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Impact of Chemical Pleurodesis used in the Management of Malignant Pleural Effusion at King Abdulaziz University Hospital, Jeddah, Saudi Arabia

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ABSTRACT

Background: Chemical pleurodesis is a widely accepted management strategy for preventing re-accumulation of a malignant pleural effusion; intrapleural bleomycin can be used for this purpose.

Objective: To review the experience with chemical pleurodesis involving bleomycin at our institution.

Design: Retrospective analysis of all patients who received bleomycin for chemical pleurodesis over 6 years (May 2006 to April 2012) at King Abdulaziz University Hospital, Jeddah, Kingdom of Saudi Arabia. Patient demographics, cancer type, and pertinent data were analyzed.

Results: The most common cancer causing malignant pleural effusion was breast cancer (32% of cases). Bleomycin was effective for pleurodesis induction, with a success rate of 85% at 30 days and 55% at 90 days and only a few adverse effects.

Conclusion: At our institution, the efficacy of bleomycin for induction of chemical pleurodesis was similar to published studies. Implementation of a management algorithm is required to further improve outcomes in patients with malignant pleural effusion.

Keywords

Chemical pleurodesis, Bleomycin, Malignant pleural effusion

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INTRODUCTION

Malignant pleural effusion complicates many advanced intrathoracic and extrathoracic malignancies and is associated with limited survival. Thus, the primary aims of management include a palliative approach to ensure symptomatic relief and better quality of life. Preventing re-accumulation of pleural fluid *via* chemical pleurodesis or the use of chronic indwelling pleural catheters are both accepted strategies for the management of these patients. The use of bleomycin for chemical pleurodesis is associated with a mean success rate of 61% (range, 58–85%)[1]. The purpose of this study is to review the chemical pleurodesis experience at our institution and to compare our success rate with published data.

MATERIALS AND METHODS

Patient Characteristics

Data from 25 patients who underwent chemical pleurodesis for malignant pleural effusion at King Abdulaziz University Hospital in Jeddah, Saudi Arabia between May 2006 and April 2012 were retrospectively reviewed. A total of 30 pleurodesis procedures were performed.

Methods of Pleurodesis

Pleural effusions were drained *via* tube thoracostomy or a small-bore catheter. The chest radiograph obtained after initial drainage was evaluated to detect the degree of lung re-expansion. Complete re-expansion was reported in patients whose lung initially re-expanded by > 90%. The patient was diagnosed with trapped lung when the post-drainage chest radiograph showed a non-expandable lung with a thick visceral peel. Chemical pleurodesis using bleomycin was initiated after drainage of the pleural effusion, once a pleural fluid drainage volume of < 150 mL/day was achieved. Bleomycin was instilled at 11 U/kg (mean, 60 IU) in 100 mL 0.9% NaCl through a tube or catheter, which was then clamped for 2 h. The drainage system was disconnected when the daily drainage was < 100 mL. Successful pleurodesis was defined as no recurrence of effusion within 30 days of the procedure on clinical and radiological follow-up. The pleurodesis was also considered successful in asymptomatic patients with a small residual effusion that either just obliterated the costophrenic angle or did not re-accumulate to or above the predrainage level, and did not require an additional procedure.

Statistical Analysis

Statistical analysis was performed using the Statistical Package for Social Science software (SPSS, version 18, IBM Corp., Armonk, NY USA). Qualitative data are presented in terms of numbers and percentages, and a chi-square test with Yates post-hoc correction was used to compare qualitative data. The quantitative data are presented as mean and standard deviation values. The "student's" *t*-test was used for comparison of two groups of quantitative data. The threshold for significance was set at $p < 0.05$.

RESULTS

Twenty-five patients underwent 30 procedures; 13 (52%) were men and 12 (48%) were women, and the mean age was 53.68 years (range, 27–80 years). The primary underlying malignancies causing malignant pleural effusion were breast cancer in 8 (32%), lung cancer in 5 (20%), gastrointestinal malignancy in 5 (20%), genitourinary malignancy in 2 (8%), lymphoma in 2 (8%) of the patients. Other malignancies (nasopharyngeal cancer, Ewing's sarcoma, and unknown primary) were found in 3 (12%) patients. Pleural effusions involved both hemithoraces, equally. Survival data after diagnosis of malignant effusion was available for 10 patients (Table 1). The median survival was 77.5 days (range, 12–300 days).

Table 1.
Characteristics of the studied cases.

Primary Cancer	N	(%)
Lung	5	20
Breast	8	32
Lymphoma	2	8
GI (gastrointestinal)	5	20
GU (genetourinary)	2	8
Other	3	12
Age		
Mean ± SD	53.6 ± 15.64	
Range	(27-80)	
Gender		
Men	13	(52)
Women	12	(48)
Effusion Site		
Right	15	(50)
Left	15	(50)
Type of Tube		
Larger bore	24	(80)
Pigtail	6	(20)

Pleural effusion drainage was performed *via* large-bore tube thoracostomy on 24 occasions (80%) and *via* small-bore catheters on 6 occasions (20%). A mean duration of 8.9 days (range, 1–33 days) was required to achieve pleural fluid drainage < 150 mL/d, prior to commencing chemical pleurodesis. Patients were rotated after instillation of bleomycin in only 6 (20%) drainage procedures. Pleural drains were removed after a mean duration of 10.1 days (range, 1–30 days). The median duration of hospitalization for the management of malignant pleural effusion was 18 days (range, 5–51 days). There were no statistically significant differences in the duration of hospital stay and the type of chest drain used for effusion drainage (Table 2).

No adverse effects were documented in 26 of the 30 (89.7%) pleurodesis procedures. However, fever was reported in 2 cases (6.7%), shaking chills in 1 case (3.3%), and chest pain in 1 case (3.3%) of the pleurodesis procedures (Table 3).

Table 2.
Duration of hospital stay according to type of tube.

Days	Large	Pigtail	
Mean ± SD	21.05 ± 13.04	22 ± 18.01	P-0.90

Table 3.
Adverse effects of bleomycin.

Side Effects			
No side effects	N (%)	26	(86.7)
Fever	N (%)	2	(6.7)
Chest pain	N (%)	1	(3.3)
Shaking chills	N (%)	1	(3)

Data regarding the success rate for pleurodesis were available for 20 drainage procedures. The recurrence rate within 30 days of follow-up was 15% (3/20), representing an 85% success rate. At 90 days, the recurrence rate was 45% (9/20), representing a 55% success rate.

Full lung expansion was noted in 18 (60%) drainage procedures, but the lungs failed to expand completely following effusion drainage in 12 (40%) cases. Poor lung expandability after drainage was attributed to; trapped lung in 8 (26%), an extensive intrapleural tumor mass in 2 (6.6%) and an endobronchial tumor causing airway obstruction in 2 (6.6%) drainage procedures. At 90 days of follow-up, the recurrence rate was higher among patients whose lungs failed to expand after effusion drainage (Table 4). The highest success rate was noted in patients with full lung expansion. However, these differences were not statistically significant (Table 4).

DISCUSSION

Pleural effusion complicates many advanced-stage intra- and extra-thoracic malignancies. The development of a malignant pleural effusion in a patient with cancer is associated with significant morbidity. Furthermore, the diagnosis of a malignant effusion usually portends a poor prognosis, with an estimated median survival of 3–12 months after diagnosis[1]. The majority of patients who present with malignant pleural effusion experience dyspnea, cough, decreased exercise tolerance, and chest pain. Thus, management goals are directed towards alleviating symptoms and improving the quality of life.

The optimal management of malignant pleural effusions has long been a challenge for physicians caring for patients with end-stage cancer. Current management strategies vary widely among institutions and range from surgical procedures requiring hospitalization to outpatient treatment. Furthermore, management of malignant effusions depends on several factors: symptoms and performance status of the patient, the primary tumor type, tumor response to systemic therapy, and degree of lung re-expansion following pleural fluid evacuation[1].

Globally, the most common primary tumor causing malignant pleural effusion is lung cancer in men and breast cancer in women[1-11]. In the current cohort, breast cancer was the most common cause of malignant pleural effusion in women, while colorectal cancer was the most common primary tumor in men. This may reflect the incidence of these cancers in Saudi Arabia, where the most common cancers are breast cancer in women and colorectal cancer in men[12]. Breast and colorectal cancers accounted for 52% of all malignant effusions in the patients in the current study, while lung cancer, lymphoma, and tumors of the genitourinary tract accounted for an additional 36%. Pleural effusions from an unknown primary tumor were responsible for 12% of all malignant pleural effusions in the current cohort and the median survival of 77 days in these patients was similar to that reported in the literature[1].

Malignant pleural effusions were drained using a conventional large-bore chest tube in 80% of our cases; this is likely to be attributable to the fact that, at our institution, the surgical department manages most cases of malignant pleural effusion. Many previous studies have used conventional large-bore chest tubes, instead of small-bore catheters, to drain malignant effusions and to induce chemical pleurodesis[2-8,13-17]. Traditionally, large-bore chest tubes are thought to be more effective as they are less prone to blockage by fibrin bands. However, the insertion of large-bore chest tubes is associated with more discomfort than small-bore catheters. Small catheters can be considered an attractive alternative that reduces discomfort and has similar efficacy[18]. Thus, recent guidelines have recommended the use of small-bore catheters as the initial choice for effusion drainage and pleurodesis induction[1]. This recommendation will need to be widely adopted.

Subsequently, 98-100% of patients with malignant pleural effusion experience re-accumulation of fluid

Table 4.
Relation of lung expansion after effusion drainage and recurrence of effusion within 90 days.

Lung Expansion after Effusion Drainage was Complete					
Patients who had fluid re-accumulation within 90 days follow-up		Yes		No	
		N	%	N	%
Yes	N(%)	4	(44)	5	(55)
No	N(%)	7	(63.6)	4	(36.4) P = 0.39
Unknown	N(%)	7	(70)	3	(30)

and recurrence of symptoms within 30 days[1,19]. In a study by Anderson *et al.*, 94 patients with malignant pleural effusions were treated with thoracentesis alone; 97% developed recurrence within 1 month, with a mean time to recurrence of 4.2 days[19]. Ruckdeschel *et al.* also demonstrated that in the vast majority of cases, the fluid recurrence after pleurodesis occurred in the first 30 days[8]. Therefore, in addition to the time point of 90 days, most studies evaluated the success of pleurodesis at 30 days [2,4-9,13-16]. Some studies have reported a long-term evaluation extending to 6 months following pleurodesis[5,9].

Bleomycin is a chemotherapeutic agent that can also be used to induce chemical pleurodesis in the management of malignant pleural effusions. The efficacy and safety of bleomycin in the current cohort were similar to those in published data, with bleomycin success rates reported in the range of 58–85% (mean, 61%)[2-7,13-18]. This study documented a similar success rate of 85% at 30 days, confirming the utility and efficacy of bleomycin for pleurodesis.

Bleomycin also has an acceptable safety profile, with fever, chest pain, and cough being the most commonly reported side effects. Martinez *et al.*[7] reported fever in 19% of the patients who received bleomycin for pleurodesis and chest pain in 22% of patients, while Ruckdeschel *et al.*[8] reported fever and chest pain in 9% of patients. The rate of side effects was lower in the current cohort, with fever in 6.3% and chest pain in 3.3% of patients. These differences might be related to study design and the number of patients involved. Overall, bleomycin has an acceptable side-effect profile when used for chemical pleurodesis.

Apposition of visceral and parietal pleura is an essential requirement for successful pleurodesis. Thus, pleurodesis is less likely to succeed if the lungs fail to re-expand after drainage of the effusion. Failure of re-expansion may be due to endobronchial tumors, extensive pleural masses, or trapped lung. In 10 drainage procedures (33.3%) in the current study, the causes of poor lung expandability were extensive intrapleural tumor masses and multiple pleural loculations causing trapped lung. Similar to the current study, 1 study found that up to 30% of patients who were evaluated for pleurodesis were unsuitable candidates because of trapped lung[9]. Another cause of poor lung expandability (in 6.6% of the patients in the current cohort) was a central tumor causing bronchial obstruction.

Patients with incomplete lung expansion following effusion drainage are considered less likely to respond to chemical pleurodesis. As noted in this cohort, the recurrence rate at 90 days was higher among patients with poor lung expansion after effusion drainage; although, the difference did not reach statistical significance. The lack of a significant difference is likely related to the small sample size included in this study. Therefore, it remains unknown how much lung expansion is necessary to justify an attempt at pleurodesis. Current guidelines recommend > 50% lung expansion, prior to attempting pleurodesis[1]. Ideally patients with trapped lungs should be managed either by the insertion of indwelling tunneled pleural catheters or by decortication in case of good performance status. However, in this series, chemical pleurodesis was attempted as a treatment option in all patients, as an alternative option (*e.g.,* insertion of tunneled indwelling pleural catheters) was not available. Most chemical pleurodesis studies exclude patients with non-expandable lungs following effusion drainage[2,3,5,7-9,13,15,16]. To our knowledge, only 2 studies have included patients who had incomplete lung expansion after fluid drainage and underwent pleurodesis[10,11]. In a study by Robinson and colleagues, 9 (90%) out of their 10 evaluable patients with partial lung re-expansion; had a successful pleurodesis. No information was given on the exact mechanism underlying poor lung expandability after fluid drainage, and the percentage of patients with trapped lung versus those with central obstruction was unclear. Kennedy *et al.* also included 4 patients with partially trapped lungs in the analysis of success, 2 of the 4 patients' experienced long-term success while failure was observed in the third case at 6 months[11].

Implementation of a management protocol in which patients are treated according to the status of lung re-expansion after effusion drainage is recommended. Adherence to a protocol may improve treatment outcomes by offering patients the options of inpatient management *via* chest tube drainage and chemical pleurodesis or outpatient management *via* tunneled indwelling pleural catheter[1].

Zimmer *et al.* documented that chest tube pleurodesis was associated with approximately 1 week of hospitalization[3]. In the current study, the length of hospital stay for the cohort was 18 days, but the exact cause of this discrepancy is not known. Possible explanations include a delay in achieving pleural fluid drainage rates < 150 mL/d before commencing pleurodesis, especially in cases of massive pleural effusion. The length of stay for patients who underwent the procedure with a large-bore chest tube was not statistically different from that for patients who underwent the procedure with small-bore catheters. Therefore, the increased length of stay in this cohort cannot be solely attributed to the type of chest tube used for pleural effusion drainage and pleurodesis.

Rotation of the patient for improving the distribution of the sclerosing agent in the pleural space has been suggested by many studies[3-6,8]. However, this procedure is uncomfortable and inconvenient for the patient. The protocol used in 2 previous studies did not allow patient rotation after bleomycin injection[2,7]. In the present study, patients were rotated during only 20% of the drainage procedures. One study, using radiolabelled tetracycline, showed that tetracycline is dispersed throughout the pleural space within seconds and that rotation of the patient did not influence distribution[20]. Additionally, a randomized trial using tetracycline, minocycline, and doxycycline, showed similar success rates for pleurodesis and duration of fluid drainage between rotation and non-rotation groups[21]. Although no data that explicitly document the role of patient rotation when bleomycin is used are available, most

recent guidelines do not recommend patient rotation after injection of a sclerosing agent[1].

The results of this study must be viewed in light of its limitations. The retrospective nature of the study is the major limitation. Furthermore, small sample size and incomplete data for some variables is likely responsible for an inability to demonstrate statistically significant relationships within this cohort.

In conclusion, this study confirmed an acceptable efficacy, similar 30 days success rate, and safe side-effect profile for the use of bleomycin to induce chemical pleurodesis when compared to previously published reports. The implementation of a hospital-based management algorithm to triage patients based on lung re-expansion after drainage of a malignant effusion, that is, using chemical pleurodesis for patients with significant lung re-expansion after effusion drainage and insertion of indwelling tunneled pleural catheters for those with a non-expandable lung, is recommended and would likely improve outcomes.

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مدى فاعلية وتأثير البليومايسين في علاج السائل البلوريالسرطاني في مستشفى جامعة الملك عبدالعزيز

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المستخلص:

المقدمة: إستخدام الأدوية الكيميائية لمنع تكرار تكون السائل البلوريالسرطاني يعتبر من الإستراتيجيات الناجعة لعلاج هذا المرض، إذ أن مادة البليومايسين الكيميائية هي من الأدوية المستخدمة لهذا الغرض.

الهدف: مراجعة مدى فاعلية هذا الدواء من واقع دراسة الحالات التي استخدم فيها هذا الدواء في مستشفى جامعة الملك عبدالعزيز، ومقارنة النتائج باالأبحاث المنشورة سابقا.

طريقة البحث: مراجعة تحليلية لكل حالات السائل البلوريالسرطاني التي تم علاجها بمادة البليومايسين خلال ست سنوات في مستشفى جامعة الملك عبدالعزيز.

النتائج: سرطان الثدي هو من أكثر السرطانات المسببة للسائل البلوريالسرطاني و قد أثبت البليومايسين فاعلية فائقة في علاج هذه الحالات بنسبة نجاح تصل إلى٨٢،٣٪.

الخلاصة: البليومايسين يمتلك فاعلية فائقة في علاج السائل البلوري السرطاني بالإلتصاق الجنبي الكيمائي، وكانت النتائج لدينا مشابهة للأبحاث المنشورة في مثل هذه الحالات، وينصح بإيجاد إستراتيجية للتعامل مع هذه الحالات وتقديم العلاج المناسب لها.