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Research

Results of chemical pleurodesis with mitoxantrone in malignant pleural effusion from breast cancer

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Abstract

Background: Carcinoma of the breast is the second leading cause of malignant pleural effusions. This study reports on the efficacy of mitoxantrone as a sclerosing agent in patients with breast cancer who had a pleural effusion as a direct consequence of metastatic disease.

Patients and methods: Over a 5-year period, 114 patients with a known breast malignancy and having recurrent symptomatic pleural effusion referred for chest tube drainage and sclerotherapy were considered eligible. They had received no prior intrapleural therapy and had a predicted survival of >1 month. All of them underwent pleural drainage and chemical pleurodesis with mitoxantrone. Survival, complications and response to pleurodesis according to clinical and radiographic criteria were recorded. The data are expressed as the mean ± standard error of the mean (SEM) and the median. The χ^2 test was used for statistical analysis. To assess the prognostic value of Karnofsky's performance status score a Cox proportional hazards model was used.

Results: The mean age of the patients was 53.5 ± 2.1 years. Effusion occurred after 38.2 ± 6.2 months (range: 1–229 months) after the diagnosis. Ipsilateral effusion was seen in 73%, contralateral in 20% and bilateral in 7%. Forty patients (35%) had pleural effusion as the first evidence of recurrence. The mean volume of effusion drained was 1020 ± 125 ml and the chest tube was removed within 5 days in 82% of patients. 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 was 15.6 ± 2 months. Karnofsky's performance status score was found to be a statistically significant predictor. Patients with Karnofsky's performance status score >70 had a median survival of 513 days, as opposed to a median survival of only 63 days for patients with a Karnofsky's performance status score <30.

Conclusions: Mitoxantrone is effective in the treatment of malignant pleural effusion due to breast carcinoma with relatively low local or systemic toxicity. Karnofsky's performance status score at the time of pleurodesis is predictive of survival.

Background

The discovery of malignant cells in pleural fluid and parietal pleura signifies disseminated or advanced disease and reduced life expectancy in cancer patients. Median survival following diagnosis ranges from 3 to 12 months and depends mainly on the stage of the disease 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 these patients, pleural 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 case of asymptomatic effusions through simple thoracentesis to more invasive methods such as thoracoscopy, pleuroperitoneal shunting and pleurectomy. In patients 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 obliteration of pleural space, is the most widely used method to control recurrent symptomatic malignant effusions.

The aim of this study was to evaluate the efficacy of mitoxantrone as a sclerosing agent in patients with pleural effusion as a direct consequence of metastatic breast cancer.

Patients and methods

Patients with a known breast malignancy and recurrent symptomatic malignant pleural effusion referred to our department for drainage and sclerotherapy between 1999 and2003 were recruited for this study.

The diagnosis of pleural carcinomatosis was established by positive pleural fluid cytology on thoracentesis or positive pleural biopsy. Other eligibility criteria included evidence of expansion of the lung after fluid drainage and absence of bronchial obstruction and or fibrosis preventing lung expansion. 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 immediately prior to or during the first 30-day interval following sclerotherapy. This study was approved by the Theagenion Cancer Research Ethics Committee and patients were included after obtaining written informed consent.

Pretreatment assessment was performed during admission and included detailed history and physical examination, full blood count, liver biochemistry, electrocardiogram, a pre-drainage base line posteroanterior and lateral chest radiograph and other imaging as clinically indicated. The patients were assigned a Karnofsky's performance status (KPS) score based on the results of history and physical examination [5,6]. The KPS score is a reliable and validated quality of life measure, consisting of a 10-point incremental scale from 0 to 100, where lower score implies poor level of independent functioning [5].

A chest tube (28–32 F) was inserted into the midaxillary line through the 5^{th} or 6^{th} intercostal space under local anesthesia and in some case additional intravenous 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 H_2O usually for 12–24 hours to achieve complete drainage of the effusion and lung expansion. 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 expanded. Thereafter the pleurodesis was carried out.

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°) every 15 minutes.

The tube then was reopened. The tube was removed if post-sclerotherapy drainage was <100 ml per day. 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 without

Table 1: TNM stage at the time of diagnosis in breast cancer patients who developed malignant pleural effusions

Stage (TNM)	Number (%) of patients (n = 114)
I	7 (6.1%)
IIA	27 (23.6%)
IIB	34 (29.8%)
IIIA	22 (19.2%)
IIIB	17 (14.9%)
IV	7(6.1%)

symptoms or not requiring repeat drainage above the post-sclerotherapy level but below the original level; and progressive disease (PD) reaccumulation to or above the original level with symptoms and requiring repeat drainage.

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 (standard error of the mean) and the median. The χ^2 test was used for statistical analysis. To assess the prognostic value of KPS score a Cox proportional hazards model was used. To facilitate interpretation of the resultant hazard ratios, KPS score as a predictor variable was rescaled so that 1-u change in hazard ratio corresponded to a 10-point change in KPS score. All analyses were performed using appropriate software (STATA® version 6.0, StataCorp LP, Texas, USA).

Results

A total of 114 women were included in this study. The mean age 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.

The interval between diagnosis of breast cancer and the development of a subsequent pleural effusion ranged from 1 month to 229 months (38.2 ± 6.2 months). One patient developed malignant pleural effusion 19 years after radical mastectomy. Sixty-eight patients (59.5%) had an estrogen receptor positive tumor. Concerning laterality, 73% of these effusions were ipsilateral, 20% contralateral and 7% bilateral.

Histology of the primary tumor was ductal carcinoma in 88 patients (77.1%), lobular carcinoms in 16 patients (14%), undifferentiated carcinoma in 6 (5.2%) and Paget's disease in 4 patients (3.7%). The TNM stage of primary tumor at the time of diagnosis of breast cancer is shown in table 1. There was an increased proportion of stages II and III.

Forty patients (35%) had pleural effusion as the first manifestation of recurrent disease, whereas 74 patients (65%) were already diagnosed as having local or distant spread before the onset of pleural effusion. These 74 patients with preexisting metastases showed a variable pattern of secondary spread. Twenty nine patients had localized breast or chest wall recurrence, 22 had bone metastases, 8 had synchronous bone, pulmonary and hepatic metastases, 6 had synchronous bone and pulmonary metastases, 3 had pulmonary metastases only, 1 had hepatic metastases only and 1 had disease in contralateral breast.

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 2).

Four patients died within one month of pleurodesis due to rapid progression of metastatic disease. At 30 days, 110 patients were alive and 64 of these (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%).

There was no statistical significant difference in overall response at 30 days between patients with estrogen receptor positive and negative tumors (54/68 patients – 79.4% versus 40/46 patients – 86.9% respectively, χ^2 test p = 0.29). There was also no statistical significant difference in overall response at 30 days between patients

Table 2: Complications related to chemical pleurodesis with mitoxantrone

Complications	Number (%) of patients (n:114)
None	70 (61.4%)
Fever	28 (24.5%)
Chest pain	25 (21.9%)
Nausea	22 (19.2%)
Vomiting	10 (8.7%)
Diarrhea	5 (4.3%)
Alopecia	3 (2.6%)
Skin Rash	1 (0.8%)
Dyspnea	1 (0.8%)
Myelosuppression	1 (0.8%)
Subcutaneous emphysema	1 (0.8%)
Abscess at drain site	1 (0.8%)

Table 3: Relationship between Karnofsky's performance status (KPS) score and survival estimate

KPS score quartile	Median survival (in months)
10–30	2.1
40–50	4.5
60	6.7
70–90	17.1

(Hazard ratio: 0.79; 95% Confidence Interval: 0.62–0.85, p value < 0.0001)

whose effusion was the first manifestation of recurrent disease and those who already had local or distant metastases (30/40 (75%) patients – versus 64/74 (86.4%) patients – respectively, χ^2 test p = 0.12).

Follow-up ranged from 14 days to 48 months with a mean of 14 ± 1.5 months. The mean survival was 15.6 ± 2 months (median:13.7 months). KPS score was a predictor concerning survival achieving statistical significance. The patients who at minimum could not work, but were able to care themselves and live at home (KPS score >70) had a median survival of 17.1 months. Conversely the patients whose general health had deteriorated to the point where hospitalization was indicated (KPS score <30), had a median survival of only 2.1 months (Cox test, p < 0.0001) (Table 3).

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 [7]. In patients with lymphoma, small cell lung cancer or germ cell neoplasms, pleural effusions may be controlled initially by systemic therapy alone. Since malignant effusions are frequently a preterminal event with a 30-day mortality rate of 29 to 50% [8,9], treatment is directed toward symptomatic relief with minimal discomfort, inconvenience and cost.

In patients with metastatic breast or non-small cell lung carcinoma (NSCLC), local palliative therapy is often required. Local treatment options include repeated thoracenteses, chest tube drainage with sclerotherapy, pleuroperitoneal shunt or pleurectomy. Repeated thoracentesis is usually a temporary measure and carries the risk for pneumothorax and pleural infection [10]. Inpatient drainage with large-bore tubes (28–36 F) is effective, with variable 30-day success rates reported between 55% and 95% [11]. For this reason, large-bore tube thoracostomy with sclerotherapy has become the most common palliative treatment for malignant effusions. It has to be mentioned that recent studies have shown that small drainage catheters (10 to 14 F) are as effective as large bore chest tubes in the treatment of malignant effusions [12]. Using imaging guidance, small tubes can be placed into loculated collections, are well tolerated and have less complication rates than the larger tubes [13].

Table 4: Survival of patients with breast carcinoma after the onset of pleural effusion.

Reference	Number of patients	Survival
Konikov et al [18]	37	mean 6.1 months
Anderson et al [19]	35	mean 9.5 months
Rosato et al [20]	50	mean 19 months (dead) mean 54 months (alive)
Martini et al [21]	33	median 14 months
Chernow et al [22]	13	mean 7.3 months
Fentiman et al [23]	105	mean 15.7 months
Raju et al [24]	122	mean 9.7 months
Saisho et al [25]	21	42.5% at 1 year 16.5% at 2 years
Present study	114	mean 15.6 ± 2 months median 13.7 months

Pleural effusion due to metastatic breast carcinoma is a frequent phenomenon. Besides the rare direct invasion through the chest wall, the pathogenesis of pleural involvement in breast carcinoma is through either lymphatic (internal mammary artery lymph node chain) or hematogenous spread. As shown in our study pleural effusion can occur as early as 1 month or as late as 19 years with a median interval of 27 months. Rojato et al [14], Raju et al [15], and Fentiman et al [16] have shown a median lag time of 24, 22 and 41.5 months respectively. When effusion occurs within 1 month of diagnosis of breast cancer, one is probably dealing with stage IV disease and clinical experience has proved that these patients have an generally poor prognosis.

Our study also confirms previous reports that TNM stages II and III at the time of diagnosis are related to consequent pleural effusion and pleural effusions most commonly occur on the same side as the primary breast carcinoma [4,13]. Fentiman and colleagues found in 99 patients with unilateral breast tumors and pleural effusions, of these 50% of the effusions were ipsilateral, 40% contralateral and 10% bilateral [16]. Raju and Kardinal observed ipsilateral effusions in 85 of 122 patients [15].

All the available data on the survival of patients with breast carcinoma after the onset of pleural effusion is shown in table 4. In all of the studies, except for the study reported by Rojato et al [14], the mean or median survival after the onset of pleural effusion ranges from 6 to 15 months, indicating a poor prognosis for this group of patients.

Our results also demonstrate that KPS scores are a predictor that achieved statistical significance. Low score at the time of pleurodesis is related to poor survival. These findings are in accord with other authors [23-25].

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% [26,27]. Because the intravenous form of tetracycline is no longer available, doxycycline has been proposed as an alternative.

Bleomycin has been studied extensively as a sclerosing agent [28,29]. Intrapleural instillation is usually well tolerated but a few patients may report mild fever or transient nausea. Pleuritc pain and rigors are rarely reported side effects. This relative lack of systemic toxicity is likely due to limited absorption of bleomycin (approximately 40%) from the pleural cavity [30]. At 30 days bleomycin has been reported to be superior to tetracycline [31].

Talc has proved to be one of the most effective sclerosing agents for treating malignant pleural effusions. Talc causes severe pleuritis resulting in effective pleurodesis but can worsen dyspnea and can result in respiratory failure [32]. Other complications associated with talc pleurodesis include fever, acute pneumonitis, granulomatous pneumonitis and empyema [33]. 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 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 [34].

Mitoxantrone is a synthetic anthracenedione that has demonstrated activity against metastatic breast cancer in previous studies [35,36]. In addition to our previous pos-

itive experience with mitoxantrone in the treatment of malignant pleural effusions, this was the main reason for us to choose this agent, despite the fact that it is more expensive than others. From a pharmacological point of view, mitoxantrone may be an especially appropriate choice due to its higher molecular weight and polarity since this may be an important factor in prolonging contact with the pleura. The mechanism of intrapleural action of mitoxantrone has not yet been established. Both the inflammatory and antineoplastic activity of mitoxantrone have been described [37,38].

Similar to the present study, in an earlier prospective study Musch et al [39] 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 [40]. Van Belle et al [41] had an overall 30-day response of successful pleurodesis of 91% in patients with breast cancer. Morales et al [42] treated a group of 21 patients with malignant pleural effusions, with instillation of mitoxantrone with a 100% response and no toxic effects. Only one study showed mitoxantrone to be ineffective [43]. Our study confirmed the majority of previous reports that mitoxantrone is an effective agent in controlling recurrent malignant pleural effusions. 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.

Competing interests

None declared.

Authors' contributions

NB conceived the study and performed the statistical analysis. TA participated in the design of the study. CT conceived of the study and participated in its coordination. All authors read and approved the final manuscript.

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