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A Randomised Prospective Trial of Surgical Against Medical Tetracycline Pleurodesis in the Management of Malignant Pleural Effusions Secondary to Breast Cancer

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Malignant pleural effusion is a frequent complication of metastatic breast cancer leading to a significant degree of morbidity. Drainage of the effusion by thoracocentesis and pleurodesis with tetracycline as the sclerosing agent is an established means of symptomatic relief in these patients. To determine whether the efficacy of tetracycline pleurodesis is improved by surgical rather than medical drainage and instillation of sclerosant, 34 patients were prospectively randomised to a trial comparing the two treatment modalities, of whom 29 were evaluable for response. The total failure rate of primary pleurodesis was 13.4%, the rate of recurrence of effusion within the first month was 24%, and only 1 patient (3.4%) required repeat aspiration in that time period. There was no significant difference in the rate of recurrence or reaspiration of effusion between the two treatment groups. Although the overall survival time from treatment of effusion is significantly longer in the surgical treatment group than in the medical treatment group ($P = 0.03$), this is likely to be due to factors other than the method of treating the effusion. We conclude that surgical tetracycline pleurodesis has no advantage over medical tetracycline pleurodesis.
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INTRODUCTION

ALMOST HALF of all patients with systemic breast cancer will develop pleural effusions at some time [1]. Although the prognosis of patients with malignant effusions is generally poor, with a reported 30-day mortality of 29 to 54% [2, 3], many patients, particularly those with breast cancer, have prolonged survival [1], and the control of symptoms due to the effusions is consequently an important aspect of their management.

Although thoracocentesis is generally an effective method for immediate relief of symptoms, thoracocentesis alone is an ineffective means of preventing recurrence of malignant pleural effusion. Anderson *et al.* [4] used thoracocentesis alone on 94 occasions and found that the mean time for the effusion to recur was 4.2 days, with the majority recurring in 1–3 days. By 1 month, 97% of the effusions had recurred. Two other studies reported 100% recurrence [5, 6]. In addition, performing repeated thoracocentesis increases the risk of complications such as pneumothorax and empyema.

Although tube drainage alone has been suggested to be an effective therapy [5], neither response criteria nor time to recurrence were reported. Instead duration of hospital stay was the criterion for assessing effectiveness. Subsequent studies have not supported the view that tube drainage alone is an effective means of controlling malignant pleural effusions [4, 7, 8]. However, the advantage of tube drainage is that it allows a better approximation of the opposed pleural surfaces when a sclerosing agent is introduced than when the agent is introduced by thoracocentesis. Indeed, pleurodesis as a result of instilling sclerosing agent is the treatment of choice of malignant pleural effusions [9]. It has been suggested that tetracycline is the agent of choice in introducing pleurodesis [9, 10]. Several prospective studies have estimated the efficacy of tetracycline pleurodesis to be between 70 and 100% [11–15], although there were significant differences among these studies in the criteria for a successful pleurodesis, as well as in patient selection and in the technique of the procedure. A retrospective study concluded that a minimum of 1 g of tetracycline should be used with adequate thoracostomy tube drainage to ensure the best possible results [2]. Although a study comparing intracavitary talc and intracavitary tetracycline for the control of pleural effusions secondary to breast cancer concluded that talc was superior to tetracycline in preventing recurrence of pleural effusion [16], the talc was inserted at the time of surgical drainage but the tetracycline was inserted some 16–24 h later, following radiological confirmation of lung re-expansion. In order to determine if insertion of tetracycline at the time of surgical drainage is superior to insertion following medical drainage (i.e. intercostal drain inserted under local anaesthesia), a randomised prospective study was performed to compare the two techniques of pleurodesis and to compare the rates of recurrent effusions and repeat aspirations for symptom control in the two groups of patients.

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PATIENTS AND METHODS

Patients

The patients who entered the trial were all attending the Combined Breast Clinic at St George's Hospital, London, U.K. Patients with cytologically proven malignant pleural effusions and histological or cytological evidence of metastatic breast cancer were randomised to receive either surgical treatment or medical treatment. Any patients who were unsuitable for general anaesthetic, were over 75 years of age, who had severe non-metastatic lung disease or who had evidence of life-threatening metastatic disease at other sites were excluded.

Procedures

Medical treatment. Medical pleurodesis was performed by insertion of an intercostal cannula into the mid-axillary line at the 7th–8th intercostal space under local anaesthesia. Fluid was aspirated at a rate no greater than 1 l every 6 h. Complete drainage was confirmed radiologically, followed by insertion of 500 mg tetracycline in 100 ml normal saline and postural alteration performed for 1 h. The drain was removed 24 h later.

Surgical drainage. Surgical treatment was performed under general anaesthesia. In all cases bronchoscopy was performed. At thoracoscopy the fluid was removed, the surfaces of the pleura inspected and 500 mg tetracycline inserted in 100 ml of normal saline. Postural alteration was performed for 1 h and the drain removed at 24 h.

In all cases, repeat chest X-ray was performed 4 weeks following the procedure, and subsequently at regular intervals, the exact length of interval depending on the symptoms and clinical status of the patient. Repeat aspiration was performed if symptomatically necessary.

RESULTS

A total of 34 patients were randomised into the study, including 1 patient who developed effusions in both the right and left pleural space on separate occasions and who was randomised separately into the study on both occasions. 17 patients were randomised to receive surgical management, and 17 to receive medical management. 29 of the 34 patients were evaluable for response. 5 were excluded for the following reasons: 1 patient was randomised to surgical treatment but did not receive it, 1 patient was randomised to medical treatment but died before this was performed, in 1 patient the drain fell out after aspiration but before pleurodesis (medical treatment group), 1 patient who did not have a pleural effusion was randomised in error (to medical treatment) and 1 patient's records could not be traced.

14 patients treated by medical pleurodesis and 15 patients treated by surgical pleurodesis were assessable for response. In the medical treatment group, the mean age at diagnosis of effusion was 59 years (range 34–77), in the surgical treatment group the mean age was 54.4 years (range 41–69), and there was no significant difference between the age of presentation of effusion in the two groups (Mann–Whitney test). 13 of the effusions occurred in the right pleural space (6 medical-treatment patients, 7 surgical-treatment patients) and 16 in the left pleural space (8 patients in each of the two treatment groups). In 6 out of 14 patients in the medical treatment group, pleural effusion was the first relapse after primary treatment, compared with 9 out of 15 patients in the surgical treatment group (not significantly different, χ^2 test with Yates' correction). Pleural effusion was present for less than 1 month at the time of pleurodesis in all patients except 3 (of 14) in the medical group, and 3 (of 15) in the surgical group. Of these 3 patients in the medical group, effusion was present for 2 months, 9 months and intermittently for 3 years in 1 patient (effusion treated by systemic therapy) before pleurodesis; of the 3 patients in the surgical group, effusion was present for 2 months (2 patients) and intermittently for 2 years (1 patient treated with systemic therapy) before pleurodesis. Only 1 patient in the surgical group had undergone previous aspiration of effusion (with concurrent systemic therapy). However, 4 patients from the medical group had undergone previous aspiration of effusion: 2 treated by aspiration alone, 1 by drainage and bleomycin pleurodesis and 1 by aspiration of effusion and concurrent systemic therapy. The patients in the medical treatment group tended to have more widespread disease at the time of presentation of the effusion (39 disease sites in 14 patients) than those in the surgical treatment group (31 sites in 15 patients, Table 1). In addition, the patients in the medical treatment group were generally more heavily pre-treated (Table 2), but not significantly so.

In 3 patients treated by surgical pleurodesis and in 1 patient treated by medical pleurodesis, there was failure of primary treatment of the effusion, that is there was a residual effusion

Table 1. Number of sites of disease at treatment of effusion in the two treatment groups, and the site of metastases

	Medical group	Surgical group
No. of disease sites		
1	3	6
2	3	3
3	5	5
4	1	1
5	1	0
6	1	0
Site of metastases		
Bone	6	8
Liver	2	0
Brain	1	0
Skin/soft tissue/local	7	6
Lung	3	2
Lymph nodes	3	1
Other	3	0

Table 2. Type and number of previous treatments for systemic disease at the time of treatment of the effusion in the two treatment groups

Previous treatment	Medical group	Surgical group
Radiotherapy		
×1	2	2
Chemotherapy		
×1	3	0
×2	0	0
×3	0	0
Endocrine therapy		
×1	6	5
×2	4	3
×3	2	1

Table 3. Results of medical and surgical tetracycline pleurodesis

Response assessment	Medical	Surgical
Failure of primary pleurodesis	1	3
Recurrent effusion (<1 month)	5	2
Re-aspiration effusion (<1 month)	1	0
Recurrent effusion (after 1 month)	3	4
Re-aspiration (after 1 month)	4	2

after pleurodesis, corresponding to a failure rate of 13.8%. On assessment 1 month after pleurodesis, 5 (of 14) patients from the medical treatment group had a recurrent effusion compared with 2 (of 15) patients from the surgical treatment group, which is not a significant difference ($P = 0.3$, χ^2 with Yates' correction). This represents a recurrence rate of 24% within 1 month of the original procedure, but only 1 patient (3.4%, medical treatment group) required re-aspiration in this period. On subsequent follow-up, 3 further patients from the medical treatment group and 4 patients from the surgical treatment group suffered recurrence of their effusion after the 1-month period, and further aspiration was necessary in 6 of these patients, 4 from the medical treatment group and 2 from the surgical treatment group. A total of 8 patients from the medical treatment group and 6 patients from the surgical treatment group had a recurrence of effusion, resulting in a total of 7 (24%) patients (5 medical treatment group, 2 surgical treatment group) requiring repeat aspiration. There was no significant difference in the total re-aspiration rate between the two groups ($P = 0.3$, χ^2 with Yates' correction). These results are shown in Table 3.

Subsequent systemic treatment in the two groups were comparable (Table 4). Survival tables were created for both groups and survival curves plotted (Fig. 1). The overall survival time from pleurodesis was significantly longer after surgical treatment than after medical treatment ($P = 0.03$, χ^2 of log-rank analysis).

DISCUSSION

Although the patients in the medical treatment group had marginally more widespread disease at presentation and had been generally more heavily pretreated, the two groups of patients were sufficiently similar to compare response rates for the two treatment modalities.

Table 4. Type and number of systemic therapies after pleurodesis in the two treatment groups

Subsequent treatment	Medical group	Surgical group
Radiotherapy		
×1	0	0
Chemotherapy		
×1	6	6
×2	2	6
×3	1	1
Endocrine therapy		
×1	4	4
×2	3	6
×3	1	2
×4	1	2
Immunotherapy		
×1	1	1

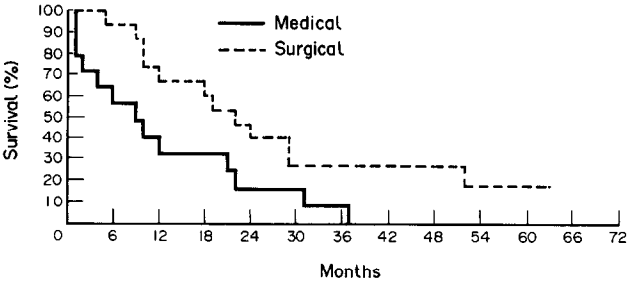

Fig. 1. Survival curves showing significantly longer survival after surgical treatment than after medical treatment ($P = 0.03$, χ^2 of log-rank analysis).

The rate of failure of primary pleurodesis was high at 13.4%, and somewhat surprisingly this was predominantly from patients treated with surgical pleurodesis. Using the presence or absence of recurrent effusion at 1 month as the criterion of response [9], the total efficacy rate of both procedures was 76%, which is comparable with those response rates previously reported [11–15]. In addition, there was no significant difference in the rate of recurrence between the two groups. Only 1 patient needed repeat aspiration during this period for symptomatic relief. Indeed, with a follow-up period extending to many months and even in some instances to many years, the total recurrent effusion rate was only 48%, and a total of 24% of patients needed re-aspiration at some stage. In both instances there was no significant difference between the recurrence or re-aspiration rates in the two groups. However, the total number of patients randomised into the study was low. Consequently, our overall results are comparable with other workers, and in addition we conclude that there is no advantage in performing surgical tetracycline pleurodesis rather than medical tetracycline pleurodesis by the above response criteria.

The only significant difference in the outcome of the two treatment groups was that the overall survival time from pleurodesis was longer in the surgical treatment group than in the medical treatment group ($P = 0.03$). However, it is the other sites of metastatic disease rather than the pleural effusion which is likely to adversely affect the prognosis in advanced breast cancer, and the most likely explanation of this finding is that the patients treated by medical pleurodesis belong to a worse prognostic group than those treated by surgery, rather than any difference attributed to the treatment of the pleural effusion.

It is likely, therefore, that the superiority of intracavitary talc inserted at surgical drainage over intracavitary tetracycline inserted after medical drainage, is a consequence of the superiority of talc over tetracycline as a sclerosing agent, rather than a consequence of the route and technique of administration. However, the major disadvantage of talc pleurodesis is that instillation of talc produces immediate parietal pleural pain and so the procedure must be performed under general anaesthesia [16], which is often inappropriate in women who may have extensive metastatic disease. However, thoracoscopy does provide additional information which may be useful in some patients. It is our practice to use tetracycline as the sclerosing agent, and this study demonstrates that medical pleurodesis is equally effective as surgical pleurodesis in the management of malignant pleural effusions associated with breast cancer, but without the disadvantages associated with general anaesthesia and surgery.

As in all forms of pleurodesis, drainage of the intracavitary space to dryness before instillation of the sclerosant is essential in reducing the likelihood of failure of primary therapy and subsequent recurrent effusions.

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Recombinant Granulocyte Colony Stimulating Factor Reduces the Infectious Complications of Cytotoxic Chemotherapy

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The aim of this study was to determine the usefulness of recombinant human granulocyte colony stimulating factor (r-metHuG-CSF) following conventional chemotherapy for small cell lung cancer. 130 previously untreated patients were randomised to receive either r-metHuG-CSF (230 μg/m²) or placebo on days 4–17 following CDE (cyclophosphamide, doxorubicin and etoposide) chemotherapy. Over all cycles, 53% of 64 patients on placebo and only 26% of 65 patients on r-metHuG-CSF had at least one experience of neutropenia with fever defined as a neutrophil count less than 1.0 × 10^9/l and a temperature ≥ 38.2°C ($P < 0.002$). It resulted in a reduction in the requirement for parenteral antibiotics from 58% in placebo patients compared with 37% in the r-metHuG-CSF group ($P < 0.02$), and a significant reduction in the incidence of infection-related hospitalisation. Chemotherapy doses were reduced by 15% or more at least once in 61% of the placebo group compared with 29% in the r-metHuG-CSF group ($P < 0.001$). 47% of the patients treated with placebo and 29% of the patients treated with r-metHuG-CSF experienced at least one cycle with a delay of 2 days or more in the administration of chemotherapy ($P < 0.04$). r-metHuG-CSF was well tolerated. There were no significant differences between the two groups in terms of response or survival.
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INTRODUCTION

ONE APPROACH to the optimisation of chemotherapy in small cell lung cancer (SCLC) is the use of relatively dose-intensive combination regimes [1]. Using such treatment, the main dose-limiting toxicity is neutropenia which carries an associated risk of infection-related morbidity and mortality, despite the use of systemic broad spectrum parenteral antibiotics [2–5]. Infectious complications, as well as hospital re-admissions, severely affect the quality of life in such patients whose prognosis remains relatively poor [6]. Furthermore, chemotherapy-induced marrow aplasia often determines treatment delays and/or reductions which might compromise therapeutic results.

Recombinant granulocyte colony stimulating factor (r-metHuG-CSF) is a glycoprotein which stimulates granulocyte