Review Article

Pleural controversies: indwelling pleural catheter *vs*. pleurodesis for malignant pleural effusions

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Abstract: Malignant pleural effusions (MPE) are frequent consequences of malignant disease and significantly impair the quality of life (QoL) of patients. There are two main options for the palliation of MPE-related symptoms: obliterating the pleural space by pleurodesis to prevent further fluid reaccumulation, or chronically draining the pleural fluid with an indwelling pleural catheter (IPC). There is controversy as to which approach is superior each having advantages and drawbacks. Pleurodesis offers a higher chance of rapid resolution of the pleural effusion with an intervention that is time limited but at the expense of a more invasive procedure, the need for a hospital stay and a higher need for repeat procedures. IPC offers an outpatient solution which is less invasive but at the cost of prolonged catheter drainages and care in a significant portion of patients who will not achieve pleurodesis. Impact on QoL, symptom relief and costs do not appear to be significantly different between the two options. Treatment of MPE should be tailored to the patient's functional status, comorbidities, prognosis and personal preferences as well as local expertise. Hybrid approaches using pleurodesis techniques and IPC concomitantly may come into play in the near future to further improve patient care.

Keywords: Pleural effusions; malignant; catheters; indwelling; pleurodesis

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Introduction

Malignant pleural effusions (MPE) are a frequent complication of cancers. They are most commonly caused by lung and breast cancers, but may be caused by almost any site of primary cancer as well as primary cancers of the pleura (1). They are present in 15% of patients with a new diagnosis of lung cancer and will eventually occur in 46% (2). It has been estimated that 150,000 patients develop an MPE every year in the United States (3).

MPE are symptomatic in the majority of cases (4). The most common presenting complaints are dyspnea (57%), cough (43%) and chest pain (26%) (4). These symptoms have been demonstrated to have a significant impact on the quality of life (QoL) of patients (5). MPE always represent a form of advanced cancer and are associated with a median survival of 3 to 12 months (1). The median survival varies according to the primary cancer site, from 3 to 6 months for non-small cell lung cancer to 6 to 24 months for breast cancer (2,6).

Traditionally, trials of MPE treatments have used pleural fluid re-accumulation on imaging, usually at a 30-day time point, as a primary outcome measure but there has been a change in paradigm towards an approach aiming for symptom relief and QoL, and for longer follow-up periods. A good example of this was noted in the recent Therapeutic Intervention in Malignant Effusion (TIME)-2 trial, which used a visual analog scale of dyspnea improvement as primary outcome (7). With this in mind, we will compare and contrast pleurodesis and indwelling pleural catheters (IPC) approaches to MPE.

Main treatment modalities & patient selection

The treatment of MPE is aimed at palliating symptoms since no intervention has been shown to improve survival in this population (8) and since survival is generally limited in cancers that have spread to the pleural space. In this

palliative setting, only patients symptomatic from their MPE should be submitted to further intervention (9). As well, further interventions in symptomatic patients should be limited to those patients who have experienced symptomatic improvement following initial therapeutic thoracentesis. The two main treatment approaches to MPE are to obliterate the pleural space via a pleurodesis procedure or to chronically drain the pleural cavity with IPC.

Pleurodesis can be performed surgically via thoracoscopy or video assisted thoracic surgery (VATS) under general anesthesia, provided the patient's condition is such that it can be tolerated. Pleuroscopy or medical thoracoscopy presents an alternative for pleurodesis in patients who cannot tolerate general anesthesia as it is usually performed under conscious sedation or even local anesthesia alone. Finally, sclerosing agents can be administered at the bedside through a small bore chest tube. While this manuscript does not intend to compare these various approaches in detail, randomized trials to date have failed to show superiority of thoracoscopic *vs*. bedside chest tube approaches to pleurodesis with regards to primary study endpoints. Nevertheless, many practitioners tout the superiority of thoracoscopic approaches based on personal experience and subgroup or secondary outcome analyses noted in the literature.

Talc is widely regarded as the best agent for pleurodesis, in particular using product from Luzenac (France) which has a good safety record (10). Concerns remain regarding the variability in talc preparations and links to severe complications such as ARDS. Many agents have also been effective including silver nitrate, tetracyclines, bleomycin and a long list of others.

IPC aimed to intermittently drain the malignant effusion in order to maintain adequate lung expansion without a more specific attempt at causing pleurodesis. Catheters are typically inserted on an outpatient basis under local anaesthesia followed by home drainage performed by a home care provider or trained family members (11). Interestingly, with drainage alone, a substantial number of patients can eventually have the catheter removed following what has been called "spontaneous pleurodesis", although the mechanism behind this process is unknown.

While many patients could be considered for either approach, certain factors may favor one over the other. Apposition of the pleural surfaces is the key in achieving pleurodesis. It is thus important to demonstrate adequate pulmonary re-expansion prior to pleurodesis, with trapped lung generally considered a contraindication to these techniques. Tunneled catheters on the other hand can be effective in controlling symptoms in patients with trapped lung (12), although symptom improvement following simple thoracentesis should be documented beforehand.

Patients with poor performance status or high surgical risk would best avoid thoracoscopic approaches, but still could be considered for either bedside pleurodesis procedures or IPC placement. Some authors have suggested that patients with longer survival should preferentially be offered pleurodesis rather than IPC, and vice-versa. Unfortunately, survival in this patient population is difficult to predict upfront although tools are being developed to assist in assigning more accurate prognosis (13). Patients with survival estimates measured in days would probably best be treated with thoracentesis and/or systemic opioids alone.

While patients with trapped lung, reduced performance status and shorter life expectancy may seem the most appropriate group to treat with IPC, patients with longer survival and good lung re-expansion have demonstrated excellent outcomes with this approach as well (14).

Malignant chylothorax had also been considered a contraindication to IPC insertion but successful management with this approach has been described (15). Pleurodesis can also be considered in these patients but has been associated with lower success rates than for MPE in general (15).

Symptom control and QoL

We have noted a welcomed shift from radiological end points to symptom palliation as primary endpoints for therapeutic trials in recent years. Both IPC treatment and talc pleurodesis have demonstrated substantial improvements in dyspnea control and overall QoL using validated assessment tools (16-19). It should be stressed that improvements resulting from both approaches are substantial, confirming the importance of comprehensive MPE treatment as part of overall care of cancer patients. Prior to 2012, only one randomized controlled trial had compared symptom improvement between pleurodesis (with doxycycline) and IPCs (20). This trial did not demonstrate a significant difference in Borg Dyspnea Score and Guyatt Chronic Respiratory Questionnaire score between groups. More recently, a propensity-matched comparison of talc poudrage *vs*. IPC did not demonstrate a significant difference in performance score (21). The TIME-2 randomized trial of IPC *vs*. talc pleurodesis also did not find a difference in its primary outcome measure of dyspnea improvement at 42 days on a visual analog scale, although improved symptoms became significant at the 6 months'

time point in favor of the IPC group (7).

While both approaches afford similar dyspnea control, pleurodesis has the advantage of potentially providing short-term definitive treatment for MPE without the perceived burden of ongoing care associated with the IPC (dressing changes, drainages, etc.). Nevertheless, this burden does not appear to have an adverse effect on overall QoL in the TIME-2 trial which noted similar improvement in both arms with a non-significant trend favoring IPC (8).

Pleurodesis rates and late recurrences

Pleurodesis rates between 60% and 100% have been reported with different sclerosing agents (22). This variability can be explained by the different agents used but also by the method used (VATS *vs.* slurry), the timing of outcome measurement, the choice of outcome, the duration of follow up, the study design (intention-to-treat *vs.* per protocol) and the population studied. By having limited follow up, trials may miss late recurrences and by not using intention-to-treat designs, trials will exclude patients who are considered for treatment but do not receive the sclerosing agent or die before outcome measurement, both leading to artificially inflated pleurodesis rates. For example, a phase III trial reported a 78% success rate following thoracoscopic talc pleurodesis, but if all enrolled subjects had been included, only 60% would have been alive and recurrence free at 30 days and an additional 33% would have experienced late recurrence beyond that time point (23). Late recurrences after 30 days post pleurodesis have also been reported in 6-38% of cases in other studies (24-27).

While pleurodesis is not the primary therapeutic endpoint for IPC treatment, a systematic review reported an overall spontaneous pleurodesis rate of 45% (28), but when limiting inclusion criteria to patients who may have been candidates for pleurodesis (re-expansion ≥80% and survival ≥90 days), pleurodesis rates climb to 70% (14). IPC related pleurodesis has been reported to occur between 29 to 59 days post placement (29-31). Although time to pleurodesis is longer, one group has reported more rapid improvements in dyspnea and QoL (within 7 days) with IPC *vs.* pleurodesis, further highlighting that pleurodesis and symptom control are not one and the same (32).

Since pleurodesis rate may not be the most appropriate method to compare these procedures, effusion control could be defined as the need for any additional ipsilateral pleural procedure during the life span of a patient. With IPC, patients who have had their catheter removed because of spontaneous pleurodesis, additional intervention will be required in 3.8% to 8.7% (29-31) of cases. Overall, 9% to 10% (29,30) of all IPC treated patients will necessitate ipsilateral re-intervention. Several comparative studies have noted decreased need for repeat procedures in IPC cohorts *vs.* pleurodesis, including the TIME-2 randomized trial (6% *vs.* 22%, P=0.03) (7,32,33).

It would appear that while pleurodesis approaches are associated with a shorter initial treatment phase, more rapid pleurodesis and absence of the need for chronic catheter care, they may also be associated with lower rates of effusion control and increased need for repeat pleural intervention.

Hospitalization procedure related

In the context of a limited prognosis, avoiding hospital stays may be an important consideration for patients. This includes not only days related to the procedure itself, but also subsequent stays caused by recurrences or complications. Since IPC insertion can be done as an outpatient, there is little debate that this approach reduces initial hospitalization over pleurodesis procedures which necessitate median stays of 4 to 7 days (26,34,35). In the recent TIME-2 trial (7), patients only necessitated a median of 4 days of hospitalization for talc pleurodesis and 0 for IPC insertion. During the following year, 23% of patients in the IPC group and 16% of patients in the talc group necessitated re-admission for drainage or drain related complications but this difference was not statistically significant. Another non-randomized study reported a reduction in all cause and effusion specific hospitalization days in IPC treated patients *vs.* pleurodesis over a 12-month period (32). As such, IPC approaches may be preferred in patients wishing to reduce the number of days spent in hospital.

Complications

The possible adverse effects of a procedure play a significant role in a patient's decision between pleurodesis or IPC. A review of the efficacy and safety of IPC revealed that 87.5% of patients did not have any complications (28). For those who did, the most frequent complication was catheter malfunction with a rate of 9.1% and the most concerning was empyema with a rate of 2.8%. Other complications included bleeding, infection, cellulitis, dislocated catheter, obstructed catheter, pain, pneumothorax, and tract metastasis. Catheter removal due to a complication is required in 8.5% of patients. Symptomatic loculation of fluid requiring fibrinolytics may also be considered as a complication of IPC and was noted in

3.9% of cases in the TIME-2 trial (7).

Complications associated with pleurodesis vary according to the agent and method of delivery used. We will focus mainly on the complications of talc pleurodesis as it is the preferred and most studied agent. Talc pleurodesis induces an inflammatory response which has been reported to cause fever and pain in 26% and 31% of patients respectively according to a Cochrane meta-analysis (36). Pain may be severe enough to necessitate the use of a patient controlled anesthesia in as many as 5% of patients (20). Pain is only reported in 5.6% of patients during IPC insertion and pain persisting beyond the immediate post-procedural period is reported in 3.2% of patients (28). Pain post-IPC insertion is usually mild enough to be managed without opiates. Pleurodesis techniques are associated with a risk of empyema of 0.4% to 4.0% (23,24) which is in the same range as that reported with IPC insertion. Talc pleurodesis has also been associated with rates of ARDS as high as 9% (37), particularly with the use of higher doses and small-particle-size talc. A large prospective trial of talc pleurodesis in 558 patients using large-particle-size Luzenac talc did not cause ARDS (10). Use of other talc preparations should be considered with caution and preferably with knowledge of talc particle size distribution and clinical data with the specific preparation. Other complications encountered following talc pleurodesis include pneumothorax, re-expansion pulmonary edema, infection of procedure site, pneumonia, pulmonary embolism, and atrial fibrillation.

Discordant results have been noted in studies comparing complication rates for IPC *vs.* pleurodesis. Non-randomized studies have suggested similar complication rates in one (32) and lower complication rates for IPC in another study (33). The TIME-2 trial demonstrated a higher rate of complications in the IPC group, although there were no statistically significant differences with regards to severe complications (7).

Cost

The cost distribution over time is different between IPC and pleurodesis. For pleurodesis, the initial cost is important due to the procedure and initial hospitalization requirements. If pleurodesis occurs, the long term cost becomes minimal as long as the effusion is controlled. On the other hand, the initial cost for IPC insertion is less important since it is an outpatient procedure but the long term cost is significant due to the cost of supplies as well as the nursing care time necessary to perform the drainages. These long term costs will accumulate until the patients dies unless spontaneous pleurodesis occurs.

Until recently, the cost of the two therapeutic options had only been compared in studies using mathematical models (38,39). A recent study based on the TIME-2 trial (40) demonstrated overall mean costs over a 1 year follow up of $4,993 for IPC *vs.* $4,581 for pleurodesis. The incremental mean cost difference of $401 (95% CI: –1,387 to 2,261) was non-significantly different, but if patients survived less than 14 weeks IPC became significantly less costly ($–1,719, 95% CI: –3,376 to –85). The median survival in the population studied was 200 days with 14% of patients being alive at 1 year. As such, cost considerations should not be the main driver in determining treatment approach, except perhaps in patients with shorter prognosis.

Combination approaches

Since IPC and pleurodesis approaches have their own strengths and weaknesses, authors have tried to combine them to create an optimal approach to MPE, a less invasive approach that combines the shorter hospital stay of IPC insertion with an increased pleurodesis rate. The first combination explored was talc pleurodesis by medical thoracoscopy with simultaneous insertion of an IPC. A 30-patient pilot study (41) demonstrated a 1.79-day median hospital stay with a 92% pleurodesis rate at 6 months and universal improvement in dyspnea and QoL. Similar results were noted in another small study (42). A second hybrid approach is currently being explored in the United Kingdom. The randomized controlled IPC-plus trial is comparing the efficacy of IPC alone *vs.* IPC plus talc through IPC as an outpatient (EUdraCT number: 2012-000599-40). The third option for combination therapy to date only reported in animal studies has been to modify IPC with a drug eluting coating to deliver sclerosing agents to the pleural space over time (43,44). With these approaches, we hope to see treatment options move closer to an ideal approach to this condition.

Conclusions

While reports on IPC treatment for MPE have increased over the past 15 years, and international guidelines on MPE treatment now include this modality as a viable approach, recent years have brought us more comparative data for this technique *vs.* pleurodesis. No clear superiority of either option has been established and both remain valid therapeutic options for patients with MPE. In certain cases, IPC appears

to offer advantages over pleurodesis, as would be the case for a patient with poor functional status who cannot tolerate pleurodesis or in the presence of a trapped lung. Pleurodesis put forward a higher chance of rapid resolution of a pleural effusion with an intervention that is limited in time, but this requires a hospital stay, a more invasive procedure and possibly the need for repeated procedures. IPC is an outpatient solution which is less invasive, but necessitates prolonged catheter drainages and care in a significant portion of patients who will not achieve pleurodesis. Successful symptom relief and QoL improvement can be achieved with both approaches without evidence for significant differences between the two options. The cost of the two interventions does not differ significantly unless the prognosis is poor, in which case IPC is less costly.

Combination approaches to treatment of MPE are actively being investigated in the hopes of further improving our treatment options for these patients.

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