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Management of Malignant Pleural Effusions

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Contents

Summary

Malignant pleural effusions (MPEs) represent a common complication of advanced malignancies. However, adequate palliation of this highly symptomatic accompaniment to cancer can be achieved in most patients by adopting the appropriate therapy.

Several options are available for the treatment of MPE. Systemic therapy may control the effusion in patients whose underlying malignancy is sensitive to anticancer agents. Repeated thoracocentesis can be appropriate for patients with limited life expectancy or slowly recurrent effusions. In the majority of the remaining cases the treatment of choice is pleurodesis with sclerosing agents administered via tube thoracostomy.

Controversy still exists as to which drug produces the best results: talc and bleomycin appear to be among the most cost-effective agents. The debate over the best agent to be used for pleurodesis refers to the difficulty in comparing results of studies using different eligibility criteria, response assessment and end-points.

This article describes the various treatments which have been reported in the literature to play a role in the management of MPEs. It is also aimed at providing guidelines in allocating patients to appropriate treatments.

Malignant pleural effusions (MPEs) are defined as an accumulation of fluid in the pleural space due to neoplastic involvement of the pleura, either by direct tumour extension or by metastatic dissemination. Only 50% of effusions developing in cancer patients are due to tumour growth in the pleural space. Other types of pleural effusions include 'nonmalignant' effusions, which are completely

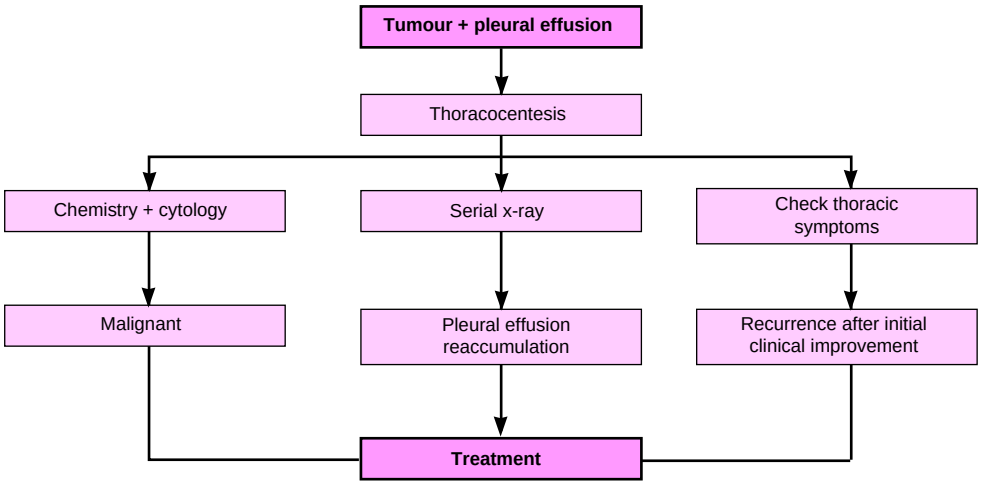

Fig. 1. Management of cancer patients with pleural effusions: following thoracocentesis, a series of physical and diagnostic tests should be performed. The need for immediate treatment can be determined from the results of diagnostic tests and clinical evaluation.

unrelated to the tumour [such as effusions associated with congestive heart failure (CHF) or infection], and 'paramalignant' effusions, which are effusions indirectly caused by the tumour (such as those due to atelectasis and lymphatic or venous obstruction).

MPEs can be the presenting sign of cancer or, more often, develop after the cancer has been diagnosed. Pleural metastases, with or without effusion, are found in approximately 3% of patients with gastric, breast and ovarian tumours while 7 to 15% are diagnosed in patients with primary lung cancer.[1-3] Nearly half of the patients with disseminated cancers[4] and up to 90% of patients with pleural mesothelioma[5] will eventually develop a pleural effusion. Lung cancers (34.8%), lymphoma/leukaemia (9.7%) and breast cancer (22.9%) account for two-thirds of all MPEs.[6] MPEs are relevant contributors to morbidity and mortality in cancer patients. At the time of diagnosis, three-quarters of all patients with pleural effusions present with thoracic symptoms.[7] The median survival time of patients with MPEs usually ranges between 6 and 12 months. The major goal of MPE therapy is cost-effective symptom palliation. Management is sometimes difficult, but in most cases the distressing symptoms can be relieved with local treatment regardless of the availability of an effective therapy for the underlying tumour. There are no unequivocal guidelines for the treatment of MPEs.[8-13] This article aims to review the management of MPEs and provide some guidelines about when and how to treat this condition.

1. Pathophysiology of Malignant Pleural Effusions

In physiological conditions in humans, around 100 to 200ml of pleural fluid is produced and reabsorbed each day.[14] Pleural effusions occur when the balance between fluid formation and reabsorption is impaired due to increased secretion or reduced reabsorption, or a combination of both. Fluid secretion may increase as the result of elevated serum hydrostatic pressure, as in CHF, or decreased serum oncotic pressure, e.g. hypoalbuminaemia. Similarly, increased negative intrapleural pressure, resulting from atelectasis or increased pleural fluid oncotic pressure, can also cause pleural fluid accumulation. These mechanisms are mainly involved in nonmalignant and paramalignant effusions. In contrast, enhanced capillary permeability, result-

ing from pleural inflammation associated with tumour involvement, and obstruction of lymphatic channels by tumour occluding stomata on parietal pleura, are mainly responsible for malignant effusion. Tumour cells are present in the pleural fluid if the tumour involves the mesothelial surface. In contrast, subserosal tumour deposits often do not yield a positive cytology.

2. Treatment

2.1 General Considerations

When treating cancer patients with pleural effusions, it is important to keep patient and disease in their proper perspective. The therapeutic approach to pleural effusion depends upon several prognostic factors such as age, performance status and prognosis, along with site and histology of the primary tumour. In all patients, it is important to assess the presence or absence of effusion-associated symptoms, the ability of thoracocentesis to relieve those symptoms, the presence of lung re-expansion after fluid evacuation, the rate of fluid reaccumulation, and the malignant nature of the effusion (fig. 1).

The vast majority of patients with MPEs have incurable disease; therefore, treatment is mainly aimed at obtaining the most effective palliation with minimum discomfort for the patient, at the lowest cost for the healthcare service. Not all MPEs need immediate therapy. If the effusion is asymptomatic or symptoms do not recur after simple thoracocentesis, deferring MPE therapy can be considered, although a delay in treatment may compromise the results of subsequent intracavitary therapy. For patients with very advanced disease and poor life expectancy (<1 month), adequate palliation can be achieved with morphine, oxygen and repeated thoracocentesis. If the primary tumour is likely to be sensitive to systemic therapy, such treatment should be given beforehand. If the tumour is unlikely to be responsive to systemic chemotherapy, tube thoracostomy with chemical pleurodesis is the treatment of choice (fig. 2).

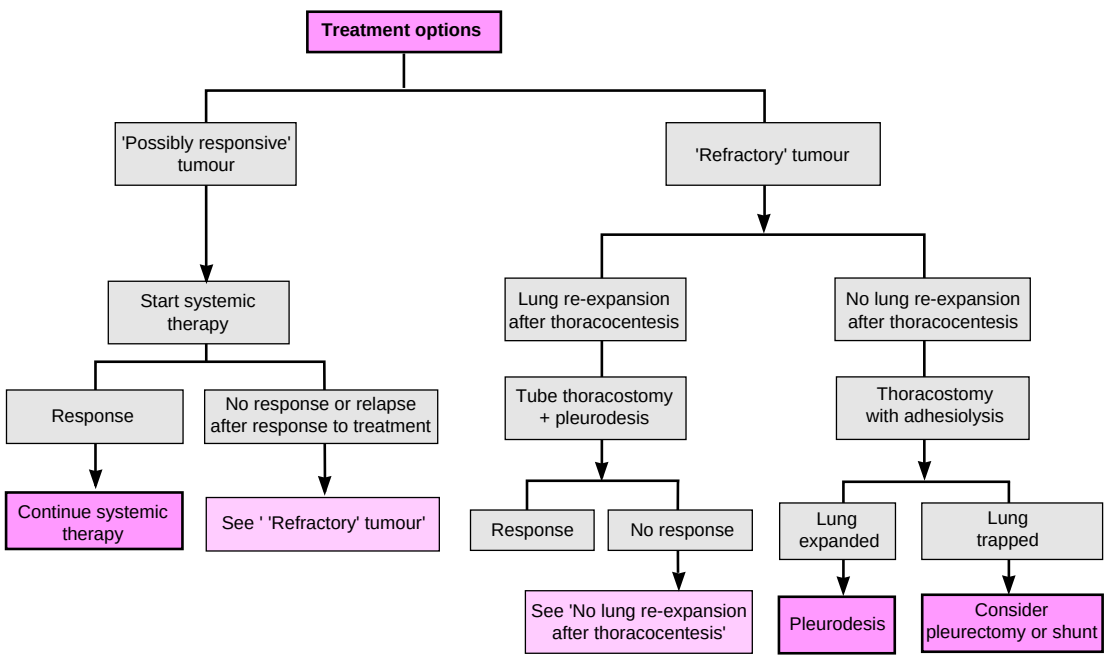

Fig. 2. Algorithm for the management of patients with known malignant pleural effusions.

However, the ability of the lung to completely re-expand after fluid evacuation is an essential prerequisite to attain pleural symphysis. In the case of trapped lung (absence of lung re-expansion), an attempt should be made to release it, or else an alternative treatment should be considered.

2.2 Systemic Therapy

High MPE response rates are observed in Hodgkin's and non-Hodgkin's lymphoma, small-cell lung cancer and testicular malignancies with systemic combination chemotherapy and/or radiotherapy. Patients with highly responsive or potentially curable tumours should receive systemic treatment as the primary therapeutic approach. In general, when the primary malignancy responds to such therapy, the effusion also responds. For patients who are severely compromised by the effusion, symptomatic thoracocenteses are appropriate during combination chemotherapy. Intracavitary treatment is indicated only in cases proven to be refractory to systemic chemotherapy. An exception to this approach can be made when methotrexate is to be given, since toxicity can result from drug accumulation and delayed release from the pleural space.[15] Close monitoring of methotrexate drug concentrations (which, if ≥0.5 μmol/L, can lead to increased toxicity) and calcium folinate (calcium leucovorin) rescue or careful thoracocentesic evacuation of as much fluid as possible before therapy can reduce the risk of this kind of toxicity.

2.3 Local Therapy

2.3.1 Mechanical

Thoracocentesis

Thoracocentesis is an essential first step in the diagnosis and treatment of pleural effusions. Repeated needle thoracocentesis can provide temporary symptomatic relief, but most effusions reaccumulate within 1 to 3 days and almost all recur within 30 days.[16] Frequent thoracocenteses bear an increased risk of pneumothorax, empyema and pleural fluid loculation. Hypoproteinaemia, which can also lead to a decrease of oncotic pressure promoting further effusion reaccumulation, is another recognised complication with repeated thoracocentesis. Repeated therapeutic thoracocentesis should thus be limited to highly symptomatic patients with responsive malignancy who will be undergoing chemotherapy, or in patients with poor life expectancy (i.e. <1 month).

Tube Thoracostomy

Tube thoracostomy can be effective *per se* in controlling MPEs. A 30-day success rate of up to 70% with tube thoracostomy alone has been reported, although long term control of effusion is rare.[17] In addition, tube thoracostomy is important in achieving optimal pleurodesis with a sclerosing agent. This is probably due to the ability of thoracostomy to allow the visceral and parietal pleura to come into contact again, thereby favouring adhesion induced by sclerosing agents. In recent years there has been an increasing interest in the use of small-bore soft catheters, in place of classical chest tubes, for drainage and instillation of sclerosing agents. Preliminary results indicate that these catheters may be equally effective with less associated morbidity.[18-20]

Pleurectomy

Stripping of the parietal and visceral pleura is effective in controlling MPE in nearly 100% of cases. However, this approach can rarely be indicated in the palliative setting since it has a similar morbidity (23%) and mortality (10%)[21] to that of an extensive operation. Pleurectomy can be considered for refractory pleural effusions, in patients with trapped lung or significant expectation of survival from their underlying tumour, or for those who are submitted to thoracotomy for other reasons (i.e. diagnosis). Early experience indicates that parietal pleurectomy by means of a video-assisted thoracoscopic technique yields results equivalent to those of the 'open' technique.[22,23]

Pleuroperitoneal Shunts

The placement of a pleuroperitoneal shunt is an alternative approach in patients with refractory effusions. A catheter is placed subcutaneously into the pleural and peritoneal spaces. A pump is manually operated to drain fluid from the pleura into

the peritoneal cavity. However, approximately 25% of the shunts become occluded during the patient's lifetime.[24] In addition, the pump requires an alert and cooperative patient for proper management.

2.3.2 Chemical

A number of intrapleural agents have been successfully used in controlling MPEs. These range from antibiotics to antineoplastic agents and immunotherapeutic approaches. Whatever class these agents belong to, their principal mechanism of action is through a chemical pleurodesis. However, the absence of an inflammatory response for bleomycin in Light's rabbit model[25] and the reasonable efficacy of intrapleural cytarabine (cytosine arabinoside; Ara-C) and cisplatin which are not pleurodesic[26] suggest that few chemotherapeutic agents may also act through a direct anti-tumour effect. Chemical pleurodesis is aimed at raising a widespread pleurisy which leads to fibrosis and consequent obliteration of the pleural space, thereby preventing further fluid accumulation. Table I summarises the agents which have been most extensively tested with percentages of activity in controlling MPEs. The success of this procedure depends on an adequate drainage of the pleural fluid and on complete re-expansion of the lung which allows opposition of the pleural layers. Prevention of pain related to instillation of sclerosing agents is an important aspect of this treatment. If not effectively managed, pain will accompany intrapleural administration of bleomycin or tetracycline in 30 to 40% of patients, and in over 90% of those receiving talc.[6]

The optimal technique for chemical pleurodesis includes the following steps:

- The fluid is drained using a chest tube and closed drainage until fluid reaccumulation is less than 100 ml/day.
- It is advisable to premedicate patients with parental narcotics and to give local anaesthesia with instillation of 10 to 15ml of 1% lidocaine (lignocaine) leaving the tube clamped for 5 to 10 minutes.

Table I. Drugs used in the treatment of malignant pleural effusions

Treatment regimen	Dose	Success rate (%)	References
Antibiotics			
Tetracycline	0.5-1g	30-80	28-39
Doxycycline	0.5-1g	60-88	42-47
Minocycline	300mg	86	48
Antineoplastic agents			
Bleomycin	60U	63-85	29,33,34,38, 51-63
Doxorubicin (adriamycin)	10-40mg	39-80	39,65-67
Cisplatin + cytarabine (cytosine arabinoside; Ara-C)	100 mg/m^2 + 1200mg	49	26
Mitoxantrone	30-40mg	50-100	17,63,68-70
Biological response modifiers			
Interferon	5-50 $\times$ 10^{6}U	38-70	73,74
Interleukin-2	10-24 $\times$ 10^6 U/m^2/day	20-37	75,76
Corynebacterium parvum	5-10mg	90-100	31,54,55
Picibanil (OK-432; OK-142; OKY-142)	10KE[a]	70-73	61,80
Others			
Talc	5-10g	90-100	32,56,81
Mepacrine	200mg	64-90	28,59,70,83
Methylprednisolone acetate	80-160mg	60	84

a 1 Klinische Einheit (KE) is equivalent to 0.1mg of dried streptococci.[27]

- The chemical agent then is introduced into the pleural space; it is convenient to leave the tube clamped for 15 to 30 minutes and to maintain closed drainage until pleural fluid production is less than 100 ml/day.
- Finally, the chest tube is removed and the patient monitored to assess possible effusion recurrence.

Antibiotics

Tetracyclines have been widely used with an average 30 to 80% success rate in achieving pleurodesis.[28-39] Fever and pain occur in 10 and 14% of cases, respectively.[40] The recommended dose is 0.5 to 1g in 50ml of dextrose 5% in water (D5W). Its mechanism of action has been attrib-

uted to a fibroblast growth factor–like activity from both direct and indirect mesothelial cell activation.[41] Cytostatic activity of tetracycline metabolites has also been postulated while its low pH does not seem to be involved. Tetracycline represents a low-cost, effective therapy without serious adverse effects. Unfortunately, the parental formulation is no longer available in most countries.

Doxycycline and minocycline have been used as tetracycline substitutes with a success rate of 60 to 88%[42-47] and 86%, respectively.[48] Unfortunately, minocycline was tested in only 1 small study and doxycycline required repeated instillations, thereby obviating any cost advantage.[12]

Antineoplastic Agents

In contrast to sclerosing agents, intrapleural chemotherapy, in addition to providing a chemical pleurodesis, has the potential advantage of treating the underlying malignancy both locally and systemically. In fact, most agents injected into the pleural or peritoneal cavity, besides yielding high intracavitary concentration of the drug, reach blood concentrations similar to those achievable with intravenous treatment.[49] However, animal experiments have shown that tumour penetration of intracavitary chemotherapy is only a few millimetres.[50] Therefore, the rationale for the use of intracavitary nonsclerosing chemotherapeutic agents is still being debated.

Bleomycin: Bleomycin is an antitumour antibiotic widely used in the treatment of MPEs, with a success rate of 63 to 85%.[29,33,35,38,51-63] Although it belongs to the class of antineoplastic agents, its mechanism of action in controlling MPEs is mainly through chemical pleurodesis, similar to that obtained with talc or tetracycline. The dose most commonly employed is 60U in 50ml of 5% D5W injected through a chest tube. Although nearly 50% of intrapleural bleomycin is absorbed into the circulation, systemic toxicity has rarely been reported. The drug is not myelosuppressive and the two most common adverse effects are pain (30%) and fever (25%), which can be reduced by prophylactic measures. Bleomycin can also be injected through small-bore soft catheters with results which are close to those obtained by adopting standard procedure.[18,20,64]

Doxorubicin (Adriamycin) and Mitoxantrone: Intrapleural doxorubicin (adriamycin) at doses of 10 to 40mg has been reported to produce an objective response in 39 to 80% of patients.[39,65-67] Adverse effects include pain (29%), fever (15%), and nausea and vomiting (29%). There have been no reports of cardiomyopathy or bone marrow suppression with this route of administration.

Preliminary studies with mitoxantrone have shown mild toxicity and activity similar to that of bleomycin or tetracycline.[17,63,68-70]

Cisplatin and Cytarabine (Cytosine Arabinoside; Ara-C): While the intracavitary use of cisplatin alone has been limited to patients with mesothelioma,[71,72] trials in patients with MPEs have mainly tested the combination of cisplatin and cytarabine, on the basis of biochemical and clinical studies showing a synergy between these 2 agents. Cytarabine and cisplatin were instilled in the pleural cavity at a dose of 1200mg and 100 mg/m^2, respectively. The reported success rate of this intracavitary combination chemotherapy is 49%, with minimal haematological toxicity and encouraging duration of response (9 months for complete responders).[26]

Biological Response Modifiers

Interferons: Interferons facilitate immune recognition and lysis of tumour cells by upregulating major histocompatibility complex (MHC) expression and by increasing natural killer cell and macrophage cytotoxic function. Intrapleural interferon-β (IFNβ) has been administered without drainage to patients with MPE, with an overall response rate of 38%.[73] Goldman et al.[74] observed a 70% response rate in 20 patients with MPE treated with local instillation of high-dose recombinant α-interferon-2b (rIFNα-2b). The most frequent adverse effect was the typical flu-like syndrome associated with IFN treatment. However, rIFNα appears to be less active than bleomycin in controlling pleural effusions.[62]

Interleukin-2 (IL-2): Intrapleural administration of recombinant interleukin-2 (IL-2) in patients

with lung cancer has shown a disappearance of cancer cells in the malignant effusion as well as improvement or resolution of pleural effusion.[75] In another study, Viallat et al.[76] assessed the tolerance and efficacy of intrapleural interleukin-2 in patients with MPEs. 96% of the patients had grade 2 to grade 3 fever, which was easily controlled with paracetamol (acetaminophen). 8% of the patients had pleural empyema. The antitumour effects of interleukin-2 may be mediated by cytotoxic T-lymphocytes and induction of non-MHC restricted 'killer' cells. Of possible relevance to the treatment of MPE is its ability to induce proinflammatory cytokines such as tumour necrosis factor and interferon-γ. IL-2 has also been used along with lymphokine activated killer (LAK) cells. This treatment has been shown to improve or resolve pleural effusions, with fever as the only adverse effect.[77]

Corynebacterium parvum

Extracts from *Corynebacterium parvum*, an anaerobic Gram-positive bacterium, given weekly at a dose of 5 to 10mg, have been found to control 90 to 100% of MPEs at 4 weeks. The lipopolysaccharide bacterial cell wall prompts an inflammatory reaction characterised by the influx of polymorphonuclear leucocytes and activated macrophages[78] which can promote adhesion of the pleural surfaces and cytotoxicity for tumour cells.[79] The effectiveness of *C. parvum* is similar to that of tetracycline and bleomycin.[31,54,55] However, fever and pain are common with these extracts and it is not widely available.

Picibanil (OK-432; OK-142; OKY-142)

Intracavitary injection of picibanil, a streptococcal preparation, has been shown to be an effective immunotherapy for patients with malignant effusions. The proposed mechanism of action is by means of an increased expression of intercellular adhesion molecule-1 (ICAM-1) on tumour cells, with a correlation between the degree of ICAM-1 increase and therapeutic effects. The reported range of activity with this agent is 70 to 73%.[61,80]

Other Agents

Talc: Talc has been used to treat MPEs for over 30 years, and it is generally considered to be one of the most effective chemical agents for pleurodesis. Talc induces an intense reactive pleuritis which is highly effective in producing pleural space obliteration. When instilled directly into the pleural cavity at a dose of 5 to 10g via poudrage, insufflation or liquid slurry, talc is effective in nearly 100% of cases with complete lung re-expansion.[32,56,81] In the past, this approach was made with a rigid thoracoscope under local or general anaesthesia. The rapid evolution of video-assisted thoracoscopic surgery (VATS) has made this procedure much easier to perform. Major drawbacks with talc sclerotherapy are the need for hospitalisation and for surgical thoracoscopy guidance. However, intrapleural talc administration can also be performed successfully by aerosolisation through a large-bore chest tube without thoracoscopy. Most frequent adverse effects are fever, which occurs in nearly 50% of cases, and pain. Occasional episodes of adult respiratory distress syndrome (ARDS) have been reported.[82] Clinical studies over the past 5 years confirm a continuing interest in talc as a chemical sclerosant, and provide evidence for its activity with low adverse effects and costs.

Mepacrine: Since 1983, intrathoracic instillation of the antimalarial drug mepacrine has been used to achieve pleurodesis. Mepacrine has been administered to 98 patients enrolled in different studies. Though objective responses were excellent, adverse effects, including pain, fever, nausea and mental status changes,[28,59,70,83] were consistently reported.

Methylprednisolone Acetate: The reported clinical data[84] offer evidence that methylprednisolone acetate, when instilled at doses ranging from 80 to 160mg per course into the pleural cavity after incomplete thoracocentesis, may act as effective palliative therapy either alone or in combination with other anticancer agents.

2.3.3 Complications of Pleurodesis

Chest pain may derive from insertion of a chest tube or from drug instillation. It usually disappears within a few days. Prophylactic use of analgesics is recommended for most pleurodesic agents.

Traction pneumothorax may result from repeated attempts to expand the lung after longstanding pleural effusion. In this case, suction is applied to the chest bottles (i.e. chest drainage system) to achieve re-expansion of the lung.

Cough can be caused by lung re-expansion after removal of pleural fluid. This symptom does not need to be treated since it is self-limiting and may be helpful in contributing to clear atelectasis.

Fever may be caused by obstructive pneumonitis or by the sclerosing agent. If pneumonia has been excluded, aspirin or paracetamol can be prescribed.

Fluid loculation is frequently associated with drainage and pleurodesis. Intrapleural injection of radiopaque material is useful in confirming this complication. Adhesiolysis through video thoracoscopy can be helpful in allowing lung re-expansion and improve results of pleurodesis.

Empyema may result from either contamination or bronchopleural communication. Culture and sensitivity of the purulent material should be obtained and appropriate antibiotic therapy started.

Metastasis on the thoracostomy track can occur especially in patients with mesothelioma and can be prevented by prophylactic use of local radiotherapy.

2.3.4 Choice of Intracavitary Treatment

Although innumerable nonrandomised trials have anecdotally documented the activity of a number of intracavitary agents in the treatment of MPEs, comparing effectiveness among the available treatments is extremely difficult due to the use of different patient eligibility criteria such as tumour histology, type of pleural involvement, the presence of concomitant systemic therapies, life expectancy and the type of drainage used. Moreover, end-points and criteria used to assess response to intracavitary treatment have differed greatly among studies. Some authors have defined the criteria to assess response to intracavitary treatment similar to those used for systemic chemotherapy, distinguishing between complete and partial responses. However, the only response criterion that can reasonably be used across investigators and institutions, as suggested by Ruckdeschel[13] and Rusch,[85] is the presence or absence of effusion recurrence after the tube is removed and whether recurrence requires further treatment.

Available randomised trials have been limited (table II) and have had several flaws, the most prominent of which has been small number of patients and use of different inclusion criteria. In addition, concomitant radiotherapy or systemic treatment for extrathoracic disease is often required and the number of patients in whom such treatment can be withheld in order to evaluate pleurodesis, as the sole variable, is limited. Finally, trials with similar design have yielded contrasting results.[33,35,54,55]

Despite these limitations, some conclusions can be drawn. The use of chemotherapeutic agents such as cisplatin and cytarabine, despite the potential advantage of treating the underlying malignancy while controlling the effusion, appears to be inferior to use of existing sclerosing agents for the control of MPEs.[26] Chemotherapeutic agents are therefore not recommended as the standard treatment of MPEs. The same applies to biological therapies which are expensive, not devoid of toxicity, and not part of standard MPE therapy in most institutions.

The most conventional and practical approach to patients with MPEs is the intracavitary administration of a sclerosing agent after complete effusion drainage, preferably by tube thoracostomy as described above. Various agents have been used to induce pleurodesis. Talc appears to be one of the most effective and inexpensive agents. However, when delivered by insufflation through a thoracoscope under general anaesthesia, which is the preferred method, the costs increase due to hospital stay and surgical procedures. Talc can be insufflated under local anaesthesia or administered by slurry through a chest tube to reduce costs and hospital stay, although appropriate doses and rate of

Table II. Results of randomised trials of intracavitary therapy for malignant pleural effusions

Year	Treatment	No. of patients	Comments (more effective drug listed)	Reference
1977	Mepacrine *vs* thiotepa *vs* thoracentesis alone	25	Mepacrine	83
1978	Tetracycline *vs* mepacrine	18	Tetracycline	28
1980	Bleomycin *vs* tetracycline	25	Tetracycline	29
1983	Chlormethine *vs* talc	37	Talc	81
1983	Normal solution (pH 2.8) *vs* tetracycline (pH 2.8)	30	Efficacy of tetracycline not related to pH	30
1985	*Corynebacterium parvum vs* tetracycline	32	ND	31
1986	Talc *vs* tetracycline	41	Talc	32
1986	*C. parvum vs* bleomycin	32	*C. parvum*	54
1987	Bleomycin *vs* tetracycline	34	ND	33
1988	Tetracycline 1 dose *vs* 2 doses	50	ND	34
1989	Bleomycin *vs* talc	29	Talc	56
1989	*C. parvum vs* bleomycin	58	Bleomycin	55
1991	Mitoxantrone *vs* pleural tube alone + isotonic NaCl	103	ND	17
1991	Bleomycin *vs* tetracycline	85	Bleomycin	35
1992	Picibanil (OK-432) *vs* mitomycin	53	Picibanil	80
1993	Mepacrine *vs* bleomycin	40	Mepacrine	59
1993	Surgical tetracycline *vs* medical tetracycline	34	ND	36
1994	Picibanil *vs* bleomycin	81	Picibanil	61
1994	Tetracycline *vs* mechlorethamine	40	Tetracycline	37
1995	Mitoxantrone *vs* mepacrine	30	ND	70
1996	Bleomycin *vs* tetracycline *vs* bleomycin + tetracycline	60	Combination of bleomycin + tetracycline	38

Abbreviation: ND = no difference.

response with this modified procedure have not been sufficiently studied. When patients are scheduled for VATS or thoracoscopy for any other reason (i.e. diagnosis, trapped lung treatment, etc.), talc can be regarded as the drug of choice.

The efficacy of bleomycin and tetracycline, or its analogues minocycline and doxycycline, is similar to that of talc. However, tetracyclines may no longer be available in most countries and doxycycline requires multiple instillations (an average of 4) usually over several days. Bleomycin, requiring a single administration, allows the chest tube to be removed early, thus reducing patient discomfort and risk of infection. Although more expensive than tetracycline, bleomycin appears to be a more cost-effective treatment in consideration of its high efficacy and shorter patient hospital stays.[86] Bleomycin plus thoracostomy can be considered the alternative of choice to talc when contraindications to surgery are present. A recent study demonstrated that the measurement of pleural space elastance (defined as the decline in pleural fluid pressure in centimetres of H_2O after removal of 500ml of effusion) is a useful test for the prediction of response to bleomycin pleurodesis.[87]

Moreover, recent experience suggests that this agent can also be successfully used through small-bore catheter, which can be particularly appealing in patients with poor general condition or short life-expectancy.[18-20]

3. Conclusions

MPEs are a common complication of advanced cancer and an important cause of morbidity and mortality. However, associated symptoms can be controlled effectively in nearly 80% of patients with drainage and intracavitary treatment. This result can be obtained with minimal toxicity and discomfort for the patient and regardless of the availability of an effective systemic antineoplastic therapy. The choice of one intracavitary agent over another is highly dependent on personal experi-

ence and preference, local drug availability, logistical aspects and costs. Best results are obtained with intracavitary administration of sclerosing agents after complete drainage of the effusion through tube thoracostomy. Talc and bleomycin are among the preferred sclerosing agents considering their high efficacy, low toxicity, acceptable costs and availability. However, whatever treatment is used, patients should be carefully selected on the basis of the underlying tumour type, prognosis, symptoms and behaviour of the effusion after thoracocentesis.

The comparison between different types of drainages to be used for pleurodesis, the use of a combination of agents with different mechanism of action and a definitive comparison between bleomycin and talc pleurodesis are the subject of ongoing randomised, prospective studies.

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