TETRACYCLINE AND QUINACRINE IN THE CONTROL OF MALIGNANT PLEURAL EFFUSIONS

A Randomized Trial

TIMOTHY C. BAYLY, MD, DANIEL L. KISNER, MD, ALLENDER SYBERT, MD, JOHN S. MACDONALD, MD, EDWARD TSOU, MD, AND PHILIP S. SCHEIN, MD

Eighteen patients with advanced metastatic malignancy who had 21 pleural effusions requiring sclerosis for control were randomly allocated to intrapleural therapy with tetracycline or quinacrine. Tetracycline produced partial or complete control of the effusion in ten of 12 trials for a median duration of 6 months (range 1.5 to 22 months). Partial or complete control was obtained in nine of ten trials with quinacrine, for a median duration of 3 months (range 1 to 13 months). All complete responders who died achieved control of their effusions until their terminal admissions despite clinical evidence of overt systemic tumor progression in the intervening period. Single-dose tetracycline therapy was accompanied by less fever ($p < 0.04$) and less pleuritic pain ($p = 0.09$) than quinacrine. Tetracycline is effective, well tolerated, easily administered, and should be considered as the initial therapy for malignant pleural effusions requiring pleural sclerosis.

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PLEURAL EFFUSION IS A COMMON COMPLICATION of malignant disease and, when recurrent, often presents a difficult management problem. Repeated thoracenteses have only a transient effect, with rapid reaccumulation of fluid being the rule.[3] Instillation of cytotoxic or sclerosing agents into the pleural space can be effective in preventing recurrence, but the agents in standard use have several disadvantages. Nitrogen mustard can produce significant pleuritic pain, nausea and vomiting, and because of systemic absorption, can contribute to the overall myelosuppression of cytotoxic therapy.[3,12,17] Thiotepa, another alkylating agent used for pleural sclerosis, is also toxic to the bone marrow.[2,7] Quinacrine, while not myelosuppressive, has the disadvantages of causing considerable pleuritic pain and fever, and requires repetitive instillations over 3 to 5 days for maximum effect.[5,6,13,15] Pleurectomy is an effective means of control, but carries a significant risk in patients who may already have compromised pulmonary function and a relatively short life expectancy.[9]

Recently, intrapleural administration of tetracycline has been reported effective in the control of malignant pleural effusions, with moderate pain and fever as the only toxic reactions.[14,16] The purpose of this study is to compare the efficacy of tetracycline with that of quinacrine, an agent in standard use, in a randomized clinical trial.

PATIENTS AND METHODS

Patients who met the following criteria were entered onto the study: 1) documented neoplastic disease with pleural effusion; 2) either pleural fluid cytology or pleural biopsy showing malignant cells, or exudative effusion without other evident cause; 3) either respiratory distress from the effusion requiring repeated thoracenteses because of reaccumulation, or an initial effusion in excess of 500 ml which reaccumulated rapidly after drainage.

After giving informed consent, 20 patients were randomized to quinacrine or tetracycline therapy. Two patients were not evaluable, one because of death 16 days after sclerosis and the other because of loss to follow-up after 2 weeks. One patient whose effusion recurred after tetracycline therapy was later treated with quin-

From the Divisions of Pulmonary Disease and Medical Oncology, Department of Medicine, Georgetown University School of Medicine, and the Vincent T. Lombardi Cancer Research Center, Washington, D. C.

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Address for reprints: Philip S. Schein, MD, Division of Medical Oncology, #2230, Georgetown University Hospital, 3800 Reservoir Road, NW, Washington, D.C. 20007.

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TABLE 1. Diagnostic Data and Response to Intrapleural Therapy

	Primary site of malignancy	Documented pleural involvement*	Toxicity	Response	Response duration and patient status
	TETRACYCLINE				
1.	Lung (muco-epidermoid)	—	Fever, pain	Complete	3 months (deceased)
2.	Lung (adenocarcinoma)	C	Fever	Complete	18+ months (alive)
3.	Lung (alveolar cell)	B	None	Failure	Deceased
4.	Renal Cell	—	None	Partial	3 months (deceased)
5.	Ovary	—	Pain	Complete	8 months (deceased)
6.	Breast	B	None	Complete	22 months (deceased)
7.	Breast	C	Fever, pain	Complete	6 weeks (deceased)
8.	Breast	A	None	Complete	3 months (deceased)
9.	Breast	C	None	Failure	Deceased
10.	Breast	—	None	Complete	14 months (deceased)
11.	Breast	C, A	Fever, pain	Complete	21 months (deceased)
12.	Breast	—	Pain	Partial	7 weeks (alive)
	QUINACRINE				
13.	Germ Cell	—	Fever, pain, pericardial friction rub	Complete	6 months (deceased)
14.	Osteosarcoma	—	Fever	Complete	2+ months (lost follow up)
15.	Renal Cell	—	Pain	Partial	13 months (deceased)
16.	Colon	B	Fever, pain	Partial	1 month (deceased)
17.	Lung (epidermoid)	B	Fever, pain	Failure	Deceased
18.	Ovary	B, C	Fever, pain	Complete	8 months (deceased)
19.	Ovary	C, A	Fever, pain	Complete	3 months (deceased)
20.	Breast	A	Fever, pain, restrictive lung disease, pleurocutaneous fistula	Complete	1 month (deceased)
21.	Breast	A	Fever, pain	Complete	3 months (deceased)
22.	Breast†	C	None	Partial	2 months (deceased)

* B = pleural biopsy; C = pleural fluid cytology; A = autopsy; — = not documented.
† Previously treated with tetracycline without response.

acrine. Three patients with bilateral pleural effusions requiring sclerosis had each hemithorax randomized and analyzed individually, to yield 22 evaluable clinical trials (Table 1).

Each patient underwent closed tube thoracostomy, usually in the eighth intercostal space and in the posterior axillary line. The tube was attached to underwater seal and the pleural cavity was drained slowly overnight. Quinacrine was administered in a dose of 100 mg dissolved in 30 ml of sterile saline, and if no adverse reaction was observed, four additional daily doses of 200 mg dissolved in 30 ml of saline were instilled through the tube.[4] Each dose was followed by 50 ml of saline to flush the tube. Tetracycline was administered as a single dose of 500 mg dissolved in 30 ml of saline, followed by 50 ml of saline. After each drug was instilled, the tube was clamped for 6 hours, and the patient was instructed to change position frequently to insure adequate pleural contact with the drug. The tube was then unclamped and if there was no significant drainage over the next 12 hours, the tube was removed. If fluid continued to drain, the tube was left in place until drainage stopped or slowed to less than 60 ml per 24 hours.

The response to therapy is classified as a complete or partial response, or a failure. A complete response is defined as a complete lack of reaccumulation of pleural fluid for at least 30 days, as evidenced by chest roentgenogram. A partial response is defined as a reaccumulation of pleural fluid within 30 days, not exceeding 50% of the volume present before sclerosis. A failure is defined as reaccumulation of fluid to greater than 50% of the volume present before attempted sclerosis.

Treatment-related pain is defined as significant if potent narcotic analgesics, such as meperidine or morphine, were required for relief. A febrile reaction to therapy is defined as a temperature elevation to 100°F or higher, temporally related to the instillation of the sclerosing agent and in the absence of concomitant infection or other cause of fever.

RESULTS

The patients' diagnoses, response to therapy and toxicity are summarized in Table 1.

Documentation of Malignancy

In the quinacrine group, intrapleural malignancy was documented by pleural fluid cytology or pleural biopsy in five of ten evaluable patients, and malignant pleural involvement was found at autopsy in two additional patients. In the tetracycline group, six of 12 evaluable effusions had positive pleural fluid cytology or pleural biopsy, and one additional patient had pleural involvement at autopsy.

Response

Fifteen of the 22 trials were performed in patients on concomitant systemic chemotherapy. Only one patient had an objective extrapleural response to chemotherapy at the time of pleural sclerosis; all others had overt systemic tumor progression subsequent to pleural sclerosis.

Tetracycline was administered in 14 trials. Two were not evaluable, one because of death 16 days after sclerosis and the other because of loss to follow-up after two weeks. In the 12 evaluable trials, eight patients had a complete response, with a median duration of 8 months and a range of 1.5 to 22 months. All complete responders who died had continued control of their pleural effusions until their terminal admissions. One complete responder had regression of bony metastases on systemic chemotherapy begun 2 days after pleural sclerosis. Two patients had partial responses, lasting in one patient until her death 2 months later and in the second patient until a recurrence of pleural effusion after seven weeks.

Quinacrine was administered in nine trials, all of which were evaluable. There were six complete responses, with a median duration of 3 months and range of 1 to 13 months. All complete responders had continued control of their pleural effusions until death. There were two partial responders, who lived one and 13 months respectively and died without increase in volume of their pleural effusions.

One patient treated with quinacrine after failure with tetracycline had a partial response lasting until her death two months later.

With the exception of patients #2 and #12 in the tetracycline group, all responders achieved continued control of their pleural effusions until their terminal admissions, despite clinical evidence of overt systemic tumor progression with or without treatment with systemic chemotherapy. Patient #2 remains in a complete remission without evidence of recurrent effusion for 18 months while receiving constant chemotherapy. Patient #12 manifested a recurrent pleural effusion despite continued systemic chemotherapy 7 weeks after initial control by sclerosis.

Toxicity

Single-dose tetracycline was accompanied by fever in four of 12 trials, compared to eight of ten with quinacrine ($p < 0.04$). Pleuritic pain requiring narcotic analgesics occurred in five of 12 trials with tetracycline, and eight of ten trials with quinacrine ($p = 0.09$). Two of the tetracycline trials and three of the quinacrine trials were conducted in patients who were already receiving narcotics for pain at other sites; however, only pleuritic pain temporally related to sclerosis was considered for purposes of the study.

Serious complications were less common. One patient who underwent bilateral sclerosis with tetracycline on the left side and the quinacrine on the right developed severe restrictive pulmonary disease and died in respiratory failure 3 months after receiving quinacrine. In addition, a pleurocutaneous fistula developed on the quinacrine-treated side. In another patient, a transient pericardial friction rub without hemodynamic compromise was noted shortly after instillation of quinacrine into the left pleural cavity.

Hospital stay was shorter in the tetracycline-treated patients (median 12 days, range 6 to 73 days) than in those treated with quinacrine (median 20 days, range 6 to 40 days), though the difference is not statistically significant.

DISCUSSION

Tetracycline is an effective sclerosing agent for treatment of malignant pleural effusions, with a control rate comparable to that of the standard agent quinacrine. Quinacrine has been found to be effective at a total dose of from 350 mg to 2000 mg in several reported series, the majority of patients having received 700 to 1300 mg.[5,6,13] Based on these data the total dose of 900 mg was selected for this study. The optimal dose of tetracycline for intrapleural administration has not been established. In this study, a dose of 500 mg was chosen, to correspond to the dose used in previous studies.[14,16] The tetracycline solution is

highly acidic, and probably induces sclerosis by an irritative effect on pleural mesothelial cells.[14]

An important aspect of treatment, and one which we feel contributed to the good results in both groups, is that complete or near complete drainage of fluid was accomplished by the use of an intercostal chest tube. This allowed for closer approximation of the parietal and visceral pleura, and therefore increased the likelihood of achieving pleural symphysis. Gravity drainage without sclerosis has been utilized in management of malignant pleural effusion, but the efficacy of this technique is not established.

Several reports have suggested that gravity drainage alone is effective. The most frequently cited study is that by Lambert *et al.*[11] In this series, a total of 22 patients were treated with gravity drainage alone and three recurrences were reported. Although superfically impressive, this series suffers from some serious inadequacies: no information on this group of patients was furnished regarding histologic documentation of pleural involvement, criteria or documentation of response, criteria for recurrence, duration of follow-up or use of concomitant systemic therapy.

The only randomized trial comparing gravity drainage alone with gravity drainage plus a sclerosing agent was reported by Izbicki *et al.*,[8] in which drainage was compared to drainage plus P^{32}. There were no statistically significant differences between response rates in the two groups. Of the 37 cases treated with drainage alone, 16 (43%) were reported to have benefited. Of these 16 responding patients, nine experienced a systemic tumor regression from concomitant chemotherapy. Taking these patients into consideration raises questions as to whether the reported 43% control rate is valid. This is in contrast to the 83–90% control rate achieved with tetracycline and quinacrine in our study.

Other investigators have found gravity drainage alone to be relatively ineffective. Anderson *et al.*[3] reported recurrences within 1 month in all seven cases treated with drainage alone. Similar experiences have been reported by Adler *et al.*[1] and Johnson *et al.*[10] The efficacy of gravity drainage alone in malignant pleural effusion is therefore not firmly established, and its role remains doubtful.

While bilateral pleural sclerosis may result in significant restrictive ventilatory impairment due to fibrothorax, the risk of this complication may be justified in patients incapacitated by dyspnea due to intractable malignant infusions. One patient in our series developed fatal respiratory failure due to restrictive lung disease after bilateral pleural sclerosis.

Although the tetracycline group contained a higher proportion of cases of metastatic breast carcinoma than the quinacrine group, this did not appear to favorably influence the response in the tetracycline group. The response rate among all trials in patients with breast cancer, 9/10 (90%), did not differ significantly from that of the non-breast cancer group, 10/12 (83%).

The concomitant use of systemic chemotherapy did not contribute significantly to the control of the pleural effusions, since 14/15 (93%) of trials in patients on systemic chemotherapy achieved control, while 5/7 (71%) of trials in patients not on chemotherapy achieved control. This difference is not statistically significant ($p = 0.20$).

Approximately one-third of the trials were done on effusions with no pleural tumor documentation. A total of 11/14 of tumor-documented effusions responded to sclerosis, for a 78% response rate. All eight non-tumor-documented effusions responded. This difference, however, is not statistically significant ($p = 0.20$).

Both tetracycline and quinacrine are effective in controlling malignant pleural effusions in cancer patients. Tetracycline is associated with a significantly lower incidence of fever and with a lesser frequency of severe pleuritic pain. In addition, since tetracycline was given as a single dose rather in contrast to the five daily doses used in the quinacrine group, pleural sclerosis with tetracycline required a shorter period of chest tube placement and therefore a shorter hospital stay. Because of its equal efficacy, lesser toxicity and ease of administration, tetracycline is preferable to quinacrine as an initial sclerosing agent.

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