Background: Treatment approaches in malignant pleural mesothelioma (MPM) patients range from mere palliation to aggressive anticancer therapy, and there is currently no consensus on the optimal therapeutic strategy. In 1999, we began a Phase II study to investigate four-modality treatment of advanced stage MPM.

Methods: From 1999 to 2004, 49 patients with International Mesothelioma Interest Group stage II–III MPM underwent four-modality treatment with intrapleural preoperative interleukin-2 (18 × 10^6 UI/day for 3 days), pleurectomy/decortication, intrapleural postoperative epideroxurubicin (25 mg/m^2 for 3 days), interleukin-2 (18 × 10^6 UI/day for 3 days), adjuvant radiotherapy (30 Gy), systemic chemotherapy (cisplatin 80 mg/m^2 day 1, gemcitabine 1250 mg/m^2 days 1 and 8 for up to six courses) and long-term subcutaneous interleukin-2 (3 × 10^6 UI/day on 3 days per week).

Results: Patients included 41 men and eight women with a median age of 61 years (range, 41–77). All patients were diagnosed with MPM by thoracoscopy before inclusion. There was no postoperative mortality. Postoperative morbidity included bleeding (n = 1) and arrhythmias (n = 3). After a median follow-up of 59 months (range, 14–81), 13 patients are still alive and the median actuarial survival is 26 months (31 and 21 months for stages II and III, respectively). The 2- and 5-year actuarial survival rates were 60.2% and 23.3%, respectively. Baseline Eastern Cooperative Oncology Group performance status significantly influenced survival time (p = 0.02).

Conclusion: The four-modality treatment that we adopted for advanced-stage MPM was feasible, well tolerated by most of the patients, and produced a favorable median survival. This treatment approach warrants further investigation.

Key Words: Mesothelioma, Multimodality treatments, Pleurectomy, Chemotherapy, Immunotherapy.

(M J Thorac Oncol. 2007;2: 237–242)
administered via the intracavitary route, is superior to IFN-α or IFN-β in neoplastic pleural effusions in patients with mesothelioma, producing an overall response (OR) rate of 40%. In phase II studies, sequential therapy with intrapleural IL-2 or intravenous IL-2 followed by subcutaneous IL-2 produced median survival times of 8.6 to 18.7 months in MPM patients.9,10

There is currently no consensus in the literature on the optimal treatment for MPM, and most centers adopt a multimodal therapeutic strategy. Trimodality therapy has been investigated in clinical studies; MPM patients undergoing trimodal therapy with cytoreductive surgery and adjuvant chemotherapy and radiotherapy achieved median survival times of 13 to 19 months.11–14 Sugabaker et al.12 demonstrated that EPP and adjuvant chemotherapy was most effective among patients with positive prognostic parameters, including epithelial histology, no nodal involvement, and clear resection margins, who achieved high 2- and 5-year survival rates (68% and 46%, respectively) and a median survival time of 51 months.12 Thus, EPP is frequently conducted in patients with positive prognostic factors, whereas P/D may be more suitable for older patients or those with more advanced disease and poorer performance at diagnosis.

In 1999, we began a phase II study to explore the therapeutic efficacy of multimodal therapy comprising immunotherapy, surgery, chemotherapy, radiotherapy, and long-term immunotherapy in patients with advanced (stage II–III) MPM.

MATERIALS AND METHODS

Study Design

This study was designed as a phase II trial to evaluate the feasibility of multimodal treatment with preoperative intrapleural IL-2, surgery (P/D), postoperative intrapleural epirubicin and IL-2, radiotherapy, systemic chemotherapy with cisplatin and gemcitabine, and long-term subcutaneous IL-2 therapy. Additionally, we aimed to determine the patterns of local and distant disease recurrence after treatment, and the rate of overall survival. The study design was approved by the local ethics committee and all patients gave written informed consent.

Patient Selection

Eligible patients were younger than 75 years of age with histologically proven stage II or III MPM diagnosed by thoracoscopy. Additional eligibility criteria included Eastern Cooperative Oncology Group (ECOG) performance status of ≤2, no history of malignancy or chemo- or radiotherapy, adequate bone marrow reserve (leukocytes ≥3500/µL, platelets ≥100,000/µL), and adequate liver (bilirubin ≤1.5 mg/dL) and renal function (serum creatinine ≤1.5 mg/dL and creatinine clearance >65 mL/min).

Treatment

The planned multimodal treatment schedule is described in Table 1. During preoperative IL-2 treatment, acetaminophen was administered in patients with fever (≥38°C). After 1 day of recovery, all the patients underwent a thoracotomy. At the operation, if the disease was minimal and considered a stage I, the patient was excluded from the study and underwent an extrapleural pneumonectomy. In case of stage II or III MPM, we performed a P/D consisting of the removal of the parietal and mediastinal pleura or areas of the visceral pleura if they were involved, with minimal resection of the lung if necessary. In case of minimal involvement of the pericardium and diaphragm, they were resected and sutured; however, they were never replaced with a mesh as for the radical P/D (neither in case of a T3 tumor). At the end of the surgical procedure, a lymph node sample was taken, and a thin catheter (pigtail 12 French) was positioned for intrapleural drug administration. The catheter was removed 1 week after the last instillation of postoperative IL-2.

During long-term postoperative IL-2 therapy, the patient’s immunologic profile was monitored via routine serum samples, and IL-2 treatment was discontinued when there was evidence of disease relapse.

<table>
<thead>
<tr>
<th>Table 1. Planned Sequential Multimodal Treatment Schedule</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Treatment</strong></td>
</tr>
<tr>
<td>IP IL-2 18 × 10^6 UI/day for 3 days</td>
</tr>
<tr>
<td>IP epirubicin 25 mg/m² for 3 days</td>
</tr>
<tr>
<td>IP IL-2 18 × 10^6 UI/day for 3 days</td>
</tr>
<tr>
<td>Radiation therapy&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>Cisplatin 50 mg/m² on day 1 and gemcitabine 1250 mg/m² on days 1 and 8 for 3–6 courses</td>
</tr>
<tr>
<td>SC IL-2 3 × 10^6 UI/day on 3 days per week</td>
</tr>
</tbody>
</table>

<sup>a</sup> After 1 day of recovery, all patients underwent a thoracoscopy to confirm the disease severity according to IMIG staging criteria. Patients with stage I disease were excluded from the study and underwent extrapleural pneumonectomy. Patients with stage II or III MPM underwent P/D, which consisted of removal of the parietal and mediastinal pleura or areas of the visceral pleura if they were involved, with minimal resection of the lung if necessary. If involved, the pericardium or diaphragm was resected and sutured.

<sup>b</sup> Radiation therapy aimed to treat all surgical scars while sparing the underlying lung parenchyma.

### Notes


chest and upper abdomen were performed 1 month after the end of radiation therapy and every 3 months thereafter. Local tumor progression was defined according to radiographic criteria; cytologic or histologic evidence of disease progression was not routinely obtained. Disease progression, according to the Response Evaluation Criteria in Solid Tumors Group (RECIST), was defined as at least 20% increase in the sum of the longest diameters of target lesions.

**Statistical Analysis**

Survival was estimated using the Kaplan-Meier product-limit method and survival curves were compared using the log-rank test. The χ² test was used for comparison between proportions, and Fisher’s exact test was used when cell frequencies were small. Statistical analysis was conducted using Stat-Soft software, and results are expressed as mean ± SD. A p value <0.05 was considered significant.

**RESULTS**

**Patient Characteristics**

From 1999 to 2004, 49 patients with IMIG stage II–III MPM were enrolled in the study. Baseline demographics and characteristics are listed in Table 2. All patients had the diagnosis of MPM confirmed by thoracoscopy before inclusion. Most patients had IMIG stage III disease, and an ECOG performance status score of 1. Nine of the 40 patients diagnosed with stage III tumors had N2 disease, whereas the remaining patients had T3 tumors (Table 2).

**Treatment Administration and Toxicity**

We did not experience any postoperative mortality. Postoperative complications included bleeding (n = 1), arrhythmias (n = 3), and air leakage (n = 6).

**TABLE 2. Patient and Tumor Characteristics**

<table>
<thead>
<tr>
<th>Variable</th>
<th>No. of Patients (n = 49)</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>41</td>
<td>84.7</td>
</tr>
<tr>
<td>Female</td>
<td>8</td>
<td>16.3</td>
</tr>
<tr>
<td>Age, y</td>
<td>Median (range)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>61 (range 41–77)</td>
<td></td>
</tr>
<tr>
<td>IMIG stage</td>
<td></td>
<td></td>
</tr>
<tr>
<td>II</td>
<td>9</td>
<td>18.4</td>
</tr>
<tr>
<td>III</td>
<td>40</td>
<td>81.6</td>
</tr>
<tr>
<td>Histologic subtype</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Epithelial</td>
<td>39</td>
<td>79.6</td>
</tr>
<tr>
<td>Mixed</td>
<td>6</td>
<td>12.2</td>
</tr>
<tr>
<td>Sarcomatous</td>
<td>4</td>
<td>8.2</td>
</tr>
<tr>
<td>ECOG performance status</td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>7</td>
<td>14.3</td>
</tr>
<tr>
<td>1</td>
<td>30</td>
<td>61.2</td>
</tr>
<tr>
<td>2</td>
<td>12</td>
<td>24.5</td>
</tr>
</tbody>
</table>

ECOG, Eastern Cooperative Oncology Group; IMIG, International Mesothelioma Interest Group.

Intrapleural IL-2 and epidoxorubicin were administered to all patients without dose reduction or interruption. All patients experienced fever during treatment and required antipyretic medication, and three patients had cutaneous complaints (mostly desquamation), which spontaneously resolved after treatment.

All patients received adjuvant systemic chemotherapy with cisplatin and gemcitabine. Each patient received an average of 5.3 cycles (range, two to six), and 259 cycles were delivered in total. Median granulocyte, platelet, and hemoglobin nadirs were 712 cells/mm³, 181,000 cells/mm³, and 10.5 g/dl, respectively; neutropenic fever occurred in 52 courses (20.1%). The most common nonhematologic toxicities were mild or moderate alopecia, nausea/vomiting, and gastrointestinal toxicity (Table 3).

Adjuvant radiotherapy, whose targets were the surgical scars and eventual residual disease, was administered in all patients. Four patients, referred by centers where the radiotherapists refused the treatment patients, were excluded from the analysis. Radiation therapy–related complications were mild. Actinic pneumonia, which occurred in most patients, was managed with corticosteroids.

Long-term subcutaneous IL-2 therapy was administered for a median of 10 months (range, 1–36) and was well tolerated. The only complications were eosinophilia, observed in 37% of patients, and a mild fever, which was managed with paracetamol 500 mg.

**Survival and Disease Recurrence**

After a median follow-up time of 59 months (range, 14–81) 13 patients are still alive. Five patients were radiographically disease free, 37 had a local relapse, and seven had both a local and systemic relapse. The median survival time was 26 months; median survival times for patients with stage II or III disease at baseline were 31 and 21 months, respectively. The 2- and 5-year actuarial survival rates were 60.2% and 23.3%, respectively (Figure 1). Baseline ECOG performance status was the only factor to significantly influence survival time (p = 0.02; Figure 2).

**DISCUSSION**

The optimal treatment for MPM remains elusive. With only limited data available from well designed, randomized trials, it is not clear whether current single or combination...
treatments offer patients a clinically meaningful benefit on survival and quality of life.

In this study, we sought to design a multimodal treatment strategy that was sufficiently effective for treatment of this aggressive disease, but did not unduly affect the quality of life of patients. As a matter of fact, the selected treatment strategy was of acceptable tolerability.

Results from our study indicate that our multimodal treatment strategy produces a survival benefit in MPM patients; the median survival of 26 months with our treatment is encouraging compared with the expected survival time of 9 months in MPM patients receiving palliative care.

The schedule of IL-2 administration in our treatment protocol, which was based on the results of previous phase II studies, is original. We aimed to induce maximal immunologic improvement by administering intrapleural preoperatively and then adjuvant IL-2, in combination with epidoxorubicin for treatment of local disease, followed by long-term

FIGURE 1. Kaplan-Meier curve of overall survival time for all patients (n = 49).

FIGURE 2. Survival according to Eastern Cooperative Oncology Group (ECOG) performance status at the time of diagnosis.
subcutaneous IL-2. Endogenous IL-2 is depleted in all advanced tumors, particularly MPM, and the resulting decrease in serum lymphocytes is an important prognostic factor for survival.8

With regard to the surgical arm, our protocol dictated that EPP was conducted in patients with IMIG stage I disease who had acceptable lung and cardiac function, and P/D was performed in patients with stage II or III disease. P/D is a less radical procedure and is associated with fewer complications than EPP; the morbidity rate for P/D is 25%, whereas significant complications occur in 50% of patients undergoing EPP.3 Thus, patients undergoing P/D are able to tolerate complex adjuvant multimodal therapy, as supported by evidence from our study in which most patients completed all scheduled treatment.

The selection of adjuvant intrapleural chemotherapy with epirubicin and systemic chemotherapy with cisplatin and gemcitabine was based on the high objective response rates achieved with these drugs in clinical studies in MPM patients.6,16,17 In our study, chemotherapy with these agents was well tolerated and suitable for coadministration with IL-2.

Despite encouraging results with adjuvant radiation therapy from one phase II study, in which MPM patients receiving hemithoracic radiotherapy in conjunction with P/D or EPP achieved a median survival time of 10 to 34 months depending on the stage of the tumor,18 a recent retrospective analysis suggests this strategy is not effective in MPM patients.19 This analysis found a median overall survival time of 13.5 months in MPM patients treated with P/D and adjuvant radiotherapy, compared with 17 to 19 months in patients who underwent EPP.19 However, it is notable that this analysis found a median survival time of 13.9 months among stage III and IV patients.19 It is obvious that lung toxicity during radiation therapy is a minor concern after EPP. However, we believe that radiation therapy, in combination with chemotherapy and immunotherapy, may be useful in patients unable to tolerate EPP who undergo P/D. Rusch et al.18 achieved an amazing 10% incidence of local relapse, much better than our 89.7%, but we must wonder which is the most important endpoint among local recurrence rate: overall survival or quality of life. Whenever a low local relapse rate does not match a long survival, it is not a crucial issue.

The four treatment modalities administered in our study were chosen to produce optimal survival and local and systemic control of MPM, without compromising the patient’s quality of life with overly aggressive therapy. Treatments were selected based on data from clinical trials demonstrating a treatment benefit with multimodal therapy,11-14 such as that by Sugarbaker et al.,12 who demonstrated, even if excluding the perioperative deaths from the survival analysis, a median survival time of 19 months in patients receiving trimodal therapy with EPP and chemo- and radiotherapy. Recently, in a phase I and II study, intraoperative intracavitary hyperthermic chemotherapy was administered to enhance locoregional control of MPM. In 20 MPM patients treated with P/D and intraoperative, intracavitary hyperthermic cisplatin lavage, the authors reported a median survival time of 26 months.20 Furthermore, the use of P/D in our study is supported by recent data from an animal study by Broomefield et al.,21 which suggests that partial surgical debulking followed by combination chemo- and immunotherapy induces a long-term immunologic memory response.

Aggressive multimodal treatment with neoadjuvant chemotherapy, similar to that used in advanced NSCLC, has been investigated in MPM patients. In a pilot study by Weder et al.,22 MPM patients receiving neoadjuvant cisplatin 80 mg/m² and gemcitabine 1000 mg/m² followed by EPP achieved a response rate of 32% and, among 16 of the 19 patients who underwent EPP, the median survival time with neoadjuvant chemotherapy was 23 months.22 Preliminary data from an extension of this study, in which 29 of 61 patients completed treatment, indicate an excellent median survival time of 26.3 months.23 However, the postoperative complication rate was high (62%) and raises safety concerns, supporting our rationale that a less aggressive treatment may be appropriate for MPM patients. Final results from this study are awaited with interest.

A drawback of our study design was the inability to measure the quality of life. Although we observed positive effects on this outcome, the study questionnaire did not allow these results to be recorded.

In conclusion, our study supports the addition of local and systemic immunotherapy to surgery, radio- and chemotherapy in MPM patients. In light of the poor life expectancy of patients with MPM, we believe that it is important to avoid aggressive treatment modalities, and to provide instead a regimen that is tolerable and able to be completed by the majority of patients. The observed 26-month median survival with our multimodal treatment is extremely encouraging. Thus, our four-modality regimen warrants further investigation in clinical trials in MPM patients.

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