Oncology Pharmacotherapy

Talc - Rationale and Use in Malignant Pleural Effusions

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Questions relating to drug use, dosing, and related issues in oncology are presented in this regular feature.

Introduction

Neoplastic diseases account for approximately 13% of the annual incidence of pleural effusions, and 75% of these effusions are secondary to malignancies of the lungs and breast or lymphoma. The most common pathogenic mechanisms that produce malignant pleural effusions (MPE) are (1) pleural metastasis resulting in increased membrane permeability beyond the capacity of lymphatic drainage, (2) metastatic disease of the lymphatic system resulting in decreased clearance of pleural fluid, (3) bronchial obstruction resulting in reduced pleural pressure, and (4) pericardial metastasis resulting in pleural fluid accumulation.

Although systemic chemotherapy is an option for treatment of patients with sensitive tumors, removal of pleural fluid followed by pleurodesis is the primary treatment of MPE. Chemical pleurodesis, also known as sclerosis or obliteration of the pleural space, involves instilling a sclerosing agent bleomycin, doxycycline, or talc — into the pleural space after fluid drainage. Tetracycline injection was one of the mainstays of treatment but is no longer available, and nitrogen mustard and quinacrine are now rarely used due to their side effects.

Approach

The goal of management is to alleviate shortness of breath (the most common symptom of MPE), cough, chest pain, and tachypnea. Table 1 summarizes the characteristics of patients who are likely to benefit from chemical pleurodesis.

Factors that govern the likelihood that a sclerosing agent will be effective are summarized in Table 2. The intent of intrapleural administration of a sclerosing agent is thought to be the creation of a chemically induced, inflammatory pleuritis that forms adhesions between the parietal and pleural surfaces. This obliterates the pleural space and prevents fluid reaccumulation. Some agents, however, do not cause pleuritis but control effusions. Prior to pleurodesis, the pleural fluid is drained by placing a chest tube, usually via the seventh or eighth intercostal space and into the pleural space connected to a water-sealed suction drainage system. The position of the chest tube, the completeness of the drainage, and the re-expansion of the lung are monitored by chest radiography. Inadequate drainage of the accumulated fluid may indicate poor tube placement, obstruction of the tube by fibrin or other debris, or loculations. The longer a chest tube is kept in place, the higher the risk of loculation formation. Loculations are pockets of pleural fluid entrapped by membranes of fibrin connecting the parietal and visceral pleura. Effective drainage of entrapped fluid may require the insertion of more than one chest tube. Fibrinolytic agents (eg, streptokinase, urokinase) are used occasionally to solubilize the membranes of fibrin.

When pleural drainage is minimal, the sclerosing agent is instilled into the pleural space through the chest tube. Minimal drainage is often defined as 100 mL or less per day to minimize dilution of the instilled agent, although there are no data to support the need for drainage to be at or below 100 mL per day. Therefore, pleurodesis generally is done within a few days of placement of the chest tube, even if drainage is more than 100 mL per day. The chest tube is clamped, and the patient may undergo frequent repositioning to uniformly distribute the agent. Suction is then resumed until pleural drainage volume is again minimal. The procedure may be repeated if necessary.

Background

Talc is a natural, asbestos-free product composed of talc, chlorite, and trace minerals (dolomite, calcite, and quartz). A powder for insufflation or slurry pleurodesis is available. Data from animal models show that talc insufflation and slurry pleurodesis denude pleural mesothelial cells within 24 hours followed by a patchy histiocytic inflammatory reaction. The irritant effect of talc resulted in inflamed edematous pleural adhesions with pleural thickening that obliterated the pleural space. The talc particle sizes ranged from 0.5 mm to 10 mm. The desired effect of adhesions occurred more often with a small particle size and uniform distribution of the agent.

Pharmacokinetics

Intrapleural talc probably drains into the parietal pleural lymphatic system and is transported to the mediastinal lymph nodes and thoracic duct where it enters the systemic circulation. Asbestos-free talc has not been associated with malignancy or extrapulmonary organ failure.

Dosage and Administration

Different dosages of talc have been studied. However, 2 g to 10 g of sterilized talc generally is sufficient to accomplish pleurodesis by talc insufflation or slurry. Doses greater than 5 g are rarely used, and many investigators use a maximum of 2 g. A dose of 10 g has been associated with the development of adult respiratory distress syndrome.
Intrapleural administration of talc, either as a slurry or as dry powder, requires that the agent be sterilized. Although talc has been used as a pleurodesis agent since 1935, no standardized sterilization protocol has been established. Dry heat, ethylene oxide, and gamma irradiation have all been used. A recent study compared the effectiveness of the various available sterilization techniques and their associated costs. Talc was obtained from six suppliers, with six 5-g samples tested for each sterilization technique. All of these samples were submitted for aerobic, anaerobic, and fungal cultures on days 1, 30, and 90 following sterilization. Suppliers also submitted six samples for culture on days 1, 30, and 90 after packaging. All unsterile specimens were positive for a bacillus species, and two also grew coagulase-negative staphylococci. No sterilized specimens had any growth of bacteria or fungi.

The cost of talc varied among suppliers, ranging from $5 to $25.10 per pound. The average price of approximately $9 per pound was used in the cost analysis. Bulk sterilized talc and aerosol unit-dose of 4-g canisters will be available once final FDA approval is obtained. The bulk sterilized talc is expected to have a pharmacy cost of approximately $500 per 40 g, and the aerosol product is expected to cost more for an equivalent amount (personal communication with Bryan Corp, January 30, 1997).

### Talc Slurry vs Talc Poudrage

Talc slurry is a mixture of bulk sterile talc with sterile normal saline; its most common administration volume is 50 mL to 100 mL. The slurry is inserted into the chest tube with a bulb syringe (Table 3). Talc poudrage involves blowing the powder or aerosol with a powder blower through a thoracoscope inserted into the pleural space. Thoracoscopic talc poudrage (TTP) is usually done under general anesthesia in an operating room, but TTP has been done under general anesthesia supplemented by intravenous sedation and narcotic analgesia, therefore not requiring an operating room, the risk of general anesthesia, and the expense of an anesthesiologist. The largest study using local anesthesia for thoracoscopy involved 102 patients. It is wise to perform the thoracoscopic talc poudrage under local anesthesia near an operating room, such as in the recovery room area, in case the procedure must be converted to a thoracotomy or if complications arise that require general anesthesia.

**Table 3.** Guidelines for Using Slurry for Pleurodesis

- **Guideline:** No known allergies or severe asthma (drug injection to TLC).
- **Guideline:** Chest tube placement by chest radiology (chest tube fluid for 48 hours).
- **Guideline:** Administer 0.4 mg of intravenous morphine or equivalent 15 minutes prior to procedure.
- **Guideline:** Administer 0.4 mg of intravenous morphine or equivalent 10 minutes prior to procedure.
- **Guideline:** Doxycycline given in 5-g increments to total 20 g. Total daily dose must be greater than 5 g. 1 g given intrapleurally through a chest tube, flush chest tube with 10 mL of sterile normal saline.
- **Guideline:** Change chest tube for 3 hours and thoracostomy patient to open chest with every 24 hours. Every 24 hours, change chest tube for 24 hours.
- **Guideline:** Monitor for signs of reaction, allergic reactions, pain, fever, and drainage volume.
- **Guideline:** After 3 hours, reinsert the chest tube to maintain drainage and suction.
- **Guideline:** Remove chest tube once drainage is minimal (≤50 mL/24 hrs).

### Adverse Reactions

#### Pain

Pleur al pain is the most common complaint among patients receiving sclerosing agents. Intrapleural lidocaine has been used to alleviate talc-induced pain, and some investigators advocate the use of 2 mg to 4 mg of morphine intravenously in combination with lidocaine. A dose between 3 mg/kg to 4 mg/kg is probably the optimal intrapleur al lidocaine dose. Researchers suggest waiting five minutes following intrapleural lidocaine administration before giving the sclerosing agent.

#### Other Symptoms

Fever is common in patients receiving talc and probably is caused by the inflammatory response produced by intrapleural talc. Other serious adverse reactions include adult respiratory distress syndrome, empyema, pulmonary edema, and respiratory failure. Adult respiratory distress syndrome may be dose-related and may be the result of talc particles reaching the lungs through the bloodstream. Poor administration technique may predispose to localized bleeding, subcutaneous emphysema, or infection at the site of thoracoscopy or thoracotomy. General anesthesia required for talc insufflation increases the risk of morbidity and mortality.

### Efficacy

Data from four studies that were deemed worthy of review by the FDA Oncologic Drugs Advisory Committee are presented in Table 4. A review article analyzed reports of 1,168 patients who were treated with chemical pleurodesis. The agents used included doxycycline, minocycline, tetracycline, bleomycin, cisplatin, doxorubicin, etoposide, fluorouracil, interferon beta, mitomycin C, Corynebacterium parvum, methyprednisolone, and talc. The success rates of the treatment regimens that are currently in use were 54% for bleomycin (15 to 240 units, 199 patients), 72% for doxycycline (500 mg, 60 patients), and 93% for talc (2.5 g to 10 g, 165 patients). In general, a complete remission (CR) was defined as no reaccumulation of fluid at 30 days. Only 10% of patients given a single dose of doxycycline achieved CR, and the majority of the patients required two to four doses to achieve a CR. No studies comparing doxycycline with other agents are available. The efficacy of bleomycin has been compared with that of tetracycline. Ruckdeschel and colleagues conducted a multicenter, prospective, randomized comparison of 74 assessable patients in which 60 units of bleomycin (38 patients) was compared with 1 g of tetracycline (36 patients) given intrapleurally for MPE. Recurrence was defined as pleural fluid reaccumulation greater than baseline, as indicated by chest radiography. The median time to recurrence was longer for bleomycin (46 days) than for tetracycline (32 days) (Table 5).

Fentiman et al and Hamed et al compared the efficacy of talc with either tetracycline or bleo-mycin in prospective, randomized studies for MPE in breast cancer patients. In general, a dose of 5 g or less is used.

### Sterilization Technique

Adult respiratory distress syndrome, with at least one death. In general, a dose of 5 g or less is used.
A nonrandomized study using historic controls compared the efficacy of 39 patients given insufflated intrapleural talc under thoracoscopic guidance against controls that consisted of 85 patients who participated in a randomized study with tube thoracostomy drainage followed by either bleomycin or tetracycline sclerosis (Table 6).7,25 Patients in the talc group were given local anesthesia supplemented by intravenous sedation, and they underwent complete pleural fluid evacuation.25 The pleurodesis was unsuccessful in two patients in the talc group, both of whom had bronchial obstruction that prevented lung re-expansion. Since the study did not randomize the patients to all three agents, the only conclusion from this study is that talc is safe and efficacious in the control of MPE. Also note in Table 6 that at day 30, only 55 of the 85 patients were "evaluable," while at day 90, more patients (73 of the original 85) were "evaluable."

Current Studies

Talc is a sclerosing agent that is now more widely available for the treatment of MPE, but its efficacy, tolerance, toxicity, and cost effectiveness remain to be determined. A phase III randomized study for patients with unilateral MPE is underway by the Cancer and Leukemia Group B (CLB-9334) that compares talc slurry (4 g to 5 g given via a chest tube) with thoracoscopic talc insufflation (4 g to 5 g). Factors being considered include efficacy, costs, time to effusion recurrence, duration of chest-tube drainage following sclerosis, extent of complications and toxicities following instillation, quality of life, and pain management. In this study, the talc slurry arm entails the following procedure: (1) A chest tube is inserted, and the pleural fluid is drained for 24 hours. (2) The lung is re-expanded to greater than or equal to 90%. (3) Within 24 to 36 hours, the patient undergoes sclerosis with 4 g to 5 g of talc in 100 mL normal saline given via the chest tube. The patient is rotated in various positions for 30 minutes each, and after two hours, the chest tube is unclamped and suction reattached. (4) The chest tube is discontinued once drainage is less than or equal to 150 mL/24 hrs. The management for the insufflated talc arm is as follows: (1) With the patient under general anesthesia, the chest is explored by a thoracoscope. (2) The lung is re-expanded to greater than or equal to 90%. (3) The chest is insufflated with 4 g to 5 g of dry talc with complete dispersion throughout the hemithorax. (4) A chest tube is placed for fluid drainage. (5) When the chest tube drainage is less than or equal to 150 mL/24 hrs, the tube is removed.

Another large, prospective, randomized trial35 (a collaborative study by Eastern Cooperative Oncology Group, Radiation Therapy Oncology Group, and Cancer and Leukemia Group B) will compare bleomycin, talc, and doxycycline for MPE with respect to time to effusion recurrence, necessity for further treatment of recurrent effusions, extent of postinstillation complications, duration of hospitalization following pleurodesis, duration of hospitalization for retreatment of MPE at time of recurrence, and survival. The treatment procedure is planned as follows: (1) A chest tube is placed and followed either with sclerosis once drainage reaches less than 250 mL/24 hours or with tube drainage for five days, whichever comes first. (2) The lung must be re-expanded. (3) Premedication with morphine and lidocaine is followed by 100 mL total volume with normal saline diluent of one of the following: 1 g of doxycycline, 60 units of bleomycin, or 5 g of talc suspension injected into the chest tube. (4) The patient is rotated in six different positions for 10 minutes per position. (5) Pain control is assessed. (6) The chest tube is continued until drainage reaches less than 250 mL/24 hrs. If drainage is more than 250 mL/24 hrs for 72 hours after the initial sclerosis, a second sclerosis is repeated; if drainage is more than 250 mL/24 hrs for 72 hours after the second sclerosis, the patient will be removed from the protocol. The patient will be followed monthly for +/−7 days thereafter for evidence of recurrence. The goal of this study is to determine the most efficacious, cost-effective sclerosing agent.

Conclusions

Control of MPE is often difficult. The increased availability of talc provides another weapon in the therapeutic armamentarium for this complication, but the results of well-performed comparative trials are required to determine its toxicity profile and effectiveness in comparison with bleomycin and doxycycline. Induction of adult respiratory distress syndrome is a particular concern.

References