initial evaluation, all patients received either chemoimmunotherapy or supportive care from the Osmangazi University Medical Faculty, Department of Chest Diseases.**
Patients: **Forty-three patients with DMPM received chemoimmunotherapy until the end of the survey; 19 patients were given supportive therapy alone after refusing chemoimmunotherapy.**
Interventions: **Drugs were administered according to the following schedule: IV cisplatin, 30 mg/m^2 qd on days 1 and 2; IV mitomycin, 8 mg/m^2 on day 1; and subcutaneous IFN-α2a, 4.5 million IU twice weekly. The courses were repeated every 4 weeks.**
Results: **Overall, 232 chemoimmunotherapy cycles were administered. A total of 10 objective responses (ORs) in 43 patients (23%) were assessed, including 2 complete responses (5%), 4 partial responses, and 4 regressions. Seventeen patients had stable disease, and 16 patients had progression. The median survival time was 11.5 months for the 43 patients who received chemoimmunotherapy and 7.0 months for the 19 patients who received supportive therapy alone. The difference in survival times between the chemoimmunotherapy and supportive therapy groups was not significant. However, the median survival time for the patients who had OR was 21.3 months, which is significantly longer than that of the patients who received supportive care alone and that of patients with progressive disease (6 months). The toxicities associated with the treatment schedule of this study were, for the most part, tolerable.**
Conclusions: **The drug combination used in this study is moderately effective and well tolerated in patients with DMPM, especially in those who responded to the treatment.**
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Key words: chemotherapy; cisplatin; interferon-α; mesothelioma; mitomycin; therapy

Abbreviations: CI = confidence interval; CR = complete response; df = degrees of freedom; DMPM = diffuse malignant pleural mesothelioma; IFN = interferon; OR = objective response; PR = partial response

Diffuse malignant pleural mesothelioma (DMPM) is an uncommon but highly lethal neoplasm.[1,2] The incidence of this aggressive tumor is still increasing.[3,4] In most reports,[5,6] the median survival time for patients with this disease is not > 1 year. It is suggested[7,8] that surgery prolongs survivalfor the relatively few patients in whom it is possible to perform a radical procedure. In many phase II studies, the results of most chemotherapeutic schedules have been disappointing. Only a few studies[9,10] claim that chemotherapy has been beneficial whencompared to supportive care alone. To date, however, no regimen has been suggested as a standard therapy for DMPM.[9] Therefore, the role of chemo-

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therapy in the management of DMPM continues to be a subject of investigation.

Recent preclinical studies[11] suggest that interferons (IFNs) may have an effect on mesothelioma cell lines. The results of initial clinical studies[12–14] have demonstrated that the antitumor activity of IFN ranges from 8 to 18% in patients with this condition. Further studies[14–16] have suggested that combining IFNs with cytotoxic drugs has the potential to increase response rates. The combination of mitomycin and cisplatin has been shown to have one of the strongest antitumor activities for treating DMPM,[17] and IFN-α has been shown to augment the activity of this combination in human mesothelioma xenografts.[18] Although there has been great interest in IFN, its role as a single agent or as one of a combination in the management of DMPM is not yet known. We therefore investigated the therapeutic activity and toxicity of combination therapy using cisplatin, mitomycin, and IFN-α2a in a group of patients with DMPM, as compared to a control group who were given supportive care alone.

Materials and Methods

Patients

Seventy-nine patients with histologically proven DMPM were enrolled into this study from January 1991 to December 1996. Fifty-five patients were entered into the treatment program, and 24 patients were given supportive therapy alone. Of the 55 patients receiving chemoimmunotherapy, 43 were considered suitable for determining response to therapy, toxicity, and survival time. The remaining 12 patients were not evaluated for response and toxicity because of inadequate follow-up after one or two treatment courses. Twenty-four of the 79 patients with DMPM were unwilling to undergo any therapy schedule, so they were given supportive therapy alone. Survival times could be determined in 19 of these patients, and this group was used as a control for comparison with the group undergoing chemoimmunotherapy. The characteristics of all patients are shown in Table 1.

The histopathologic examination of biopsy specimens from all patients was performed by faculty members in our pathology department. The last 29 samples were also examined by Dr. Allen R. Gibbs from Llandough Hospital, UK. These samples were treated with hematoxylin-eosin, alcian blue, and mucicarmine histochemical stains. Immunohistologic confirmation of carcinoembryonic antigen and Leu-M1 were obtained in these last 29 samples, and carcinoembryonic antigen, vimentin, and keratin were obtained in the other samples.

The eligibility criteria for all study participants are as follows: (1) hospitalized man or hospitalized nonpregnant woman with "measurable" or "nonmeasurable" disease (as defined in Materials and Methods); (2) no earlier therapy for DMPM (chemotherapy, radiotherapy, intracavitary therapy, or surgery); (3) a Karnofsky performance status of $\geq 50\%$; (4) an adequate serum biochemical profile (bilirubin level < 1.5 times the mean of reference range, creatinine level < 1.5 times the mean of the reference range, and creatinine clearance > 60 mL/min); (5) normal findings on urine analysis; (6) WBC count $> 4 \times 10^3/\mu L$, hemoglobin concentration > 10 g/dL, and platelet count $> 100 \times 10^3/\mu L$; and (7) clinically normal auditory function. The patients were excluded if they had significant cardiopulmonary, cerebrovascular, psychiatric, or renal disease (or a combination of these conditions), or peripheral polyneuropathy. Written or verbal informed consent was obtained from all participants before beginning any treatment.

After the histopathologic diagnosis was made, all patients were classified according to the International Union Against Cancer

Table 1—*Characteristics of Patients With Histologically Proven DMPM*

Characteristics	Chemoimmunotherapy Group	Supportive Therapy Group
Patients	43	19
Mean age, yr (range)	55.4 (26–75)	59.6 (33–90)
Gender		
Male	20	9
Female	23	10
Asbestos exposure, No. (%)	41 (95)	15 (79)
Mean asbestos exposure duration, yr (range)	33.8 (2–66)	26.8 (2–70)
Stage, No. of patients (%)		
I	17 (40)	7 (37)
II	7 (16)	3 (16)
III	15 (35)	7 (37)
IV	4 (9)	2 (10)
Histopathologic subtype, No. of patients (%)		
Epithelial	24 (56)	11 (58)
Mixed	8 (19)	4 (22)
Sarcomatous	6 (14)	2 (10)
Unidentified	5 (11)	2 (10)
Mean Karnofsky performance status, (range)	70 (50–90)	70 (50–90)
Smoking, No. of patients (%)	18 (42)	4 (21)
Mean symptom duration, mo (range)	3.6 (0.5–12)	3.9 (0.3–14)

staging system. The results of thoracic, abdominal, and brain CT scans, bone scans with ^{99}Tc, and other related tests formed the basis for classification.[19,20]

Drug Schedule

The drug schedule included IV cisplatin, 30 mg/m^2 qd on days 1 and 2; IV mitomycin, 8 mg/m^2 on day 1; and subcutaneous recombinant IFN-α2a, 4.5 million IU twice weekly on days 1, 4, 8, 12, 16, 20, 24, and 26. The courses were repeated every 4 weeks. IV cisplatin was administered in 500 mL of normal saline solution over 2 h (with pre- and postcisplatin hydration and antiemetics). To prevent nephrotoxicity, pre- and postcisplatin hydration and diuresis were carried out by administering 1 L of normal dextrose solution over the same 2 h, with furosemide given with each liter of dextrose and 10% mannitol. Emesis was prevented by giving ondansetron, or with metoclopramide and dexamethason in combination. To prevent fever, paracetamol was administered before and after IFN application.

Before each course of treatment, the patients received a complete physical examination, chest radiography, ECG, respiratory function tests, CBC count, serum biochemistry tests, and urine analysis. In addition, the patients were screened for side effects on days 7 and 14 of the course of drug administration. Side effects were graded according to the toxicity scale of the World Health Organization.[21]

Evaluation of Response

Initially, the patients' diseases were classified as either measurable or nonmeasurable, according to the appearance of the lesion on CT scan at the time of diagnosis. Disease with bidimensionally measurable lesions was considered "measurable." When the tumor size was not clearly defined, it was deemed "nonmeasurable."

The response to treatment was determined after the third course of therapy by means of thoracic CT scan, and other scans were used if indicated. The evaluation of the response by the physicians was not blinded.

A complete response (CR) was defined as the complete disappearance of all measurable or nonmeasurable lesions and the absence of signs and symptoms for > 4 weeks without the appearance of new lesions. A partial response (PR; for measurable disease) was defined by a decrease of $> 50\%$ compared to pretreatment measurements in the sum of the products of the perpendicular diameters of all measurable lesions, and no appearance of new lesions over a period of 4 weeks. Regression (for nonmeasurable disease) occurred when there was a definite decrease in tumor size for lesions not bidimensionally measurable (as agreed on by two independent investigators), and no appearance of new lesions over a period > 8 weeks. Pleural effusion alone was not accepted as a measurable or nonmeasurable disease. Stable disease, both measurable and nonmeasurable, was characterized by $< 50\%$ reduction or $< 25\%$ increase (in relation to the tumor size at entry) in the sum of the products of the perpendicular diameters of all measurable lesions over a period > 8 weeks, with no new lesions appearing. For nonmeasurable disease, stable disease had no clear-cut change in nonmeasurable tumor size, with no new lesions appearing over a period > 8 weeks. Progressive disease (for measurable disease) showed an increase in the product of two perpendicular diameters of all measured lesions by $> 25\%$ over the initial tumor size at entry; for nonmeasurable disease, it was defined as a definite increase in tumor size. Patients demonstrating a CR or PR or regression were considered to have had an objective response (OR).

The patients displaying stable disease or an OR were scheduled to receive six chemotherapeutic courses, except when tumor progression, death, or unacceptable toxicity occurred. Furthermore, it was decided that if any patient revealed progressive healing after these 6 courses, chemotherapy would be continued with up to 10 courses. The duration of survival and response were calculated from the time treatment began.

Statistical Analysis

Patient characteristics according to treatment regimen were compared using the Pearson X^2 test for discrete variables. The duration of survival and the median and mean event times (95% confidence interval [CI]) were estimated according to the Kaplan-Meier method. The differences in time distributions between groups were tested for statistical significance using the log-rank test.

Results

Beginning in January 1991, a total of 62 patients (43 treated with chemoimmunotherapy and 19 treated with only supportive care) were monitored until the end of the survey in the first part of 1998. The patient characteristics were not significant for both groups (Table 1).

Response

Overall, 232 cycles were administered to the 43 patients (median, 5.4 cycles; range, 2 to 10 cycles). According to thoracic CT findings, 17 patients had measurable disease and 26 had nonmeasurable disease. Among the 43 patients, assessments were made on 10 ORs (23%; 95% CI, 11 to 36), 2 CRs (5%; 95% CI, 2 to 11), 4 PRs (9%; 95% CI, 1 to 18), and 4 regressions. Seventeen patients (40%) had stable disease and 16 patients (37%) had progression. One of the two CR patients had mixed cell type, stage I disease, and a 54-month survival time. The other CR patient had epithelial cell type, stage I disease, and a 36-month survival time. The four PR patients had the following characteristics: epithelial, sarcomatous, epithelial, and mixed cell type; stage III, II, II, and IV disease; and 28.5, 13, 5, and 11.5 month survival time, respectively. The third patient (epithelial cell type, stage II disease, and 5 month survival time) died from myocardial infarction during PR. The four patients with regression had epithelial cell type; stage IV, I, I, and III disease; and 13, 21.3, 49, and > 70 month survival time, respectively. The fourth patient, with a survival time > 70 months, is living at the time of this writing.

Of the 24 patients with epithelial cell type, 7 patients (29%) had an OR, 11 had stable disease, and 6 had progression. Of the eight patients with mixed cell type, two patients (25%) had an OR, two had stable disease, and four had progression. Of the six patients with sarcomatous cell type, one patient had

an OR, two had stable disease, and three had progression. The response rates were determined according to the patient's stage of disease. Among the 17 patients with stage I disease, 4 patients (24%) had an OR, 8 had stable disease, and 5 had progression. In the seven stage II patients, two patients (29%) had an OR, three had stable disease, and two had progression. In the 15 patients with stage III disease, 2 patients (13%) had an OR, 5 had stable disease, and 8 had progression. Finally, in the four patients with stage IV disease, two patients had an OR, one had stable disease, and one had progression.

Survival Time and Time of Progression

Of the 43 patients who received chemoimmunotherapy, the median survival time was 11.5 ± 1.3 months (range, 1.5 to > 70 months), and the mean survival time was 15.5 ± 2.2 months (95% CI, 11.1 to 19.8). The median time of progression was 8.0 ± 0.5 months (95% CI, 7.1 to 8.9). The median survival time of the 19 patients who received supportive therapy alone was 7.0 months (range, 1 to > 24 months). There was not a significant difference in survival times between chemoimmunotherapy or supportive therapy groups (log-rank = 0.52; degrees of freedom [df] = 1; $p = 0.469$). The median survival times of patients according to their response status, cell type, and stage of disease are shown in Table 2.

The median survival time of the CR patients was 36.0 ± 9.0 months (95% CI, 27.4 to 62.6). For PR patients, the median survival time was 11.5 ± 3.9 months (95% CI, 3.9 to 19.1); for regression patients, median survival time was 21.3 ± 18.0 months (95% CI, 0.0 to 56.6); and for patients with stable disease, median survival time was 16.0 ± 0.8 months (95% CI, 14.4 to 17.6). The median survival time for the 27 patients with an OR or stable disease was 16.0 ± 0.9 months (95% CI, 14.3 to 18.0). The median survival time of the patients with a PR may have been affected by the early death of the patient who died of myocardial infarction (see Response section). Objective responders had a significantly longer median survival time than patients with progressive disease (log-rank = 18.96; df = 1; $p < 0.001$) and the patients who received supportive care alone (log-rank = 5.36; df = 1; $p = 0.0206$). When we compared the median survival time of 27 patients with an OR or stable disease to that of the patients with progressive disease, we again estimated a significant difference between them (log-rank = 48.91; df = 1; $p < 0.001$), but there was no statistically significant difference between the survival times of those 27 patients and the survival times of the patients who received supportive care alone (log-rank = 3.29; df = 1; $p = 0.0698$).

Kaplan-Meier survival curves for patients who received and did not receive chemotherapy are shown in Figure 1.

For patients receiving chemotherapy, the 1-year survival rate was 49% (21 patients), the 2-year rate was 12% (5 patients), and the 5-year rate was 2% (1 patient). For the control group, the 1-year survival rate was 39% (seven patients). The difference in the 1-year survival rate between the chemotherapy and control groups was not significant.

Table 2—*Relationship of Survival Time to Response, Stage, and Cell Type for Patients With DMPM

Variables	Survival Time, Mo	95% CI
Chemotherapy group	11.5 ± 1.3	8.9–14.1
Objective response	21.3 ± 12.3	0.00–45.3
Progression	6.0 ± 0.5	5.0–7.0
Stage I	12.0 ± 2.3	7.6–16.4
Stage II	13.0 ± 8.8	0.0–30.1
Stage III	7.0 ± 1.9	3.2–10.8
Stage IV	11.3 ± 3.0	5.4–17.2
Epithelial	14.3 ± 2.9	8.7–19.9
Mixed	6.0 ± 3.1	0.0–12.1
Sarcomatous	7.0 ± 6.4	0.0–19.6
Stage I and epithelial	16.0 ± 2.5	11.0–20.9
Control group	7.0 ± 2.1	2.9–11.1

*Data are expressed as median ± SD or as specified.

Toxicity

All 43 patients who received chemotherapy could be evaluated for toxicity. The toxicity of the drug combination was mild and well tolerated. There were no treatment-related deaths. All findings related to toxic side effects are shown in Table 3.

Myelosuppression was mild to moderate, occurring mostly after the fourth or fifth cycle. Most patients suffered from prolonged and delayed nausea and vomiting that affected the quality of their daily life. Almost all of the patients with these symptoms responded well to orally administered ondansetron. In addition to nausea and vomiting, toxic reactions included prolonged constipation (7 patients), anorexia (6 patients), and flu-like symptoms (12 patients). Life-threatening toxicity took the form of pulmonary edema in one patient and encephalopathy in another patient; the edema occurred after the third chemotherapy course, and the encephalopathy occurred after the second course. Both patients survived after adequate treatment and support. We were not able to determine why these conditions developed. A mitomycin-induced pneumonitis occurred in a 69-year-old woman after the fifth course of her therapy. The condition was reversed by

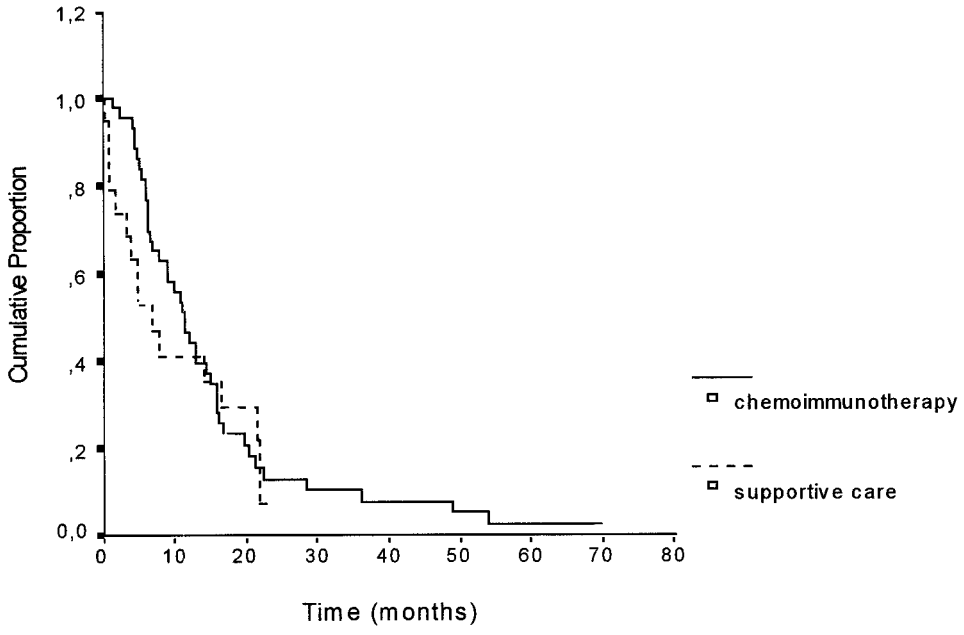

FIGURE 1. Kaplan-Meier survival curves for DMPM patients receiving chemoimmunotherapy and patients receiving supportive therapy alone.

discontinuing the drug and administering short-course oral steroid therapy.

DISCUSSION

To date, no treatment schedule to improve the course of DMPM has been reported.[22] Surgery, radiotherapy, chemotherapy, multimodality, and supportive care alone have been applied with disappointing results.

In recent years, however, it has been claimed[8,9,23] that an aggressive surgical treatment, extrapleural pneumonectomy, for which a limited number of patients are usually eligible, results in only a modest improvement in overall survival. In a multimodality approach that included extrapleural pleurectomy, chemotherapy, and radiotherapy, 2-year and 5-year survival rates for the entire cohort were 45% and 22%, respectively, with a median survival time of 21 months among the patients without mediastinal and transdiaphragmatic involvement.[8] In another study, multimodality treatment of 49 nonmeasurable patients with Butchart stage I DMPM resulted in a median survival time of 22 months and a 3-year survival rate of 34%.[23]

Most of the patients with DMPM had unresectable disease at presentation. Thus, systemic therapy was the only treatment option for them.[8,9,12,15,19,23–25] In our series, 17 patients (40%) had stage I disease, and only 9 patients (21%) had epithelial cell type and stage 1 disease. New drugs that are used as single agents or in combination have continued to be an area of active investigation. Various trials of chemotherapeutic agents have been performed over the years, but few have shown clear benefit; most of the studies have been too small in scale to accurately measure the responses. Additional problems include heterogeneity of the patient populations, use of second-line drugs, and a possibility of erroneous pathologic diagnoses.[9,15,19,25]

Of the chemotherapy agents that have been studied,[9,25] anthracyclines, platinum compounds, and alkylating agents have demonstrated small but noteworthy activity against mesothelioma. Mitomycin is one of the most active drugs, producing 21% OR in one study, but with notable pulmonary toxic reactions.[9,26] In all series', cisplatin given at standard

Table 3—*Patients With Specific Toxicities**

Toxicity	World Health Organization Grade			
	1	2	3	4
Neutropenia	5	5	2	0
Anemia	13	12	1	0
Thrombocytopenia	2	1	0	0
Nausea/vomiting	17	10	10	0
Fever	18	14	0	0
Nephrotoxicity	11	1	0	0
Neurotoxicity	3	2	0	0
Diarrhea	4	2	0	0
Allopecia	8	1	0	0

*Only the highest grade is reported for each patient.

doses has shown modest activity, yielding response rates of < 20%.[9,27,19] Recently, new chemotherapeutic agents such as mitoxantrone, paclitaxel, and trimetrexate have been tried as single agents with disappointing results.[24,28,29]

Combinations of chemotherapeutic drugs have also been tested in numerous studies; most have shown no advantage over single-agent chemotherapy.[9,25] Among the cisplatin-based regimens, cisplatin given with mitomycin provided a 26% response rate with two CRs.[30]

In recent years, immunotherapy containing IFNs has shown some success in the treatment of solid tumors.[11,12,31,33] Although all forms of IFN have antiproliferative activity, IFN-α has been most extensively studied.[12,33] Preclinical studies have all suggested that IFN-α may display a certain activity in mesothelioma cell lines, by way of a direct inhibitory effect and its capacity to upregulate surface expression of major histocompatibility complex class I molecules involved in tumor recognition.[11,12,31–36] Some investigators have attempted to apply the preclinical positive results with IFN-α as a single agent or in combination at the clinical level. As a single agent, IFN-α has been used on a limited number of patients. At dosages that ranged from 3 to 18 million IU/d, investigators[12] observed only four ORs in 25 patients. On the other hand, only marginal activity (1 responder among 13 assessable patients) was seen with the systemic administration of recombinant IFN-α2b.[13] Previous studies have not shows IFN-α to be effective as a single agent in the treatment of DMPM.

Sklarin et al[18] have shown the moderate activities of cisplatin and mitomycin to be markedly increased by the addition of IFN-α in human mesothelioma xenografts. This and other such findings suggest that it may be possible to enhance the effects of other immunomodulatory or antiproliferative agents to which mesothelioma is partially responsive by combining the agents with IFN-α. After the study by Sklarin et al,[18] IFN-α and active chemotherapy agents were tried in certain combinations.[14–16,37]

In a study by Tansan et al,[37] a combination similar to the one used in this study was administered. In the former study, cisplatin, 50 mg/m^2, mitomycin, 10 mg/m^2, and IFN-α2b, 10 million units IM, were given 4 h before and immediately before (IV, same dose) cisplatin administration. The investigators concluded that the addition of IFN-α2b to cisplatin and mitomycin did not result in an OR higher than that previously reported. Among 19 patients, these researchers observed only two PRs. The overall median survival time was 15 months for the chemotherapy group; this was not significantly different from that of the control group (whose members had not received chemotherapy for 8 months).[37]

In our series, the OR rate was 23% and the median survival time of the chemotherapy group was 11.5 months. This was not significantly longer than the 7-month median survival time of the patients receiving supportive care alone.

In another combination study[15] including IFN-α2a, 26 previously untreated patients received weekly cisplatin combined with the IFN. The OR (all partial) rate was 35%, and the median survival time was 12 months. The response rate was higher than that found in this study, but the median survival time was similar. Their responders had a median survival time of 25 months (range, 9 to 32 months) vs 8 months for nonresponders. Similarly, in our series, objective responders had a significantly longer median survival time (21 months) than nonresponders (6 months). In a phase II study using subcutaneous IFN-α, 9 million IU qd, and IV doxorubicin, 25 mg/m^2 weekly, 16% of patients with mesothelioma exhibited a PR to the combination of the two drugs.[14] There was no clinical evidence of side effects for this drug combination, and it did not appear that patient survival was significantly prolonged.[2,14] Doxorubicin combined with IFN was no more effective than either agent used alone, and toxicity was unacceptably high.[14]

In our series, for stage I disease, the median survival time was 12 months. For both stage I and epithelial cell type patients, the median survival time was 16 months. Otherwise, the median survival time of the patients with OR was 21.3 months (Table 2). In the series with the multimodality approach,[8,23] the median survival times of 21 and 22 months, respectively, were not much different from the median survival times of this study; the former studies focused on the early (stage I) disease.

Because no phase III study has compared the survival of DMPM patients given active systemic treatment to that of patients receiving no treatment, the survival rate of untreated mesothelioma patients can only be determined from retrospective studies. Such studies[24,37] suggest a median survival time of 5 to 8 months. Our study is worthy of consideration in this respect because our control group consisted of patients receiving supportive care alone from the beginning of the study. The median survival time for the control group was 7 months, which is similar to that reported in other studies.[24,37]

For the patients receiving chemotherapy, the 1-year survival rate was 49%; the 2-year survival rate was 12%, and the 5-year survival rate was 2%. For the group receiving supportive care alone, the 1-year survival rate was 39%. In the series of patients treated with a multimodality approach, the 5-year

survival rate was 22% in one study[8]; in the other study,[23] the 3-year survival rate was 34%. We are not able to compare these rates to those of our study because in our series, the number of patients with stage I disease is only 17, the number of stage I disease and epithelial cell types cases occurred nine times, and 2 patients are still alive, one 70 for months and other for 17 months.

Toxicities associated with the treatment schedule in this study were, for the most part, tolerable. Two patients experienced life-threatening side effects: one patient had pulmonary edema, and the other patient had encephalopathy. The causes of these conditions could not be determined. Both patients recovered with careful support. Myelosuppression occurred mostly after the fourth or fifth cycles, and most patients suffered from prolonged and delayed nausea and vomiting. These cases were all managed by adequate supportive care.

We conclude that the drug combination used in this study is moderately effective and well tolerated in patients with DMPM, especially in responsive patients. Unfortunately, the overall response rate is low and the median survival time is not long enough to consider this treatment regimen to be of general benefit to all DMPM patients. However, responsive patients (with OR) had significantly longer survival times than both nonresponders and patients who received supportive care alone. Future investigations should be aimed at determining which patients will be responsive. On the other hand, this and other well-defined studies[9,10,30,38] indicate that mesothelioma may not be totally chemotherapy resistant. Therefore, although overall response rates have not been not sufficient, further investigations of various drug combinations and doses should be tested for effectiveness against mesothelioma.

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References

1 Hillerdal G. Pleural malignancies including mesothelioma. Curr Opin Pulm Med 1995; 1:339–343
2 Selcuk ZT, Coplu L, Emri S, et al. Malignant pleural mesothelioma due to environmental mineral fiber exposure in Turkey: analysis of 135 cases. Chest 1992; 102:790–796
3 Baris YI. Asbestos and erionite related chest diseases. Ankara, Turkey: Semih Ofset Matbaacılık Ltd Company, 1987; 8–139
4 McDonald JC. Health implications of environmental exposure to asbestos. Environ Health Perspect 1985; 62:319–328
5 Alberts AS, Falkson G, Goedhals L, et al. Malignant pleural mesothelioma: a disease unaffected by current therapeutic maneuvers. J Clin Oncol 1988; 6:527–535
6 Vogelzang NJ. Malignant mesothelioma: diagnostic and management strategies for 1992. Semin Oncol 1992; 19:64–71
7 Sugarbaker DJ, Jaklitsch MT, Liptay MJ. Mesothelioma and radical multimodality therapy: who benefits [review]? Chest 1995; 107(suppl):345S–350S
8 Sugarbaker DJ, Norberto JJ. Multimodality management of malignant pleural mesothelioma. Chest 1998; 113(suppl): 61S–65S
9 Ryan CW, Herndon J, Vogelzang NJ. A review of chemotherapy trials for malignant mesothelioma. Chest 1998; 113(suppl):66S–73S
10 Hunt KJ, Longton G, Williams MA, et al. Treatment of malignant mesothelioma with methotrexate and vinblastine, with or without platinum chemotherapy. Chest 1996; 109: 1239–1242
11 Bowman RV, Manning LS, Davis MR, et al. Chemosensitivity and cytokine sensitivity of malignant mesothelioma. Cancer Chemother Pharmacol 1981; 28:420–426
12 Christmas TI, Manning LS, Garlepp MJ, et al. Effect of interferon alpha 2a on malignant mesothelioma. J Interferon Res 1993; 13:9–12
13 Ardizzoni A, Penucci MC, Castagneto B, et al. Recombinant interferon alpha-2b in the treatment of diffuse malignant pleural mesothelioma. Am J Clin Oncol 1994; 17:80–82
14 Uphan JW, Musk AW, van Hazel G, et al. Interferon alpha and doxorubicin in malignant mesothelioma: a phase II study. Aust N Z J Med 1993; 23:683–687
15 Soulié P, Ruffié P, Trandafir L, et al. Combined systemic chemoimmunotherapy in advanced diffuse malignant mesothelioma: report of a phase I-II study of weekly cisplatin/interferon alfa-2a. J Clin Oncol 1996; 14:878–885
16 Wadler S, Schwartz EL. Antineoplastic activity of the combination of interferon and cytotoxic agents against experimental and human malignancies: a review. Cancer Res 1990; 50: 3473–3486
17 Chahinian AP, Norton L, Holland JF, et al. Experimental and clinical activity of mitomycine-C and *cis*-diamminodichloroplatinum in malignant mesothelioma. Cancer Res 1984; 44:1688–1692
18 Sklarin NT, Chahinian AP, Feuer EJ, et al. Augmentation of activity of *cis*-diamminodichloroplatinum (II) and mitomycine C by interferon in human malignant xenografts in nude mice. Cancer Res 1988; 48:64–67
19 Aisner J. Current approach to malignant mesothelioma of the pleura. Chest 1995; 107(suppl):332S–344S
20 Rusch VS, Ginsberg RJ. New concepts in the staging of mesotheliomas. In: Deslauriers J, Lacquet LK, eds. International trends in general thoracic surgery. St. Louis, MO: CV Mosby, 1990; 336–343
21 Miller AB, Hoogstraten B, Staquet M, et al. Reporting results of cancer treatment. Cancer 1981; 47:207–214
22 Ruffié P. Mesothelioma chemotherapy. Eur Respir Rev 1993; 3:194–203
23 Baldini EH, Recht A, Strauss GM, et al. Patterns of failure after trimodality therapy for malignant pleural mesothelioma. Ann Thorac Surg 1997; 63:334–338
24 Vogelzang NJ, Weissman LB, Herndon JE, et al. Trimetrexate in malignant mesothelioma: a cancer and leukemia group B phase II study. J Clin Oncol 1994; 12:1436–1442
25 Ong ST, Vogelzang NJ. Chemotherapy in malignant pleural mesothelioma: a review. J Clin Oncol 1996; 14:1007–1017
26 Bajorin D, Kelsen D, Mintzer DM. Phase II trial of mitomycine in malignant mesothelioma. Cancer Treat Rep 1987; 71:857–858
27 Zidar BL, Green S, Pierce HI, et al. A phase II evaluation of cisplatin in unresectable diffuse malignant mesothelioma: a Southwest Oncology Group study. Invest New Drugs 1988; 6:223–226
28 Van Breukelen FJM, Mattson K, Giaccone G, et al. Mitoxantrone in malignant pleural mesothelioma: a study by the

EORTC Lung Cancer Cooperative Group. Eur J Cancer 1991; 27:1629–1633
29 Meerbeeck JV, Debruyne C, Zandwijk NV, et al. Paclitaxel for malignant pleural mesothelioma: a phase II study of the EORTC Lung Cancer Cooperative Group. Br J Cancer 1996; 74:961–963
30 Chahinian AP, Antman K, Goutsou M, et al. Randomized phase II trial of cisplatin with mitomycine or doxorubicin for malignant mesothelioma by the Cancer and Leukemia Group. Br J Clin Oncol 1993; 11:1559–1565
31 Einhor S, Strander H. Interferon therapy for neoplastic diseases in man in vitro and in vivo. Adv Exp Med Biol 1987; 110:159–174
32 Foon KA. Biological response modifiers: the new immunotherapy. Cancer Res 1989; 49:1621–1639
33 Bielefeldt-Ohmann H, Fitzpatrick DR, Marzo AL, et al. Potential for interferon-alpha-based therapy in mesothelioma: assessment in a murine model. J Interferon Cytokine Res 1995; 15:213–223
34 Wivel NA, Pitha PM. Interferon treatment of meth-A sarcoma cell effects on the malignant phenotype and expression of tumour specific and H2 antigens. Int J Cancer 1982; 30:649–654
35 Belardelli F, Gresser I, Maury C, et al. Antitumour effects of interferon in mice injected with interferon-sensitive and interferon-resistant Friend leukemia cells. Int J Cancer 1982; 30:813–820
36 Balkwill FR, Mowshowitz S, Seilmain SS, et al. Positive interactions between interferon and chemotherapy due to direct tumor action rather then effects on host drug-metabolizing enzymes. Cancer Res 1984; 44:5249–5255
37 Tansan S, Emri S, Selçuk T, et al. Treatment of malignant pleural mesothelioma with cisplatin, mitomycine C and alpha interferon. Oncology 1994; 51:348–351
38 Shin DM, Fossella FB, Umsawardi T, et al. Prospective study of combination chemotherapy with cyclophosphamide, doxorubicin, and cisplatin for unresectable or metastatic malignant pleural mesothelioma. Cancer 1995; 76:2230–2236