Recombinant Interferon Alpha-2b in the Management of Malignant Pleural Effusions

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Twenty-one patients with malignant pleural effusion (MPE) were prospectively entered into a nonrandomized, single-armed study to evaluate the efficacy and safety of recombinant interferon (IFN) alpha-2b (INTRON A; Schering-Plough; Kenilworth, NJ) as an intrapleural palliative agent. From March 1989 through February 1993 (48 months), 21 patients were entered into the study. No symptomatic effusion recurred and no substantial side effects were associated with treatment. This suggests recombinant IFN alpha-2b represents a safe and effective intrapleural agent for the palliation of MPE.

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Key words: interferon; intrapleural therapy, malignant pleural effusion

Abbreviations: IFN=interferon; MPE=malignant pleural effusion

Malignant pleural effusion (MPE), commonly associated with various neoplasms, almost always signifies inoperability and poor overall prognosis. Although MPE does not imply the terminal phase of an underlying malignancy, it does represent a significant source of morbidity for affected patients and thus mandates treatment. Several treatment modalities are currently available for patients with MPE (Table 1). These modalities are associated with variable degrees of success and substantial side effects.

Recent European trials utilizing various preparations of interferon (IFN) intrapleurally in small numbers of patients have demonstrated variable degrees of success in patients with MPE. The purpose of this study is to evaluate recombinant IFN alpha-2b as a nonsclerosing, intrapleural agent for the palliation of patients with MPE. We examined its efficacy and safety in this capacity.

MATERIALS AND METHODS

From March 1989 through February 1993, 21 consecutive patients with symptomatic MPE were offered treatment with intrapleural IFN. All patients offered this form of treatment accepted it with full knowledge that other, more conventional forms of treatment were available. These 21 patients were selected based on the following criteria: (1) presence of MPE; proved cytologically; (2) presence of symptoms related to MPE; (3) excluding thoracentesis, no prior local treatment had been administered; and (4) life expectancy at the time of treatment exceeded 1 month.

All patients were first evaluated with standard chest radiographs to determine the extent of the baseline effusion. Using standard technique, a No. 28 or No. 32 F thoracic catheter was introduced into the affected hemithorax via the sixth, seventh, or eighth intercostal space in the midaxillary line. Treatment was begun once drainage was <50 mL over an 8-h period (mean, 3.8 days; range, 2 to 7 days). A solution consisting of 10 million U of recombinant IFN alpha-2b diluted in 100 mL 0.9 normal saline solution was instilled into the affected hemithorax followed by clamping of the chest tube for 6 h. Patients were encouraged to change positions frequently to distribute the solution maximally throughout the chest. The chest tube was then unclamped and placed to suction, and the affected hemithorax was maximally drained. IFN was instilled a second time in a similar fashion 24 h later. Twenty-four to 48 h later, when drainage was <50 mL for 24 h, the chest tube was removed. Serial radiographs of the chest were then obtained at 1, 2, 3, and every 6 months for surviving patients.

The following parameters were assessed during the follow-up period: (1) clinical improvement noted as the absence of dyspnea, and (2) radiographic assessment of the effusion compared with immediate posttreatment study. Failure of treatment was defined as recurrence or persistence of symptomatic MPE.

This study was approved by the investigational review board of the medical center. All study subjects gave informed consent prior to participation in the study.

RESULTS

Of 21 patients initially evaluated, 6 were excluded from the study group. In five patients, death occurred within the first month after treatment. Two of
these patients were found to have a marked amount of tumor bulk within the thorax (one with osteogenic sarcoma of the left chest wall and another with contiguous spread of a primary breast carcinoma to the chest wall). A third patient with advanced pancreatic cancer died 3 weeks after treatment. Two patients, one with widely metastatic adenocarcinoma of unknown primary and another with advanced ovarian carcinoma, died within 2 weeks of treatment. One patient was unavailable for follow-up.

Of the remaining 15 patients who constitute the study group (Table 2), there were no recurrent symptomatic pleural effusions. Thirteen of these patients died of their underlying malignancy 7.35 months (mean) posttreatment (range, 1 to 39 months). Nine patients died at home following treatment. The other four patients died of causes unrelated to their underlying malignancy while hospitalized (traumatic hip fracture, GI bleed, contralateral pneumonia, and a subsequent esophageal carcinoma).

Autopsies were performed on 2 of the 13 study subjects. Neither demonstrated scarring of the visceral or parietal pleural surfaces. One patient who had been treated with intrapleural IFN for a right MPE demonstrated a left MPE at autopsy but no pleural effusion on the right. The other patient had no residual effusion at autopsy.

The two remaining patients are currently alive and asymptomatic at 5.5 and 3.5 months after treatment.

In all patients, the intrapleural application of IFN elicited a positive subjective response of a “cool, soothing sensation.” There were no reported sensations of pain, burning, or discomfort. No patient experienced adverse respiratory symptoms during the treatment period. Two patients experienced transient episodes of pyrexia, which were attributed to the treatment. Both responded rapidly and completely to oral acetaminophen administration. No other adverse effects of treatment were noted.

**Table 1—Treatment Modalities for Malignant Pleural Effusion**

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Success Rate, %</th>
<th>Disadvantages/Morbidity</th>
<th>Reference No.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chest tube (alone)</td>
<td>0-80</td>
<td>Infection/empyema</td>
<td>1, 3, 4</td>
</tr>
<tr>
<td>Tetracycline</td>
<td>25-100</td>
<td>Pain, fever</td>
<td>1, 3</td>
</tr>
<tr>
<td>Quinacrine</td>
<td>64-100</td>
<td>Fever, pain, nausea, hypotension, hallucinations</td>
<td>3, 4</td>
</tr>
<tr>
<td>Bleomycin</td>
<td>63-85</td>
<td>Bone marrow suppression, leukopenia</td>
<td>6-3</td>
</tr>
<tr>
<td>Nitrogen mustard</td>
<td>7-85</td>
<td></td>
<td>3, 4, 17</td>
</tr>
<tr>
<td>5-Fluorouracil</td>
<td>66</td>
<td></td>
<td>4</td>
</tr>
<tr>
<td>Thoracoscopic talc poudrage</td>
<td>90-100</td>
<td>Fever and pain; requires general anesthesia</td>
<td>8-12</td>
</tr>
<tr>
<td>Pleurectomy</td>
<td>87-100</td>
<td>Air leak, bleeding, pneumonia, empyema, cardiac failure, respiratory failure</td>
<td>1, 2, 4</td>
</tr>
</tbody>
</table>

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In all patients, the intrapleural application of IFN elicited a positive subjective response of a “cool, soothing sensation.” There were no reported sensations of pain, burning, or discomfort. No patient experienced adverse respiratory symptoms during the treatment period. Two patients experienced transient episodes of pyrexia, which were attributed to the treatment. Both responded rapidly and completely to oral acetaminophen administration. No other adverse effects of treatment were noted.

**DISCUSSION**

A variety of methods have been employed in the management of MPE, but none has emerged superior (Table 1). The agents vary, but their effect is similar: they commonly produce sclerosis of the pleural surfaces to achieve control of the effusion. In contrast, IFN does not have a sclerosing effect in the pleural cavity.15 Although the exact mechanism of action is unknown, intrapleural IFN can render the pleural space free of malignant cells in a malignant effusion.15 The antiproliferative and cytotoxic effects of IFN form the theoretical basis of its therapeutic effectiveness.

Several studies suggest that intrapleural IFN affects the course of MPE.13-17 Cascino et al.,13 in Italy, employed natural beta-IFN in a closed technique and experienced only minimal success. Rosso et al.,14 using a similar technique of aspiration followed by instillation of natural beta-IFN, showed a complete or partial response in 11 of 29 patients with recurrent MPE. Jereb et al.,15 in Yugoslavia, using aspiration followed by instillation of a crude IFN preparation, demonstrated the ability to render the pleural space free of malignant cells in patients with MPE but they were unable to demonstrate a clinical response to treatment. However, Goldman et al.,16 utilizing nee-
dle aspiration and chest tube drainage followed by instillation of IFN alpha experienced a 70% clinical response in 14 patients. More recently, Davis et al., at Wake Forest, were unable to demonstrate a complete or partial response in 15 patients treated with simple needle aspiration followed by instillation of IFN alpha-2b. They were able to demonstrate effusion stabilization utilizing this technique. In our study, closed chest tube thoracostomy drainage was employed. This may explain the difference we experienced. Incomplete drainage of MPE is likely to effect maximal obtainable results. Certainly, this is consistent with what has been found when other investigators have employed chest tube thoracostomy drainage alone has been shown to be effective in controlling MPE in up to 50% of cases, this must be considered as a factor in the present study.

Clearly, there is yet no optimal approach to the patient with recurrent MPE. The use of intrapleural IFN requires further investigation in a larger, randomized, controlled study.

REFERENCES
1 Hood RM. Surgical diseases of the pleura and chest wall. Philadelphia: Saunders, 1986; 57-77