Intrapleural Tetracycline in Malignant Pleural Effusions

A Randomized Study

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Intrapleural instillation of tetracycline (TCN) has been shown to be effective in preventing the recurrence of malignant pleural effusions. Although the precise mechanism of action is unknown, it has been postulated that the pH of the TCN solution may be an important factor. Thirty patients with malignant pleural effusions were randomized in a double-blind trial to receive intrapleural administration of either 500 mg of tetracycline in solution (pH = 2.8) or a solution of similar pH and appearance. All patients had chest tube drainage of their effusion. There were 24/30 patients evaluable. There were 9/13 patients in the TCN group and 1/9 patients in the control group who had no reaccumulation of fluid ($P < 0.05$). These results would suggest that the efficacy of TCN as a sclerosing agent is not related to its acidic pH and that intrapleural TCN is more effective than chest tube drainage alone for control of malignant effusions.

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RECURRENT MALIGNANT pleural effusions present a difficult management problem for both the patient and physician. Simple thoracentesis usually has a transient effect and is associated with a high rate of re-accumulation of the pleural fluid. To prevent recurrence of the effusion, various agents have been used. Intrapleural instillation of radioisotopes,[1] talc,[2] nitrogen mustard,[3] quinacrine,[4] 5-fluorouracil,[5] bleomycin,[6] and thiotepa[7] have all exhibited varying degrees of success. Pleurectomy has also been used to control the effusion, but carries a significant morbidity risk. Chest tube drainage alone has a response rate of approximately 55%.[8]

A number of recent investigations have shown that chest tube drainage followed by instillation of tetracycline hydrochloride (TCN) is effective in preventing the recurrence of malignant effusions.[4,9–12] Although the exact mechanism whereby TCN produces pleural symphysis is unknown, it has been postulated that the pH of the TCN solution is an important factor. This report describes a prospective randomized double-blind study conducted to assess the effectiveness of TCN as a sclerosing agent and to determine whether its effectiveness is related to its acid pH.

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Method

Thirty patients with biopsy-proven malignancy (Table 1) and recurrent pleural effusion were randomized in a double-blind fashion to receive TCN or a control solution. All patients had at least one needle aspiration attempt prior to the insertion of the chest tube. The patients had to have an expected survival of at least one month and a Karnofsky Score of at least 40% (disabled, requires special care and assistance). A chest tube was inserted and attached to water seal drainage with suction for a minimum of 24 hours.

The patients in the TCN group received an intrapleural instillation of 500 mg of TCN in 50 cc of saline. The control group received 0.6 cc of multivitamins in 50 cc of saline to which 5 cc of 0.1 N HCL was added to make the color and pH of the solution similar (pH 2.8). The titratable acidity of the TCN solution was 1.93×10^{-4} M/ml; that of the multivitamin solution was 1.45×10^{-5} M/ml. This was followed by 20 cc of saline to clear the tubing of medication. The chest tube was clamped for two hours with the patient's position changed every five minutes for 30 minutes to insure adequate dispersal. The chest tube was then unclamped and allowed to drain for an additional 12–24 hours until the drainage was minimal. Two patients had bilateral pleural effusions and received TCN on one side and placebo on the other side. In one patient who had disease progression after instillation of the first agent, the code was broken, a chest tube was reinserted, and the alter-

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TABLE 1. Characteristics and Responses of Patients

Tumor	Sclerosing agent*	Response to sclerosing agent†	Duration response to sclerosing agent‡	Concurrent chemotherapy	Response to chemotherapy†
1. Breast	TCN	CR	3 mo	Halotestin	P
2. Unknown primary	TCN	CR	3 mo	Cis-platinum Adriamycin	P
3. Lung	TCN	CR	6 mo	No	—
4. Breast	TCN MVI	CR S	6 mo+	Tamoxifen, Cytoxan methotrexate, 5-FU	PR
5. Lung	MVI TCN	P CR	10 mo	No	—
6. Breast	TCN	CR	34 mo+	Adriamycin, Cytoxan, vincristine; Megace	PR
7. Colon	TCN	CR	3 mo	Mitomycin C	P
8. Breast	MVI	CR	3 mo	Vincristine, Cytoxan, Adriamycin	P
9. Lung	TCN	CR	6 wk	No	—
10. Unknown primary	TCN	CR	9 mo	No	—
11. Breast	MVI	PR	2 mo	Tamoxifen, 5-FU, Cytoxan	P
12. Hodgkin's	TCN	PR	3 mo	No	—
13. Lung	MVI	S	5 mo	Ifosfamide, 5-FU	P
14. Breast	TCN	S	1 mo	No	—
15. Unknown primary	TCN	S	1 mo	No	—
16. Breast	MVI	P	2 wk	Cytoxan, 5-FU, methotrexate	P
17. Pancreas	MVI	P	2 wk	No	—
18. Breast	MVI	P	4 mo	Adriamycin, Cytoxan	P
19. Lung	TCN	P	3 mo	No	—
20. Pancreas	MVI TCN	P NE	1 wk	No	—
21. Lung	TCN	NE	LTFU	No	—
22. Breast	TCN	NE	LTFU	Adriamycin, Cytoxan, vincristine, tamoxifen	LTFU
23. Esophagus	MVI	NE	3 wk	No	—
24. Lung	MVI	NE	3 wk	No	—
25. Lung	TCN	NE	2 wk	No	—
26. Breast	TCN	NE	3 wk	No	—
27. Breast	TCN	NE	2 wk	No	—
28. Lung	MVI	NE	LTFU	No	—
29. Lung	MVI	NE	3 wk	No	—
30. Ovarian	MVI	NE	3 wk	No	—

* TCN: tetracycline; MVI: multivitamin (control group).
† CR: complete response; PR: partial response; S: stabilization; P: progression; NE: non-evaluable.
‡ LTFU: lost to follow-up.
Adriamycin: doxorubicin; Cytoxan: cyclophosphamide; Halotestin: Upjohn.

nate agent given. Patients were evaluated with PA, lateral, and right and left lateral decubitus chest x-rays every two weeks for two months, then monthly or as indicated by the clinical course. In order to be evaluable, the patient had to survive one month after instillation of the sclerosing agent.

Complete response (CR) was defined as the lack of accumulation of fluid; partial response (PR) a 50% de-

crease in the effusion; stabilization, the effusion recurred but required no further therapy; progression, symptomatic re-accumulation of the effusion requiring repeat thoracentesis or chest tube.

In none of the patients was the underlying tumor under adequate control. The majority of patients developed their effusions while receiving various chemotherapeutic regimens (Table 1).

Results

The patients' diagnoses and response to therapy are summarized in Table 1. Of the 30 randomized patients 11 were not evaluable (eight early deaths, three lost to follow-up). A CR was seen in 1/9 (11%) controls and 9/13 (69%) TCN patients ($P < 0.05$); PR in 1/9 (11%) controls and 1/13 (8%) TCN patients; stabilization in 2/9 (22%) controls and 2/13 (15%) TCN patients; progression in 5/9 (55%) controls and 1/13 (8%) TCN patients. The overall response rate (CR + PR) was 77% in the TCN patients with a range of six weeks to 34 months. This is compared with a 22% response rate in the control group and a 2–3 month survival. All responders had control of their effusions until they expired from their underlying malignancy.

Thirteen of the 30 patients received systemic chemotherapy following chest tube placement (Table 1). In only two of these patients (4 and 6) was the underlying tumor controlled with chemotherapy. These were equally divided between the two treatment groups with seven receiving TCN and six receiving placebo. There were 6/7 responses of the effusion in the TCN chemotherapy group and 2/6 responses in the control chemotherapy group suggesting that concurrent chemotherapy did not effect the recurrence rate of the effusion.

Both the TCN and chest tube were well tolerated. There was no significant fever (>37.5°C) or chest pain after instillation of the sclerosing agent. The only complication was a pleurocutaneous fistula in one patient receiving TCN.

Discussion

Recurrent malignant effusions are often the cause of significant debilitation and may be a major limitation to the quality of life in patients with terminal carcinoma. Palliation with minimal toxicity is the therapeutic goal in this situation. Initially, simple thoracentesis will result in adequate symptomatic relief and diagnosis, but 90% of these effusions will recur. Repeated thoracentesis is, therefore, not a practical approach to the problem. As a result, various treatment modalities have been advocated to prevent recurrent effusion. However, it is difficult to objectively evaluate the efficacy of the treatment protocols. Definitions of response vary with each investigator, some assessing the interval of time to reaccumulate the fluid, others measuring the amount of time the patient remains asymptomatic. The control of malignant effusions is a palliative measure and the morbidity of the procedure must be evaluated against the benefit derived.

Chest tube drainage alone has been found to be effective in controlling recurrent effusions in approximately 55% of patients.[8] Various intrapleural sclerosing agents have been utilized to increase the effectiveness over chest tube drainage alone. The therapeutic result of all the agents evaluated appears to be related to their ability to cause pleural inflammation and resultant sclerosis of the pleural surfaces.

The addition of intrapleural radioisotopes or nitrogen mustard does not seem to increase the efficacy of chest tube drainage alone.[1,8] Intrapleural radioisotopes are impractical because of their cost and the inconveniences associated with their instillation. In addition, bone marrow depression and the danger of systemic irradiation make them a less attractive form of therapy. Nitrogen mustard instilled into the pleural cavity is systemically absorbed. The resulting bone marrow depression may compromise the patient's ability to receive any systemic chemotherapy. Other sclerosing agents including talc,[2] quinacrine,[4] 5-fluorouracil,[5] bleomycin,[6] and thiotepa[7] have met with variable success but are associated with significant morbidity. Pleurectomy has been successful but carries the risk of a major surgical procedure.

Intrapleural TCN is gaining popularity because of its overall efficiency, convenience, cost, and apparent lack of significant side effects.[8] Several studies have demonstrated the effectiveness of TCN in controlling malignant effusions. Reported response rates vary from 80–100%, but only two of these are controlled trials. One study comparing TCN with quinacrine showed both were effective but toxicity was less with TCN.[4] Preliminary data in a controlled study comparing TCN to chest tube drainage alone showed responses in 13/18 TCN patients (72%) compared to 4/11 controls (36%).[12]

In the current study, the overall response rate (CR + PR) of patients receiving intrapleural TCN was 77% with a CR of 69%. This is compared with an overall response rate of 22% in the control group. In addition, there was no significant toxicity from the TCN. The only complication was a pleurocutaneous fistula which persisted until the death of the patient.

As with other sclerosing agents, the mechanism whereby pleural symphysis is achieved with TCN is thought to be the result of pleural irritation, inflammation and subsequent fibrosis of the pleural surfaces.

Sahn and Good[13] in an attempt to correlate the effectiveness of the sclerosing solutions, measured the pH of the various agents. They postulated that the efficacy of a solution was related to its extreme pH. However, subsequent animal studies did not confirm this hypothesis.

Although numbers in the current study are small, the results suggest that the mechanism whereby TCN induces pleural symphysis is unrelated to the pH of the solution. Equal numbers of patients in each group received concurrent chemotherapy making this a less likely explanation for higher response rate in the TCN group. The exact mechanism of TCN-induced pleural sclerosis remains unclear.

In the management of malignant pleural effusions at least one attempt at needle drainage should be made for diagnostic studies and as a therapeutic maneuver. In a small number of patients the effusion may not reaccumulate. The majority of patients, however, will have a rapid recurrence of the fluid. Ideally, control of the underlying malignancy would prevent further reaccumulation but few patients fall into this category. With recurrence of the effusion after the initial drainage procedure, a chest tube should be inserted and a sclerosing agent instilled. This study confirms the effectiveness and lack of significant toxicity of intrapleural TCN in preventing recurrent malignant effusion.

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