Malignant Pleural Effusion Treated by Tetracycline Sclerotherapy*
A Comparison of Single vs Repeated Instillation

Lance Landwater, M.D.,† William R. Hix, M.D., F.C.C.P.;‡
Mitchell Mills, M.D.,§ Robert S. Siegel, M.D.;∥ and
Benjamin L. Aaron, M.D., F.C.C.P.¶

Fifty patients with malignant pleural effusion were randomized to receive one or two doses of tetracycline sclerotherapy. We found that a single sclerotherapy treatment with tetracycline at a dose of 20 mg/kg was as effective as two sclerotherapy treatments and provided symptomatic relief in 46 of the 50 patients.

Malignant pleural effusions frequently occur in patients with disseminated breast and lung cancer.1 Malignant lymphomas, ovarian carcinoma, mesotheliomas, sarcomas, as well as genitourinary and gastrointestinal malignancies, can also cause malignant pleural effusions.2,3 These patients are often symptomatic with chest discomfort and respiratory embarrassment and require treatment for palliation. Chemotherapy, radiation therapy, repeated thoracocenteses, intrapleural instillation of sclerosing agents or talc, and pleurectomy have all been utilized to treat malignant effusions and control their recurrence.4 Instillation sclerotherapy is considered to have the least morbidity, mortality, and fewest side effects, while effectively preventing recurrent pleural effusion.1,4,6 Tetracycline is considered to be the least toxic, least expensive, and easiest sclerosing agent to administer.7-11 Some authorities recommend repeating the tetracycline instillation on two or more successive days,12 although there is no published scientific basis for multiple instillations.

The purpose of this study was to determine if effective pleurodesis could be obtained with a single instillation of tetracycline, thus eliminating the expense, nursing care, and patient discomfort from repeated instillations. A group of patients receiving a single instillation was compared with a second group who received instillations on two consecutive days.

**Patients and Methods**

Fifty patients with progressive dyspnea or chest discomfort secondary to malignant pleural effusion were entered into the study between June 1985 and January 1987. The primary malignancies responsible for the pleural effusions are listed in Table 1. Patients were alternately assigned to receive either a single instillation of tetracycline (group 1) or to have instillation of tetracycline on two consecutive days (group 2). The study was approved by the Committee on Human Research, and the patients entered gave written, informed consent.

Using local anesthesia, a 28 Fr or 32 Fr thoracostomy tube was placed into the affected hemithorax by the usual percutaneous technique. The pleural effusion was allowed to drain by gravity into a chest drainage reservoir over several hours during the daytime, or overnight if the tube was placed in the evening. The position of the chest tube and completeness of evacuation of the effusion was confirmed by portable chest x-ray film. The chest tube was then clamped, and 20 mg/kg (maximum of 2 g) of tetracycline in 50 ml of normal saline solution was injected through the tube into the pleural space. An additional 50 ml of normal saline solution was injected to clear the tube. Some patients also received 20 ml of 1 percent lidocaine with the tetracycline solution to serve as a topical anesthetic. The patient was then turned into the supine, right, and left lateral decubitus positions for ten minutes each, with the bed flat, to insure that the tetracycline came into contact with all pleural surfaces. The chest tube was then unclamped and the drainage system connected to 20 cm water suction. Patients in group 2 received a second instillation by the same method on the following day. Suction was maintained until the total drainage was less than 150 ml per day, at which time the chest tube was removed.

Follow-up was obtained on each patient to determine if a symptomatic effusion recurred. A small pleural effusion detected on chest x-ray film that remained asymptomatic and required no further treatment was not considered a treatment failure. Patients

| Table 1—Primary Cancers Causing Malignant Pleural Effusion |
|-----------------|------------------|
| **Breast**       | 27               |
| **Lung**         | 9                |
| **Gynecologic**  | 4                |
| **Renal cell**   | 1                |
| **Esophageal**   | 1                |
| **Bladder**      | 1                |
| **Adenocarcinoma with unknown primary** | 3 |
| **Sarcoma**      | 1                |
| **Lymphoma**     | 2                |
| **AIDS—Kaposi sarcoma** | 1 |

1196 Malignant Pleural Effusion (Landwater et al)

*From the Divisions of Cardiothoracic Surgery and Hematology and Oncology, The George Washington University Medical Center, Washington, DC.
†Cardiothoracic Surgery Fellow.
‡Associate Professor of Surgery.
§Clinical Professor of Surgery.
∥Assistant Professor of Medicine.
¶Professor of Surgery.

Manuscript received August 28; revision accepted November 25.
with recurrent pleural effusion, causing dyspnea or other respiratory compromise, who required thoracocentesis or re-sclerosis were deemed treatment failures.

RESULTS

As can be seen from Table 2, there was a total of eight recurrent effusions in the 50 patients, but only four required retreatment. In the 25 group 1 patients who received one dose of tetracycline sclerotherapy, there were four recurrent effusions, three of which required additional treatment. Of the 25 group 2 patients, four had recurrent effusions, but only one was of sufficient size to produce symptoms and require retreatment. All recurrent symptomatic effusions were treated with tetracycline sclerotherapy, and there have been no recurrences in this group of four patients. The success rate in this series for control of symptomatic malignant pleural effusions was 92 percent and there was no significant difference between one or two instillations of tetracycline sclerotherapy. A total of 86 percent of the patients remained free of pleural effusion after tetracycline sclerotherapy, and 50 percent of the patients with recurrent effusions were symptom free and required no additional therapy.

DISCUSSION

Malignant pleural effusion occurs in as many as 50 percent of patients with cancer at some point in the course of their disease. Symptomatic effusions require treatment for relief of respiratory compromise. The ideal form of treatment should result in little morbidity, have a low cost, provide predictable results, and be easy to administer.

Numerous treatment modalities have been reported for control of malignant pleural effusions. Repeated thoracocentesis is an ineffective means of controlling malignant effusion. The mean time for an effusion to recur after a single thoracocentesis is four days, with the majority recurring in one to three days. Repeated thoracocenteses increase the risk of complications, including hemorrhage, pneumothorax, empyema, and pleural fluid loculation.

Pleurectomy is very effective in controlling malignant pleural effusions; Martini et al reported satisfactory results in 99 percent of patients with this technique. However, pleurectomy carries a significant morbidity and mortality rate and is unsuitable for the majority of patients with malignant pleural effusion. Martini et al reported 10 percent mortality and 23 percent morbidity for this procedure.

Some malignant pleural effusions appear to respond to external radiation therapy, particularly those secondary to lymphomas. Fifteen lymphoma patients followed by Anderson et al had a good initial response of 88 percent, but half had recurrence of their effusion.

Instillation sclerotherapy via tube thoracostomy is the favored treatment for malignant pleural effusion by most authors. Numerous instillational agents have been tried, including radioactive phosphorous and gold, 5-fluorouracil, nitrogen mustard, quinacrine, t alc, tetracycline, bleomycin, and thio-TEPA. For a sclerosing agent to be effective, it must create an inflammatory pleuritis between the visceral and parietal pleural surfaces that eventually results in a symphysis between these layers, thus preventing fluid reaccumulation. Tetracycline is particularly effective in creating pleural symphysis due to its low pH and the caustic effect of the acidic solution on the mesothelial cells of the pleura. The addition of lidocaine to the tetracycline solution does not appear to alter its pH, and is therefore not detrimental to its sclerosing action.

Tetracycline was effective in controlling malignant pleural effusions in 83 to 100 percent of the cases reported. The dose of tetracycline administered, method of delivery, and number of sclerotherapy treatments given is not uniform in the medical literature. Light recommends a dose of 20 mg/kg of tetracycline diluted in 50 ml of normal saline solution. Other reports recommend a dose of 15 mg/kg, or 1 g maximum; 15 to 20 mg/kg in 75 ml of sterile water; 300 mg of tetracycline; and 500 mg of tetracycline per sclerotherapy.

Other instillational agents provide adequate control of malignant pleural effusions but have undesirable side effects. Quinacrine instillation had a response rate of 70 percent but resulted in fever in 95 percent, pain in 39 percent, nausea and vomiting in 39 percent, and hallucinations and hypotension in 10 percent of patients. Objective response rates with nitrogen mustard ranged from 27 to 87 percent. Nausea and vomiting developed in 40 to 90 percent, and mild leukopenia developed in nine out of ten patients. Talc instillation had a response rate of 90 to 100 percent but required general anesthesia and a limited thoracotomy in one reported series, although talc poudrage may be done by thoracoscopy using local anesthesia.

We elected to evaluate a standard dose of tetracycline solution, 20 mg/kg, or 2 g maximum, in 50 ml of normal saline, with or without the addition of lidocaine. Patients were then sclerosed once or twice and evaluated for effectiveness of effusion control. We found that one dose of tetracycline was as effective as two doses, and our response rate for symptomatic control was 92 percent. Eighty six percent of our
patients were entirely free of recurrent effusion. Our patients suffered minimal morbidity from tetracycline pleurodesis. Local pleuritic pain was controlled with analgesics or the addition of lidocaine to the tetracycline solution. Low grade fever was occasionally noted. Most chest tubes were removed within three to five days.

We recommend tetracycline sclerotherapy as a safe, effective, and well-tolerated method to palliate symptomatic malignant pleural effusion. We found no benefit from multiple instillations.

REFERENCES
1 Anderson CB, Philpott GW, Ferguson TG. The treatment of malignant pleural effusions. Cancer 1974; 33:916-21
5 Fracchia AA, Knapper WG, Carey JT, Franco JA. Intrapleural chemotherapy for effusion from metastatic breast carcinoma.

Cancer 1970; 36:626-29
6 Hausheer F, Yarbro JW. Diagnosis and treatment of malignant pleural effusion. Sem Oncolog 1985; 12:54-75
16 Wallach HW. Intrapleural therapy with tetracycline and lidocaine for malignant pleural effusions. Chest 1978; 73:246

Plan to Attend
54th Annual Scientific Assembly
Anaheim
October 3-7, 1988