Malignant pleural effusions: Management options

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Abstract

Malignant pleural effusion represents advanced metastatic malignancy and is associated with poor median survival. Incidence remains high and continues to rise, in part due to changing population demographics. This therefore represents a significant healthcare burden.

Management is predominantly palliative in nature and multiple interventions are available within conventional treatment paradigms, all of which are proven to result in statistically significant patient benefit.

This chapter further explores the methods available in the management of malignant pleural effusion along with the pitfalls, complications and alternatives. Recent advances within the field are discussed with an exploration of likely future directions including the role of ultrasound as a prospective predictor and the role of intrapleural fibrinolytic therapy.

Keywords

Malignant pleural effusion; talc pleurodesis; indwelling pleural catheter; palliative care; unexpandable lung; autopleurodesis; thoracic ultrasound

Overall Approach and Patient Perspective

The presence of a malignant pleural effusion represents advanced metastatic disease and in the vast majority of cases is incurable, leading to the requirement of a predominantly palliative or symptom-control approach, with the primary aim of relieving dyspnoea. It is associated with a significant reduction in life expectancy and an estimated median survival of between 3 and 12 months.[1, 2] This figure is influenced by a number of other factors including performance status and tumour type but can be risk stratified to predict prognosis using a number of tools including the LENT score and the more recently published and more accurate PROMISE tool.[2]

Interventions available to patients and clinicians in the management of malignant pleural effusion include therapeutic pleural aspiration, indwelling pleural catheters (IPCs) or talc pleurodesis either using talc slurry instilled via an intercostal chest drain or talc poudrage administered during thoracoscopy. Each management option has various indications, roles and sequelae, and is dependent on multiple factors including availability, the underlying pathophysiology and patient choice (amongst others). The varied treatment options results in a complex pathway for patients in order to navigate difficult decision making [Figure 1].

Epidemiology and relevance

Overall cancer incidence worldwide continues to increase, with a projected increase of 68% between 2012 and 2030.[3] Incidence within the UK has increased by 7% over the last ten years.[4] This may be explained at least in part by increases in life expectancy along with overall changing population demographics towards a more elderly population, especially in more developed countries.

Metastatic malignant disease of the pleura is already seen commonly in clinical respiratory medicine and may complicate the management of almost all cancer subtypes. Increases in overall cancer incidence have resulted in a concomitant increase in the incidence of malignant pleural disease, and

in particular malignant pleural effusion. A similar increase has been evident in the incidence of primary pleural malignancy with around 2700 cases of malignant pleural mesothelioma diagnosed annually in the UK.[5]

The approximate incidence of malignant pleural effusion across the combined population of the United Kingdom and United States is thought to be in the region of 300,000 per year, with the UK's incidence accounting for more than 40,000 of those cases alone.[1, 6]

As a result, malignant pleural disease represents a significant and increasing burden on healthcare resources. The management may be complex and varied with multiple options available. This chapter will explore the options available with particular reference to a patient centred approach as well as the exploration of recent and projected future developments in the field.

Symptom control

At present, conventional interventions for malignant pleural effusion all demonstrate statistically and clinically significant improvements in dyspnoea scores and quality of life measurements irrespective of the method chosen. The AMPLE study, published in late 2017 confirmed the original findings from the TIME2 trial in 2012, both of which randomised patients to either talc slurry pleurodesis or indwelling pleural catheter (IPC). AMPLE measured mean improvements in dyspnoea using a visual analogue scale between 0 and 100mm. Improvements of 14.5mm in the IPC group and 17.4mm in the talc pleurodesis group were demonstrated respectively after only one day, and these were maintained throughout the full 12 month follow up period. This served to further consolidate the findings from TIME2 which had originally demonstrated that 74% of patients undergoing drainage and talc pleurodesis experienced clinically significant improvement in their breathlessness compared with 86% of patients with IPCs, although the difference between the two groups was not statistically significant. Mean improvements of 30.2mm and 37mm were recorded respectively at

day 42 on a visual analogue scale and were far in excess of an established clinically significant difference of 19mm. Outcomes from both studies also resulted in similar improvements in quality of life measurements between the treatment arms, however AMPLE used the EQ-5D score in contrast to the cancer specific EORTC QLQ-30 measurement recorded in TIME2.[7, 8]

The mechanism by which these interventions achieve improvements in dyspnoea has yet to be fully defined. The resolution of simple compressive atelectasis by drainage of fluid, leading to improvements in oxygenation is evident in the literature but appears unlikely to fully explain the underlying pathophysiology, as these results are independent of the degree of lung re-expansion. [9, 10] The actual pathophysiology of dyspnoea may therefore be better explained by the increase in pleural pressure from a large effusion. This may in turn lead to diaphragmatic inversion, abnormal or paradoxical movement, or diaphgram dysfunction (potentially related to muscle stretch). The subsequent return of normal diaphragmatic shape, position and function following drainage may therefore be likely to best account for improvements in dyspnoea.[11, 12]

The optimum volume of fluid to be removed during an intervention in order to achieve symptom control also remains unclear. When undertaking therapeutic aspiration, the British Thoracic Society (BTS) Guidelines suggest that less than 1500ml be drained in one attempt.[13] Literature review suggests that this limit is conservative as significantly larger volumes are documented as having been safely aspirated, including one case of 6.5 litres in one sitting.[14] The perceived increased risks of re-expansion pulmonary oedema and pneumothorax have led to retention of these conservative recommendations. The first indications of one of these complications may be the development of a cough or chest pain and so these features are often used as an indication for discontinuation of the procedure.[13-15] It should also be noted that complete removal of fluid leaving a dry pleural space is not required if symptomatic benefit is the goal. Large volume aspiration of approximately one litre of pleural fluid, allowing residual effusion to remain, has been shown to be effective in the improvement of dyspnoea in over 80% of patients.[16] This would appear to confirm that the

proposed mechanism of dyspnoea in these cases is likely primarily related to diaphragmatic pressure and the subsequently altered breathing mechanics in contrast to lung function compromise, passive atelectasis or lung compression.

Therapeutic Pleural Aspiration

Pleural aspiration is considered first line in many investigation and management algorithms including the current BTS Pleural Disease Guidelines.[1] Repeated therapeutic aspiration may be considered as a management option in patients with a reduced life expectancy of less than four weeks or for frail or elderly patients of poor ECOG performance status. This is unlikely to be an acceptable long term management option in those with a prognosis of longer than one month due to associated risks, including the formation of adhesions and septations between the parietal and visceral pleura. The individual risks associated with any pleural intervention such as post-procedural bleeding or pleural infection should be considered cumulative with each procedure, consequently reducing the acceptability of this approach, particularly when other treatment options are available.[1]

It has been suggested that in the context of systemic chemotherapy, management of malignant pleural effusions may be adequately achieved by therapeutic pleural aspiration alone. It may be possible to avoid further intervention in select cases of small cell lung cancer, lymphoma and highly chemosensitive breast cancer, however there remains a high risk of re-accumulation with more than 90% of these effusions recurring and requiring further, more definitive intervention. As a result, there is a lack of consensus with regards to the validity of this treatment option in most tumour types.[17]

Pleural aspiration is a simple and effective intervention that not only results in significant short term benefit with low patient morbidity, but it may also be used to direct future management options and

patient selection when making decisions with regards to definitive management by allowing easy assessment of unexpandable lung.

Despite its current position in conventional algorithms, the role of therapeutic aspiration may be subject to change. The increasing popularity of indwelling pleural catheters has demonstrated their role as an alternative in those patients with limited prognoses. Drainage in the community may provide more appropriate palliation than recurrent day case hospital admissions for therapeutic aspiration and IPCs also provide a longer term solution with little additional morbidity compared with aspiration. Their flexibility of use means that they may be inserted in patients with or without unexpandable lung and as a result could be considered as an alternative first line investigation or intervention in the management of malignant pleural effusion.

Long Term Management: Intercostal chest drain and talc pleurodesis

The high rate of pleural effusion recurrence following simple aspiration means that long term management must be considered. Prior to the advent and widespread use of indwelling pleural catheters, pleural fluid drainage and talc pleurodesis was considered the exclusive traditional first line definitive management option for malignant pleural effusion. This position is reflected in the BTS Pleural Disease Guidelines originally published in 2010.[1]

A number of drawbacks associated with pleurodesis remain. These include recognised failure rates, the requirement for adequate visceral and parietal pleural apposition, along with a mean length of inpatient stay associated of 5-7 days.[18] Other documented adverse effects include fever and pain.[19]

Long Term Management: Indwelling pleural catheters

The current 2010 BTS Pleural Disease Guidelines place indwelling pleural catheters as a second line management option in the long term management of malignant pleural effusion, predominantly suitable for those patients in whom talc pleurodesis is either inappropriate or has been unsuccessful. Their use in clinical practice however, has significantly increased over the last decade and as a result IPCs now represent a joint first line definitive option with the decision often based on patient preference. There is also a clear indication for first line use in patients with unexpandable lung in whom talc pleurodesis is not indicated. The current evidence supports this position, with significant improvements in dyspnoea in 86% of patients in the IPC arm of the TIME2 trial, without statistically significant differences when compared with those undergoing talc pleurodesis. There were also no statistically significant differences when comparing quality of life measurements. These findings were corroborated by the AMPLE study from 2017.[1, 7, 8]

Despite statistically significant increases in the frequency of adverse events such as pleural infection, catheter tract metastases and catheter displacement or blockage, IPCs provide an ambulatory treatment option allowing for the domiciliary management of malignant pleural effusions. This result is greater patient independence and autonomy.

Benefit has also been suggested from the statistically significant reduction in the number of subsequent pleural procedures required in those patients undergoing IPC insertion when compared with those receiving talc pleurodesis. This has been widely accepted as a positive patient centred outcome, however patients with an IPC in situ have their pleural space accessed often multiple times per week and although this may not considered a distinct procedure performed in hospital, equivalent to aspiration or chest drain, the clinical significance of this measurement is therefore less clear.[7, 8]

Pleurodesis versus IPCs

Pleurodesis Agents and Efficacy

In the UK, the most commonly used pleurodesis agent is talc slurry which is instilled into the pleural space via an intercostal chest drain. This can be performed easily at the bedside and pleurodesis success is documented as 70-80%.[19, 20] Multiple other agents are available and are used worldwide such as bleomycin, tetracycline, iodine and autologous blood. Alternative methods are also used and talc pleurodesis may also be performed via poudrage at local anaesthetic thoracoscopy. In an attempt to determine the superiority of talc administration methods, the open-label, multicentre randomised controlled TAPPS trial (ISRCTN47845793) was designed to compare talc poudrage with talc slurry with a primary outcome measure of pleurodesis failure at three months which is defined as the need for further ipsilateral pleural intervention for fluid management. This has recently completed however results are currently awaited.[21]

A Cochrane review recently published in 2016, suggested that the most efficacious method of pleurodesis may be talc poudrage ahead of alternatives such as tetracycline and bleomycin. It was also suggested however, that superiority over talc slurry or doxycycline is unclear. This is primarily due to significant heterogeneity between individual studies, their primary and secondary endpoints and how these were recorded.[19]

Predicting pleurodesis success remains difficult but a number of predictors have been proposed.

1. Drain size

   The results from the TIME1 randomised control trial suggest that chest drain size may play a role in pleurodesis success, although the mechanism for this has not been completely elucidated. Overall pleurodesis efficacy within the trial was in keeping with previous figures as failure rates of between 20 and 30% were demonstrated. It was established that small 12Fr Seldinger chest drains failed to meet non-inferiority criteria with regards to pleurodesis success when directly compared with 24Fr large bore drains. Pleurodesis failure for the small Seldinger drains was

recorded as 30% versus 24% for the large bore drain group suggesting that a larger calibre of drain may be required to improve efficacy. Despite a significantly higher rate of drain dislodgement prior to a clinical decision to remove in the smaller Seldinger group, this failed to account for the difference in pleurodesis success. Of note, it was also demonstrated that there were no clinically significant detrimental effects from non-steroidal anti-inflammatory drug use on pleurodesis efficacy despite previous long term controversy over their use.[18]

2. Sonographic features

It is thought that sonographic features seen on simple bedside thoracic ultrasound may be a useful tool in predicting and identifying pleurodesis success. It may in turn be possible to reduce associated inpatient length of stay. The SIMPLE study (ISRCTN16441661) is a multicentre, randomised controlled trial which has been designed using ultrasound to identify pleurodesis success with the primary outcome measure of a reduction in hospital length of stay during the initial hospitalisation. The premise for this study is based on an observational animal study in rabbits that suggested echogenic fibrin strands demonstrated on ultrasound may be associated with higher pleurodesis success.[22, 23]

It has also been suggested separately that it may be possible to pre-emptively use ultrasound to predict those patients who are likely to have unexpandable lung and who are therefore not suitable for consideration of pleurodesis due to subsequent lack of apposition following drainage.[24] Various thresholds have been suggested but it is thought that M-mode displacement of less than 1.2mm in the atelectatic lung may be a good predictor of unexpandable lung. This could subsequently be used to allow patients to proceed directly to a definitive procedure, in contrast to the current method of assessing for unexpandable lung using imaging such as a chest radiograph following a large volume therapeutic aspiration.[25]

IPC Drainage and Autopleurodesis

Autopleurodesis, or spontaneous pleurodesis related to the catheter, is a recognised outcome of long term catheter drainage, although the frequency with which this occurs varies widely. Figures reported vary from 23% up to 65%.[7, 26, 27]

A number of factors may influence IPC related autopleurodesis.

1. Drainage Frequency

A lack of clarity persists with regards to the frequency with which drainage of an IPC should be performed. This has not been previously defined, however current standard practice is often characterised by alternate day drainage. Wahidi et al. compared aggressive daily drainage with conventional treatment consisting of alternate day drainage using a multicentre randomised controlled trial. The ASAP trial, published in 2017, demonstrated aggressive management resulted in a statistically significant increase in the rate of autopleurodesis at 12 weeks as well as a reduction in the time taken for it to be achieved. Autopleurodesis was achieved in 47% of patients compared with 24% in the control arm (p=0.003). The median time to autopleurodesis was significantly reduced from 90 days to 54. There were no significant differences found in the frequency of adverse events seen. Quality of life and patient satisfaction measures between the two groups were also not significantly different.[26]

2. Talc instillation

Although indwelling pleural catheters and talc pleurodesis are often presented as two distinct, mutually exclusive interventions, the IPC-PLUS trial, published by Bhatnagar et al. in 2018 has demonstrated that instillation of a talc slurry through the IPC as a day case procedure, in patients without evidence of lung entrapment is feasible and resulted in a pleurodesis rate of 43%. When compared with the autopleurodesis rate of 23% in the placebo goup, this represents a statistically significant improvement (p=0.008). There were also statistically significant

improvements seen in quality of life measures and symptom scores with no significant difference seen in the number of adverse events. [27]

These two methods of IPC management allow patients the opportunity to be managed in an ambulatory or domiciliary setting, but also improve the likelihood of pleurodesis to prevent unnecessary ongoing burdensome treatment and reduce cost. The IPC-PLUS trial in particular, challenges previously held positions of two distinct treatment modalities and represents a significant change in practice, establishing this combined treatment option as valid treatment choice.

It may be possible to infer from the results of these two trials that consideration of a combined approach of daily drainage and talc instillation in IPC patients may be of value. It could be suggested that an even greater pleurodesis rate along with a further reduction in overall duration of treatment might be seen by way of a synergistic effect but this has yet to be adequately tested by means of a randomised controlled trial.

This paradigm shift is important to consider; however, although rates of autopleurodesis are improved in IPC patients following either talc instillation or daily drainage, it should be noted that pleurodesis success is still significantly lower (at around 50%) when compared to conventional methods such as talc poudrage with an in patient stay (around 80%). No direct comparison has been performed to date but this conclusion may not be appropriate, as the primary treatment goal of an IPC is long term symptomatic management and not explicitly pleurodesis.

Healthcare Burden and Cost Considerations

It has been estimated that per-patient costs associated with pleurodesis and the accompanying inpatient stay are approximately £1320. This results in an approximate cost of £33 million per year in the UK alone based on an estimate of the number of procedures performed.[22]

One of the significant benefits of IPCs is the initial reduction in time spent in hospital at the time of the procedure. The TIME2 trial confirmed this finding which has advantageous consequences for patients with limited life expectancy, but also may result in advantages for hospital services under pressure by reducing bed pressures. The TIME2 trial also found that IPCs reduced the number of subsequent pleural procedures required. These findings led to the hypothesis that IPCs may offer cost advantages over traditional pleurodesis.[7]

Thomas et al. published the AMPLE study in 2017 as a follow on study from TIME2. This was a randomised controlled trial designed to investigate the impact of IPC versus pleurodesis in malignant pleural effusion, specifically focusing on inpatient days with the primary end point set as the total number of days spent as an inpatient to either death or to 12 months. This endpoint was chosen as an appropriate patient centred outcome given that reducing inpatient stays in patients with limited prognosis is a valuable objective. Inpatient bed days may also be used to consider the financial impact and organisational or structural implications within the healthcare structure. The trial was designed however, to only record those whose inpatient stay crossed midnight and consequently did not take into account patients undergoing day procedures and therefore may have underestimated the amount of time spent in hospital by those with known poor median survival.

This study demonstrated that there was a statistically significant reduction in the number of inpatient days in patients managed with an IPC when compared with those receiving standard traditional care of a drain and talc pleurodesis. During trial development, an arbitrary clinically significant difference of 5 days was selected. The median difference of 2 days between the two groups failed to meet this cut off.

This study therefore demonstrated that there was a considerable requirement for inpatient management in malignant pleural effusion in both the IPC and pleurodesis groups. Combined figures showed median stays of 10 days and a mean of 14.5. IPC patients had a median of 10 inpatient days and a mean of 12.7 when compared with 12 and 16.3 for the talc pleurodesis group. There was also

no statistically significant difference between the number of inpatient days in each group once the admission for initial management was excluded. Despite statistically significant reductions in inpatient bed days in the IPC group, this data questions the perception of IPCs as providing a true ambulatory management option given the high number of inpatient bed days in both groups and the lack of clinical significance demonstrated. Results may also be confounded further by not accounting for day case admissions as days spent in hospital. [8]

The authors suggest that health economic analysis was not carried out due to worldwide variance in equipment, procedural and inpatient costs. It has been possible however, to perform cost analysis on the comprehensive TIME2 dataset. Overall, this showed no significant difference in cost between the IPC and talc pleurodesis groups, however this was performed prior to the publication of ASAP or IPC-PLUS. A higher initial cost was incurred in the pleurodesis group due to a longer initial inpatient hospital stay, but regular IPC drainage led to significantly higher ongoing costs. Subsequent further analysis suggested that IPCs were a less costly alternative in patients with limited survival. IPC cost effectiveness is therefore influenced by patient longevity and autopleurodesis rates which are now known to be modifiable via increased frequency of drainage or outpatient talc instillation. It was suggested that in a patient population with a median survival of 6 months both treatment options are similarly cost effective, however within a health economic context, talc pleurodesis would appear to be superior if median patient survival is extended to 12 months. [28]

Future directions

Current methods to identify patients who are not suitable for consideration of talc pleurodesis due to unexpandable lung include detection via simple chest radiography following therapeutic aspiration or the use of pleural manometry. The role of manometry in clinical practice remains unclear. It is advocated by some proponents, however the cumbersome, complicated equipment

and prolonged procedure times have prevented its widespread acceptance.[29] Several prospective techniques have therefore been suggested that may assist with the identification of these patients, allowing them to proceed directly to a more appropriate intervention, such as an IPC, avoiding unnecessary procedures.

1. Sonographic Pleurodesis Prediction

Unexpandable lung may be identified prior to aspiration by measuring cardiac pulsation induced lung movement using motion mode (M-mode) ultrasound. Although an appropriate cut-off value has yet to be fully defined and validated, it is suggested that movement detected using M-mode of greater than 1.2mm is predictive of fully expandable atelectatic lung. A value less than this is highly suggestive of unexpandable lung [Figure 2]. A single centre, retrospective observational study published recently in 2018 used an M-mode cut off of 2mm and demonstrated a sensitivity of 91% and specificity of 88% using this technique to detect unexpandable lung. Further study is required to adequately define and validate appropriate M-mode cut-off values.[24, 30, 31]

The role of ultrasound to predict pleurodesis success in those patients with adequate pleural apposition also remains unclear. Sonographic echogenicity, which represents a higher complexity or density of fluid was associated with higher pleurodesis success in an animal study performed in rabbits. It is thought that this may reflect higher protein concentrations which increase fibrin activation and subsequently improve efficacy of the pleurodesis agent. Echogenicity is a non-specific ultrasound finding and so the role in predicting pleurodesis success requires further investigation.[1, 22, 23, 32]

2. Biomarker Pleurodesis Prediction

The development of biomarkers has dramatically increased over recent times with advancement of the era of personalised medicine. In a respiratory context, progress has been most marked in asthma and airways disease with the emergence of the crucial role of biomarkers such as the

fraction of exhaled nitric oxide (FeNO).[33] Serum mesothelin is also thought to have an increasingly important role in the investigation and management of some pleural diseases such as malignant pleural mesothelioma.[34]

The PROMISE study published by Psallidas et al. in 2018 was a multicohort study using datasets from five randomised controlled trials and was designed to assess the role of biomarkers in predicting pleurodesis success and survival. Three biomarkers were identified as accurate predictors of survival, however unfortunately all eight biomarkers examined in the prediction of pleurodesis outcomes were unsuccessful. These included tumour necrosis factor α, (TNFα), TNFβ, interleukin 6, and fibroblast growth factor 2 (FGF2). [35] Although unsuccessful in predicting pleurodesis outcome in this instance, potential has been shown with the development of a prognostic survival score using biomarkers and further investigation is warranted.

3. Fibrinolytics for multiloculated malignant effusion

Management of multiloculated malignant pleural effusion presents a challenging dilemma as these effusions often cannot be adequately drained to relieve symptoms using conventional methods, with residual pleural effusion also preventing pleurodesis attempts. This leads to reduced symptom benefit, an increased frequency of pleural interventions and generally inadequate palliation of symptoms. Local anaesthetic thoracoscopy has been suggested as a potential solution by causing disruption of septations and clearance of the pleural space prior to either pleurodesis or IPC insertion, however there are a number of impediments. This approach requires patients to be relatively fit and have a good performance status to undergo the procedure. Also, in those patients with unexplandable lung, septations and loculations often recur with the effusion which in turn complicates ongoing management with an IPC. It has therefore been suggested that unification of the pleural space may be possible using fibrinolytic

therapy to break down septations, particularly given the positive outcomes associated with its use in pleural infection.[36, 37]

The consideration of the role fibrinolytics in malignant pleural effusion is not a new concept and multiple previous trials have been conducted with variable success. Two small randomised controlled trials demonstrated improvements in drainage and lung reexpansion, but no effect on pleurodesis success.[38-40] TIME3 was a randomised controlled trial of 71 patients published in 2018 and was designed with greater patient centred outcomes in mind by assessing dyspnoea and pleurodesis failure. No statistically significant differences were demonstrated, however radiographic appearances improved which was a finding in keeping with previous studies. It is thought however that results may have been confounded by patient selection. Approximately 80% of patients enrolled had a performance status of 3-4 resulting in a relatively frail cohort in whom improvements in dyspnoea may have been more difficult to detect or perceive. The results may therefore not be applicable to the wider population with malignant pleural effusion and intrapleural fibrinolytics may still have a role in selected circumstances. Further study may also be indicated with particular reference to the IPC population, as this is a group who may self-select as a fitter, more ambulatory cohort.[36]

Conclusions

Malignant pleural effusion remains a significant clinical problem resulting in substantial healthcare burden including inpatient stay and cost. Median survival and prognosis are limited and so therefore all interventions should be considered with a palliative perspective.

Several methods are available in the management of malignant pleural effusion including indwelling pleural catheters and traditional chest drainage and talc pleurodesis. The popularity of IPCs have

risen significantly over recent times, cementing their position in clinical practice as joint first choice treatment option, although difficulties still remain.

Despite the availability of multiple new and emerging techniques, patient selection and predicting treatment success remain difficult due to complications such as unexpandable lung and multiloculated effusions.

The poor prognosis and palliative outlook from malignant pleural effusion means that future studies should be measured using patient centred outcomes wherever possible.

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