THE MANAGEMENT OF MALIGNANT
PLEURAL EFFUSIONS

Richard W. Light, M.D.

Professor of Medicine Vanderbilt University
Nashville, Tennessee, USA

Malignancy is one of the most common causes of exudative pleural effusions with approximately 200,000 cases occurring annually in the United States (1). During the course of their disease, approximately 50% of patients with breast cancer, 25% of patients with lung cancer and 20% of patients with lymphoma or leukemia will develop a pleural effusion (1). The prognosis of patient with malignant pleural effusion is poor with a mean life expectancy of 4 – 6 months. Many patients with malignant pleural effusions have the quality of their life diminished by shortness of breath. If the shortness of breath is relieved with a therapeutic thoracentesis, then consideration should be given to the performance of a procedure which will prevent the reaccumulation of pleural fluid and hopefully reduce the shortness of breath of the patient. If the patient does not have the quality of their life diminished by dyspnea, no treatment is recommended because most such patients never become dyspneic from their pleural effusion (2).

There are several options available for treating a malignant pleural effusion (1). The presence of a malignant pleural effusion indicates that the tumor is disseminated and therefore it cannot be cured with surgery. If the tumor is responsive to chemotherapy, chemotherapy should be administered. If the patient has such a malignancy, a thoracentesis prior to chemotherapy is indicated because the chemotherapy may become sequestered in the pleural effusion (3). Unfortunately most malignancies that produce pleural effusions do not respond to chemotherapy although the percentage that does is gradually increasing. A rare patient can be cured with systemic chemotherapy, but it is certainly the exception rather than the rule for patients with malignant pleural effusions to be cured with chemotherapy.

The best way to prevent the accumulation of pleural fluid in patients with malignant pleural effusions is not definitely known. The two main options are the implantation of an indwelling pleural catheter or an attempt to produce a pleurodesis by the injection of a sclerosing agent intrapleurally (4). Both procedures have their advocates (4,5).

Over the past decade the implantation of an indwelling pleural catheter is being used more and more frequently for symptomatic pleural effusions. The tunneled indwelling catheter can be placed with the patient as an outpatient by pulmonologists, surgeons or interventional radiologists. It is best placed under ultrasound guidance in an endoscopy suite. In the original article (6) in 1999 reporting on the use of the
indwelling catheter 144 patients were randomized to have their malignant pleural effusions treated with an indwelling catheter with intermittent drainage every 48 hours or to receive pleurodesis with doxycycline 500 mg. In this study (6) the authors concluded that the indwelling catheter was preferred because its insertion required less hospitalization (often none) and was associated with at least as much symptom relief as was pleurodesis. Tremblay et al. (7) subsequently reported a series of 250 tunnelled pleural catheter insertions in 223 patients. Most of the catheters were inserted on an outpatient basis and 90.1% of the patients required no further ipsilateral pleural procedures (7). They concluded that the indwelling catheter should be considered a first-line treatment option in the management of patients with malignant pleural effusion (7).

When the indwelling catheters are inserted, pleurodesis occurs spontaneously in about 50% of patients (8). Warren et al (9) reported a series of 231 indwelling catheters in 202 patients. Two hundred ten of the catheters were inserted as outpatients (9). They reported that they were able to remove 58% of the catheters and reaccumulation of pleural fluid occurred in only 5 of these 134 patients (3.8%) (9). Van Meter et al. (8) recently reviewed 19 studies with 1370 patients who were treated with tunneled pleural catheters for malignant pleural effusion. They reported that symptomatic improvement occurred in 95.6% of patients and spontaneous pleurodesis occurred in 45.6%. Serious complications were rare and included empyema in 2.85%. They concluded that prospective randomized studies comparing the tunnelled indwelling catheter to pleurodesis are needed before the indwelling catheter can be definitively recommended as a first-line treatment of malignant pleural effusion.

One of the biggest problems with the indwelling catheters is that the suction bottles are very expensive costing several hundred per month which can be problematical in developing countries. Al-Halfawy et al (10) have provided a solution to this by using a surgivent. The surgivent is an accordion type apparatus that is frequently used to drain surgical wounds. It can be attached intermittently to the indwelling catheter and can be reused so the cost is minimal (10).

The primary alternative to insertion of an indwelling catheter is the creation of a pleurodesis by inducing inflammation of the pleura. If the inflammation is of sufficient intensity, fibrosis of the pleura will develop, the visceral and parietal pleura will fuse and there will be no potential space in which pleural fluid can accumulate. When pleurodesis is attempted, there are two main questions that need to be answered before the procedure is attempted: (a) Should the pleurodesis be done with thoracoscopy or through a chest tube, and (b) How should the pleural inflammation be induced?

There is no strong evidence that pleurodesis via thoracoscopy is superior to pleurodesis via tube thoracoscopy. If a pleurodesis is attempted, are the results with thoracoscopy superior to those with tube thoracoscopy? The largest randomized controlled study on this subject was reported by Dresler et al. (11). In this multicenter study, 482 patients were randomized to receive 4 to 5 g of talc, either administered as a slurry in 100 ml saline through a chest tube or insufflated during thoracoscopy. The Kaplan-Meier curves for the proportion of patients with a recurrence were essentially superimposable with a very slight advantage to the group that received the slurry (11). In a second randomized study (12) 57 patients were randomized to receive talc slurry via tube thoracostomy or talc insufflation via thoracoscopy. These authors reported that there was no difference in recurrence, chest drainage duration or complications between the two groups (12). Since talc insufflation
One concern about talc is that its intrapleural administration has been associated with the development of ARDS and death in some patients. The incidence of ARDS has varied markedly from series to series and most of the reported cases have been from the United States. In the first week after talc administration, there were 13 respiratory deaths in the 449 patients (2.9%) in the study of Dresler et al. (11) discussed above. Maskell et al (17) randomized 20 patients with malignant effusions to receive 20 mg/kg tetracycline 4 grams of mixed talc with most particles < 15 um. They reported that the patients who received mixed talc had a significantly greater decrease in the diethylene triamine pentaacetic acid (DTPA) clearance, a significantly greater decrease in the SaO₂, and a significantly greater increase in the C-reactive protein (17). It appears that the acute lung injury is dependent upon the size of the talc used. Maskell et al (17) subsequently randomized 48 patients to receive mixed talc or graded talc in which most particles <15 um had been removed. They reported that the patients who received the graded talc had a significantly smaller increase in the alveolar to arterial oxygen gradient, a significantly smaller decrease in the PaO₂ and a significantly smaller increase in the C-reactive protein. Janssen and coworkers (18) in a multicentre, open-label, prospective cohort study of 558 patient who received 4 g of calibrated French large-particle size talc for malignant effusion reported that there no instances of ARDS. However, seven patients did develop pulmonary infiltrates which they attributed to re-expansion pulmonary edema in 2, cardiogenic pulmonary edema in 1 and respiratory failure unrelated to talc in 1 (18). I am not convinced that the pulmonary infiltrates in some of these patients were not related to the talc. In general, if one elects to use talc as a pleurodesing agent, only large sized talc should be used.

Tetracycline derivatives are the second most common agent for pleurodesis. Tetracycline
itself was the most popular agent in the 80s, but its use decreased in the late 80s when pharmaceutical companies ceased to make parenteral tetracycline. However, the companies continued to produce parenteral doxycycline and minocycline which were shown to be as effective as tetracycline (1). At the present time doxycycline 500 mg is my agent of choice. If parenteral doxycycline or minocycline are not available, the tablets or capsules of these antibiotics can be dissolved in saline and filtered and used for pleurodesis (19).

When treating a dyspneic patient with a malignant effusion, should an indwelling catheter be inserted or should pleurodesis be performed? There have been a couple of recent studies comparing the indwelling catheter with pleurodesis. Fysh et al (20) compared the number of in-hospital days throughout the remainder of the patient's lives in 34 patients who elected to receive an indwelling catheter and 31 patients who elected talc pleurodesis. They reported that median number of hospital days was significantly greater in the pleurodesis group (18 days) than in the indwelling pleural catheter group (6.5 days). Moreover, the median number of hospital days related to the effusions was significantly greater in the pleurodesis group (10 days) than in the indwelling pleural catheter group (3 days). The patients in the indwelling catheter group also spent a smaller percentage of their remaining lives (8.0%) in the hospital compared with the pleurodesis group (11.2%) (20). Thus, it appears that implantation of an indwelling catheter is a viable option for the treatment of a malignant pleural effusion.

Davies et al. (21) randomized 106 patients to receive the indwelling pleural catheter or talc pleurodesis through a chest tube. They reported that there was a statistically significant improvement in dyspnea in the IPC group compared to the talc group at 6 months (21). The length of the initial hospitalization was significantly shorter in the IPC group with a median of 0 days compared with 4 days for the talc group (21). Twelve patients (22%) in the talc group required further pleural procedures compared with 3 (6%) in the IPC group. Nine patients in the indwelling catheter group experienced serious adverse effects including five pleural infections while only five patients in the talc group experienced a serious side effect.

In summary, the indwelling pleural catheter is a reasonable alternative to pleurodesis in many patients and appears to be associated with less days in the hospital. There is no good evidence that pleurodesis via thoracoscopy is any more effective that pleurodesis via tube thoracostomy. Talc is the agent used most commonly for pleurodesis but only large particle talc should be used. Reasonable alternatives to talc are the tetracycline derivatives, silver nitrate and iodojodopovidone. Randomized controlled studies are needed to identify the optimal way to manage patients with symptomatic malignant pleural effusions.

REFERENCES
