# Treatment of Malignant Pleural Effusions with a Combination of Bleomycin and Tetracycline

## *A Comparison of Bleomycin or Tetracycline Alone versus a Combination of Bleomycin and Tetracycline*

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**BACKGROUND.** Treatment of patients with malignant pleural effusions is mostly palliative. Tetracycline and bleomycin are the two most commonly used agents for the treatment of pleurodesis. In this study, the authors used a combination of the two drugs for this particular purpose.

**METHODS.** Sixty patients with massive malignant pleural effusions were divided in 3 equal groups in a simple randomized manner. Tetracycline (20 mg/kg [maximum of 2 g] in 50 mL of normal saline) was administered through a chest tube in Group 1. Group 2 received bleomycin (1 U/kg [maximum of 60 U] in 50 mL of normal saline). Group 3 received the above 2 preparations (tetracycline, 20 mg/kg [maximum of 2 g] in 40 mL of normal saline and bleomycin, 1 U/kg [maximum of 60 U] in 30 mL of normal saline) instilled one after the other, while the chest tube was clamped for 5 minutes in the interim. Follow-up examinations were performed at 7 days, 30 days, 60 days, 90 days, and 6 months.

**RESULTS.** There was no significant difference in the complete response rate of the 3 groups during the first 4 months. At the end of the study, Group 3 had a significantly higher complete response rate (70%) compared with Groups 1 and 2 (35% and 25%, respectively) ($P = 0.02$).

**CONCLUSIONS.** The response to use of a combination of bleomycin and tetracycline for the treatment of patients with pleurodesis is superior to that achieved by either of these agents used alone. ***Cancer* 1996; 78:2498–501.**

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**KEYWORDS: malignant pleural effusion, pleurodesis, tetracycline, bleomycin.**

Malignant pleural effusion is a common complication of patients with malignancies.[1] It often results in significant pulmonary symptoms such as dyspnea and chest pain. Treatment of malignant pleural effusion is a major problem because of its recurrent nature.[2,3] Repeated thoracocentesis has a 97% recurrence rate at 1 month but may be appropriate for patients with limited survival.[2] Intrapleural instillation of anticancer drugs or sclerosing agents has been proven to be effective in preventing the reaccumulation of pleural effusion.[4]

Bleomycin and tetracycline are the two most commonly used agents for pleurodesis.[5] As an alternative to the use of these agents singly, the authors have tried a combination for the treatment of patients with pleurodesis and believe the achievement of a long term (6 months) response rate of 70% makes this combination superior to either agent used alone.

TABLE 1
The Causes of Malignant Pleural Effusions in 60 Patients

| Types of malignancy | Number (no.) |
|---|---|
| Breast carcinoma | 21 |
| Lung malignancies | 19 |
| Lymphoma | 4 |
| Other malignancies | 16 |
| Total | 60 |

## PATIENTS AND MATERIALS

Sixty patients with histologically or cytologically proven massive malignant pleural effusions were studied from January 1994 until April 1995. At the time of the study all patients were receiving chemotherapy (a mean of 8.95 ± 8.63 weeks) and 21 patients were also receiving tamoxifen. Despite these therapies, all had persistent massive pleural effusions, and all were symptomatic with progressive dyspnea, chest effusions, or chest discomfort. There were 27 males and 33 females with an age range of 30 to 68 years (mean 53.55 ± 9.1 years). The causes of their malignant pleural effusion are shown in Table 1. Thirty-nine patients had right-sided pleural effusion and 21 had pleural effusion on the left side. Fourteen of 60 pleural effusions were hemorrhagic (23.3%), but the remainder (76.7%) were serofibrinous. Informed written consent was obtained from all patients prior to the study and they were then assigned to three groups of 20 patients each in a simple randomized manner. Group 1 received a single instillation of tetracycline, Group 2 received a single instillation of bleomycin, and Group 3 received a single instillation of a combination of bleomycin and tetracycline.

A 28-French thoracostomy tube was inserted into the sixth intercostal space into the involved hemithorax under local anesthesia. The tube was connected to a water-sealed drainage system. Complete removal of the pleural effusion through the chest tube was allowed over several hours and was confirmed by a subsequent chest X-ray film. All patients received intrapleural instillation of 10-15 mL 1% lidocaine before the instillation of suspensions. A suspension of 20 mg/kg of tetracycline (maximum of 2 g) in 50 mL of normal saline was administered through the tube in Group 1. Group 2 received 1 u/kg of bleomycin (maximum of 60 units) in 50 mL of normal saline. The last group received the above 2 preparations (20 mg/kg of tetracycline [maximum of 2 g in 40 mL of normal saline] and 1 u/kg of bleomycin [maximum of 60 units in 30 mL normal saline]) instilled one after the other, while the chest tube was clamped for 5 minutes in the interim. After the instillation of the suspensions, the chest tube was clamped and patients were repositioned every 15 minutes for 2 hours to ensure a uniform dispersion of the agents. After 24 hours, the tube was connected to 15-cm water suction. It was removed when drainage was <50 mL per 8 hours and chest X-ray film indicated full expansion of the lungs. Local pleuritic pain was controlled with analgesics.

All patients were followed for recurrence of pleural effusions for 6 months. Chest X-ray films were taken monthly and a complete blood count, including hemoglobin, leukocyte count, and platelet count, was performed. Extra films were obtained for those patients who developed dyspnea. Follow-up examinations were recorded at 7 days, 30 days, 60 days, 90 days, 120 days, and 6 months.

The criteria for response were those described by Ostrowski.[6] Complete response (CR) was considered to be present when no accumulation of pleural effusion was detected within the first 30 days by clinical examination and chest X-ray film. Partial response was defined when the effusions recurred but did not require aspiration within the first month. Treatment failure was determined when the patient required thoracocentesis or resclerosis because of dyspnea or chest discomfort secondary to reaccumulation of pleural effusion within the first 30 days. The same criteria were used during each subsequent 30 days of follow-up. However, the number of case fatalities from each month were added to those of the following month (Table 2).

### Statistics

Chi-square (Pearson) test and Fisher's exact test were used to analyze the data. A $P$ value of $<0.05$ was considered statistically significant. Statistics were determined using SAS program language (SAS Institute Inc., Cary, NC).

## RESULTS

Six patients died during the study (two in Group 1, one in Group 2, and three in Group 3). The responses of all groups to management within 6 months are shown in Table 2. At the end of the first month, Group 1 had a 90% CR rate. Group 2 achieved a 70% CR rate, and the CR rate was 95% in Group 3. However, there was no significant difference between the CR rates of the three groups ($P = 0.05$). After 3 months, the CR rates were 65%, 45%, and 90% in Groups 1, 2, and 3, respectively. This difference also was not statistically significant ($P = 0.05$). At the end of the study (6 months), the percentage of CR rates was 70% in Group 3, 35% and 25% in Groups 1 and 2, respectively. Therefore, Group 3 had a significantly higher complete response rate compared with the other groups ($P =$

TABLE 2
Response Rate of the Three Groups within 6 Months of Follow-Ups

| | 30 days | | | | 60 days | | | | 90 days | | | | 120 days | | | | 6 mos | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | CR | PR | F | E | CR | PR | F | E | CR | PR | F | E | CR | PR | F | E | CR | PR | F | E |
| Group 1 | 18 | 1 | 1 | 0 | 16 | 3 | 1 | 0 | 13 | 3 | 3 | 1 | 11 | 4 | 3 | 2 | 7 | 6 | 5 | 2 |
| Group 2 | 14 | 6 | 0 | 0 | 10 | 7 | 2 | 1 | 9 | 8 | 2 | 1 | 5 | 11 | 3 | 1 | 5 | 5 | 9 | 1 |
| Group 3 | 19 | 1 | 0 | 0 | 18 | 2 | 0 | 0 | 18 | 1 | 0 | 1 | 15 | 3 | 0 | 2 | 14 | 2 | 1 | 3 |

CR: complete response; PR: partial response; F: failure; E: combination of case fatalities from the same as well as the preceding month(s).

TABLE 3
Recurrence Rates in the Surviving Patients of Each Group

| | 30 days | | 60 days | | 90 days | | 120 days | | 6 mos | |
|---|---|---|---|---|---|---|---|---|---|---|
| | RR | % | RR | % | RR | % | RR | % | RR | % |
| Group 1 | 2/20 | 10 | 4/20 | 20 | 6/19 | 31.58 | 7/18 | 38.89 | 11/18 | 61.11 |
| Group 2 | 6/20 | 30 | 9/19 | 47.37 | 10/19 | 52.63 | 14/19 | 73.68 | 14/19 | 73.68 |
| Group 3 | 1/20 | 5 | 2/20 | 10 | 1/19 | 5.26 | 3/18 | 16.67 | 3/17 | 17.65 |
| *P* value | 0.06 | | 0.02 | | 0.006 | | 0.002 | | 0.002 | |

RR: recurrence rate.

TABLE 4
Side Effects of Instillation of the Selected Agents in All Groups

| | GI symptoms (no.) | Fever (no.) |
|---|---|---|
| Group 1 | 4 | 1 |
| Group 2 | 3 | 1 |
| Group 3 | 3 | 2 |

GI: gastrointestinal.

0.02), whereas there was no significant difference in CR rates between Groups 1 and 2 ($P = 0.59$).

The recurrence rates in the surviving patients of each group during the 6 months of follow-up are shown in Table 3. The recurrence rates were significantly less in Group 3 patients within 90 days ($P = 0.006$) and 180 days ($P = 0.002$) of instillation compared with the other 2 groups.

It should be mentioned that the side effects of the instillation agents were minimal and similar among the three groups. The patients had minor gastrointestinal symptoms such as nausea and vomiting and fever (Table 4). No drug-related deaths were noted.

## DISCUSSION

Treatment of a malignant pleural effusion is mostly palliative for relief of the patient's chest discomfort and respiratory distress. A variety of surgical and medical treatment modalities have been used in patients with malignant pleural effusions.[7–9] Although the rate of reaccumulation of effusions is low after pleurectomy, this procedure is associated with significant morbidity and mortality.[10] Thus, chest tube drainage with instillation of anticancer drugs or sclerosing materials is the preferred method of therapy by many centers. The agents used include gold, talc, quinacrine hydrochloride, bleomycin, tetracycline, nitrogen mustard, radioactive phosphorus, doxorubicin, 5-fluorouracil, thiotepa, mitomycin, chloroquine, cisplatin, mitoxantrone, etoposide, and *Corynebacterium parvum*.[5,11–18] The selection of a sclerosing agent should be based on its efficacy, toxicity, and cost.

Tetracycline is safely used as a pleural sclerosing agent. The CR rate of tetracycline in the treatment of pleurodesis varies from 54–100% of cases.[19,20] The recurrence rate within 3 months of instillation has been reported to be 53% for tetracycline.[21]

Although the acidic solution of tetracycline was claimed to induce pleural symphysis through its destructive-irritant effect on the mesothelial cells of the pleura,[22] more recent evidence shows that its actual mechanism of action may be through stimulation of the mesothelial cells to release a growth factor-like activity for fibroblasts.[23]

Bleomycin has been reported to be 20–67% effec-

tive in controlling malignant effusions.[20] Some authors have found it to be superior to tetracycline.[21] The long term CR rate of bleomycin at 6 months has been reported to be 34.6%.[6] The recurrence rates 30 and 90 days after the instillation of bleomycin have been reported to be 36% and 30%, respectively.[24] However, in the current series, the recurrence rates were 30% and 52.63%, respectively, and both were much higher than those of Group 3 patients during the same period of time.

Although 45% of bleomycin instilled into the pleural cavity is absorbed systemically, its mechanism of action in pleural symphysis remains unclear. It may induce an inflammatory reaction that may lead to pleurodesis in the pleural space.[25]

In this study, although the short term benefits of the use of bleomycin, tetracycline, or their combination were similar, the long term results were quite different. The use of a combination of bleomycin and tetracycline effectively prevented the recurrence of malignant pleural effusions in 70% of patients in the current study after 6 months of attempted pleurodesis, which was superior to either of these agents when used alone.

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