Safety And Efficacy Of Mitoxantrone In The Palliative Treatment Of Malignant Pleural Effusions Due To Breast Cancer

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Citation

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Abstract

The purpose of this study was to assess the efficacy and safety of mitoxantrone in the palliative treatment of pleural effusions due to breast cancer.
114 patients with a known breast malignancy and recurrent symptomatic pleural effusion referred for chest tube drainage and sclerotherapy were studied. They had received no prior intrapleural therapy and had a predicted survival of >1 month. Survival, complications and response to pleurodesis according to radiographic criteria were recorded. The data are expressed as the mean +/- SEM and the median.
The mean age of the entire group was 53,5 +/- 2,1 years. The mean volume of effusion drained was 1020 +/- 125 ml and the chest tube was removed within 5 days in 82% of patients. There were no deaths related to the procedure. Side effects of chemical pleurodesis included mainly fever, chest pain, nausea and vomiting. At 30 days 64 patients (56,3%) had a complete response (CR) and 30 patients (26,3%) partial response (PR) to pleurodesis (overall response: 82,6%). At 60 days the overall response was 78,5% (CR:53,5%, PR: 25%). The mean survival of the entire population was 15,6 +/- 2 months. Mitoxantrone is effective in the treatment of malignant pleural effusion due to breast carcinoma without causing significant local or systemic toxicity.

INTRODUCTION

The discovery of malignant cells in pleural fluid and parietal pleura signifies disseminated or advanced disease and a reduced life expectancy in cancer patients. Median survival following diagnosis ranges from 3 to 12 months and is dependent on the stage and type of underlying malignancy. The shortest survival time is observed in malignant effusions secondary to lung cancer and the longest in ovarian cancer, while malignant effusions due to an unknown primary have an intermediate survival time [1]. Currently, lung cancer is the most common metastatic tumor to the pleura in men and breast cancer in women. Together, both malignancies account for approximately 50-65% of all malignant effusions [2].

About 7 to 11% of patients with breast carcinoma develop a malignant pleural effusion during the course of the disease [3]. In 43% of those patients, the effusion is the first symptom of metastatic disease [4].

The general approach to managing malignant effusions is determined by symptoms, performance status of the patient, expected survival and response of the known primary tumor to systemic treatment. Intervention options range from observation in the case of asymptomatic effusions through simple thoracentesis to more invasive methods such as thoracoscopy, pleuroperitoneal shunting and pleurectomy. In a patient with reasonable survival expectancy and good performance status, every attempt should be made to prevent recurrence of the effusion. Intercostal tube drainage with instillation of a sclerosing agent, resulting in the obliteration of pleural space, is the most widely used method to control recurrent symptomatic malignant effusions.

Aim of this trial was to study 114 patients with breast cancer who had a pleural effusion as a direct consequence of metastatic disease and to assess the efficacy of mitoxantrone as a sclerosing agent.

METHODS

Over a 5-year period (1999-2003), all patients with a known breast malignancy and recurrent symptomatic malignant

pleural effusion referred to our department for drainage and sclerotherapy, were eligible to participate in this study.

The diagnosis of pleural carcinomatosis was established by positive pleural fluid cytology on thoracentesis or positive pleural biopsy. There should be evidence of reexpansion of the lung after the drainage without evidence of bronchial obstruction or fibrotic trapped lung. Eligibility also required that the patients had received no prior intrapleural therapy and had a predicted survival of >1 month. Patients were ineligible if they had a history of obstructive jaundice or surgery within the previous month. No patient had systemic chemotherapy a immediately prior to or during the first 30-day interval following sclerotherapy. One hundred and fourteen (114) patients fulfilled all the above eligibility criteria.

This study was approved by the Theagenion Cancer Research Ethics Committee and patients were included after giving their written informed consent.

A chest tube (28-32F) was inserted into the midaxillary line through the 5 th or 6 th intercostal space under local anesthesia and in some case additional iv benzodiazepines and/or narcotics. The pleural effusion was drained to dryness initially by gravity and followed if necessary by suction from a wall-mounted suction pump using a pressure of 20 cm H2O usually for 12-24 hours to achieve complete drainage of the effusion and lung reexpansion. Daily tube outputs were recorded and when drainage fell below 100 ml in a 24-h period, posteroanterior and lateral chest radiographs were obtained to assure that the fluid had been sufficiently evacuated, there were no loculated collections and the lung had fully reexpanded. Then the patients were eligible for pleurodesis.

Fifty ml of normal saline solution containing 2 mg/kg lidocaine were infused through the chest tube. After 15 minutes, a pleurodesis solution containing a mixture of 40 mg mitoxantrone and 20 ml normal saline was infused into the pleural cavity, after which the tube was clamped for 2 hours, while the patients changed position (rotated 90 ^{o}) every 15 minutes.

The tube then was reopened. If the post-sclerotherapy drainage was <100 ml per day, the tube was then removed. Complications related to the procedure were recorded. Post-sclerotherapy posteroanterior and lateral chest radiographs were obtained immediately after tube removal in order to be compared with others obtained 30 and 60 days later.

The radiographic response was determined on posteroanterior and lateral chest radiographs by observing the level of fluid meniscus overlying the costophrenic or vertebrophrenic angles and was determined as follows: complete response (CR): no reaccumulation of pleural fluid; partial response (PR): reaccumulation of fluid above the post-sclerotherapy level but below the original level; progressive disease (PD): reaccumulation to or above the original level.

Survival was calculated from the day of diagnosis of pleural effusion to the day of death or to the last day of follow up if alive.

The data are expressed as the mean +/- SEM and the median.

RESULTS

One hundred and fourteen women were included in this study. The mean age of the entire group was 53,5 +/- 2,1 years. Forty-four of the patients (38,5%) were premenopausal at the time of diagnosis of breast cancer and 70 (61,5%) were postmenopausal.

All patients who were included in the study had a tube thoracostomy procedure and a subsequent intrapleural administration of mitoxantrone in order to achieve pleurodesis. The mean volume of effusion drained was 1020 +/- 125 ml (range: 350-1450 ml). Chest tube was removed within 5 days in 82% of patients (range: 2-10 days).

There were no deaths attributable to the thoracostomy procedure. Two patients experienced vasovagal reflex during the procedure with systemic hypotension and intense pleuritic pain. Hypotension was treated with intravenous fluids and the pain was controlled with narcotics. These episodes lasted 30 and 45 minutes respectively. The two patients recovered without incident.

The most frequently reported complications related to pleurodesis were fever, chest pain, nausea and vomiting (Table 1).

Figure 1

Table 1

Complications	Number of patients	
None	70/114	(61,4%)
Fever	28/114	(24,5%)
Chest pain	25/114	(21,9%)
Nausea	22/114	(19,2%)
Vomiting	10/114	(8,7%)
Diarrhea	5/114	(4,3%)
Alopecia	3/114	(2,6%)
Skin rash	1/114	(0,8%)
Dyspnea	1/114	(0,8%)
Myelosuppression	1/114	(0,8%)
Subcutaneous emphysema	1/114	(0,8%)
Abscess at the drain site	1/114	(0,8%)

Legend: Complications related to chemical pleurodesis with mitoxantrone.

Four patients died within one month of pleurodesis due to rapid progression of metastatic disease. At 30 days, 110 patients were alive and 64 out of them (56,3%) had a complete response and 30 (26,3%) had a partial response. The overall response to chemical pleurodesis with mitoxantrone was 82,6%. Twenty patients (17,4%) had progressive disease and revealed reaccumulation of fluid to or above the original level. At 60 days the overall response was 78,5% (CR:53,5% and PR:25%). Follow up ranged from 14 days to 48 months with a mean of 14 +/- 1,45 months. The mean survival of the entire study population was 15,6 +/- 2 months (median:13,7 months).

DISCUSSION

Pleurodesis from the Greek words pleura and desis (binding together) is intended to achieve a symphysis between parietal and viscera pleura, in order to prevent accumulation of either air or fluid in the pleural space [5].

Management of malignant pleural effusions depends on the underlying malignancy, extent of disease, potential effectiveness of treatment and performance status. In patients with lymphoma, small cell lung cancer or germ cell neoplasms, pleural effusions may be con trolled initially by systemic therapy alone. In patients with metastatic breast or non-small cell lung carcinoma, local palliative therapy is often required. Since malignant effusions are frequently a preterminal event with a 30-day mortality rate of 29 to 50% [6,7], treatment is directed toward symptomatic relief with minimal discomfort, incovenience and cost.

Local treatment options include repeated thoracenteses, chest tube drainage with sclerotherapy, pleuroperitoneal shunt or pleurectomy. Repeated thoracentesis is usually a temporizing measure and carries the risk for pneumothorax and pleural infection [8]. Inpatient drainage with large-bore tubes 28-35 F) is effective, with variable 30-day success rates reported between 55% and 95% [9]. For this reason, large-bore tube thoracostomy with sclerotherapy has become the most common palliative treatment for malignant effusions. Tube thoracostomy however, requires hospitalization, is expensive, uncomfortable and has associated complications including empyema.

Numerous sclerosing agents have been used to treat malignant pleural effusions. Until recently, tetracycline was the most commonly used sclerosing agent with response rates ranging from 25 to 100% [10,11]. Because the iv form of tetracycline is no longer available, doxycycline has been proposed as an alternative.

Bleomycin has been studied extensively as a sclerosing agent [12,13]. Intrapleural instillation is usually well tolerated but a few patients may report mild fever or transient nausea. Pleuritic pain and rigors are rarely reported side effects. This relative lack of systemic toxicity is likely due to limited absorption of bleomycin (approximately 40%) of the pleural cavity [14]. At 30 days bleomycin has been reported to be superior to tetracycline [15].

Talc has proved to be one of the most effective sclerosing agents for treating malignant pleural effusions. It has not gained universal acceptance because of its complications. Talc causes severe pleuritis resulting in effective pleurodesis but can worsen dyspnea and can result in respiratory failure [16]. Other complications associated with talc pleurodesis include fever, acute pneumonitis, granulomatous pneumonitis and empyema [17]. Talc is instilled either as a slurry via chest tube or insufflated via thoracoscope.

Many other chemotherapeutic agents such as doxorubicin, cisplatin and cytarabine combination, etoposide, fluorouracil and mitomycin have been used for sclerotherapy. In addition radioactive isotopes, corynebacterium parvum, interferon and recombinant interleukin-2 have been instilled in the pleural space for treatment of malignant pleural disease. Response rate have been variable and less than optimal. Side effects are not inconsequential and thus none of these agents have gained widespread use [18].

Mitoxantrone, an anthracycline derivative has been demonstrated to be effective in the treatment of peritoneal and pleural effusion. Mitoxantrone with its high molecular weight and high polarity exhibits a decreased pleural

clearance with prolonged high peak concentrations intrapleurally, favorable factors for local intrapleural treatment. The mechanism of intrapleural action of mitoxantrone has not yet been established. Both the inflammatory and antineoplastic activity of mitoxantrone intrapleurally have been described [19,20]. There are enough data about the efficacy of mitoxantrone in the trteatment of malignant pleural effusions. In a prospective study in 18 patients, Musch et al [21] reported a 30-day success rate of 75%. A comparative study including bleomycin and mitoxantrone showed almost an equal 30-day response of 64% and 67% respectively [22]. Van Belle et al [23] had an overall 30-day response of successful pleurodesis of 91% in patients with breast cancer. Morales et al [24] treated a group of 21 patients with malignant pleural effusions, with instillation of mitoxantrone with a 100% response and no toxic effects.

There is only one study which proved mitoxantrone ineffective. Groth et al [25] presented a prospective randomized trial on the treatment of malignant pleural effusions with intrapleural mitoxantrone versus placebo (pleural tube alone with instillation of isotonic NaCl). Their data suggest no statistically significant difference between the two arms with respect to response and response duration.

Our study confirmed the majority of previous reports that mitoxantrone is an effective agent in controlling recurrent malignant pleural effusions. The overall 30-day response rate was 82,6%. The procedure was well tolerated and side effects were mild and rare.

To develop new treatment plans for the management of pleural effusions, one must consider several requirements. First, no treatment regimen should exacerbate patients' symptoms, since palliation is the main aim. Second, seriously ill patients should not be subjected to procedures associated with high mortality and morbidity. Third, since about half the patients with pleural effusion will have no other clinically apparent metastases, treatment should be local rather than systemic. To be successful, the local treatment has to be effective and given at the first sign of the effusion, because inadequate or delayed treatment may eliminate the possibility of any subsequent therapy being effective, by producing loculation of the effusion.

CONCLUSIONS

Pleural effusions can have a significant impact on the quality of life in patients with end-stage malignancy. Breast cancer is very often related to malignant pleural effusions during its course. Chemical pleurodesis via bedside thoracostomy has been shown to be effective and has become a common therapeutic approach. Using this approach we found mitoxantrone to be highly effective at controlling malignant pleural effusions and decreasing the associated symptoms of dyspnea and pain. Our data justify further studies in a controlled setting to elucidate the biological action and prognostic relevance of mitoxantrone in the treatment of malignant pleural effusions and to compare this agent with others.

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