Optimizing the study of tunneled intrapleural catheters for malignant pleural effusions

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The optimal therapy for malignant pleural effusions is relatively understudied considering half of patients with cancer develop them during their life span, yielding an annual US/European incidence of 750,000 cases.^{1,2} The challenges studying this disease are numerous and discussed later in this article. Attempting to accelerate pleurodesis by a variety of sclerosis agents was the classic approach and remains popular today. Maintaining lung expansion by a tunneled intrapleural catheter (TIC) so that a pleurodesis could occur naturally began in approximately 1986 with the off-label use of a chemotherapy therapy infusion port and then a peritoneal dialysis catheter in 1994, which was modified to an intended-use device by adding a 1-way valve and popularized by Putnam and colleagues.³ Interest in this technology has grown steadily and is preferred at many cancer centers because of the avoidance of inpatient hospitalization, as described in the AMPLE study by Thomas and colleagues.⁴

Before discussing AMPLE, it is important to review briefly the relevant thoracic surgical contributions to cooperative group science that led up to the current study. In the early 1990s, visionary leaders at the Cancer and Leukemia Group B (CALGB) supported introduction of a National Institutes of Health U10 grant organized by Dr David Sugarbaker to both increase the ability of surgical oncologists to participate in clinical trials and enable study of then newly coined “video-assisted thoracic surgery” (VATS, now “thoroscopic surgery”).⁵ CALGB 9334, which compared chest tube talc slurry with VATS poudrage for malignant pleural effusions, successfully accrued 501 randomized patients, the largest for the lung disease site.⁶ The success of the then relatively novel accrual-based capitated model with payments made directly to its many participating surgeons did not go unnoticed and contributed to disrupting the traditional medical oncology-based cooperative group resource allocations.

CALGB 9334 demonstrated equivalence between bedside talc slurry and VATS pleurodesis, and because there

Pleural compliance curves useful for categorizing effusions.

Central Message

Aggregating patients with malignant pleural effusion with diverse malignancies and physiologies simplifies study enrollment but reduces investigator detection of optimal therapeutic subgroups.

See Editorial Commentaries pages 1260 and 1262.

were more pneumonias for those who underwent a general anesthetic, the former became more popular.⁶ However, surgeons today still will opt for a thoroscopic approach to pleurodesis because of the option to free lung, more precisely apply sclerosant, and obtain tissue for diagnostic studies.

There was naturally an interest in capitalizing on the success of 9334 because the infrastructure for accruing these patients was still in place. Comparing the then only TIC (PleurX, BD, Franklin Lakes, NJ) with the less-invasive talc slurry arm of 9334 seemed like an obvious choice, and CALGB 30102 was born.⁷ In addition to Putnam and colleagues' randomized study,³ experience was growing with the use of TIC, and single-institution reports compared its use with talc pleurodesis and suggested benefit for those with trapped lungs.^{8,9} Supporting articles are described in comprehensive reviews and in the [Appendix E1](#).¹⁰

Unfortunately, CALGB 30102 failed to accrue despite an existing proven infrastructure. In retrospect, failure should have been predictable, and the reason is relevant to this current discussion.⁷ Patients and investigators who had equipoise between 2 inpatient-based therapies no longer tolerated randomization when a TIC arm enabled early discharge or hospitalization avoidance. Although this generated healthy discussions on how to enable an alternative trial design to accommodate the roughly even split of

patient preference toward each arm, the trial was terminated early. Nevertheless, there was sufficient participation to demonstrate better effusion control for patients with TIC, particularly those with trapped lungs.⁷

The recently published AMPLE trial was well designed and showed a 2-day reduction of hospital stay at 1 year of follow-up for the patients with TIC compared with those who received pleurodesis.⁴ Because TIC is an ongoing therapy, there were fewer reinterventions for pleural effusion in this group. Quality of life was similar (trending better at 12 months for TIC), and the stay reductions roughly equaled that expected by avoiding hospitalization for the initial pleurodesis. Because this difference was approximately one fifth of the total hospitalization required by both groups, the investigators questioned the clinical importance of the results. The randomization scheme attempted to balance patients with known trapped lungs; however, with only 2 to 3 such patients in each arm, referral avoidance for the study seems likely. Of patients screened, 35% were not eligible with the most common reason being patient refusal. Although accrual was respectable, it took 28 months to complete at 9 high-volume centers, suggesting that there is a larger population of patients who were not referred to be evaluated for this trial.

The results of AMPLE were similar to that of TIME2 published in 2012, which took more than 4 years to recruit 106 patients from 7 UK hospitals.¹¹ Notably, dyspnea control was similar at first but favored TIC at 6 months. Quality of life was similar, and hospitalization was less for TIC.¹¹ Another randomized trial that needs to be noted is the NVALT-14, which took 34 months to accrue 98 patients from at least 8 different centers.¹² TIC was not better than talc in terms of the dyspnea score but was superior for hospital stay and reinterventions.

Although we applaud these investigators for their study of an important problem, difficulty with accrual and failure to detect meaningful differences between treatment arms suggest problems with methodology. Although the population being studied is similar in general terms of having a relatively poor survival, it is diverse in terms of 4 major categories (Table 1): ability to achieve pleurodesis, availability of competing technologies, disease and survival-related factors, and socioeconomic/behavioral concerns. The overlapping primary end points are not unlike what we see in the testing of many lung chemotherapeutic agents without controlling for specific driver mutations and other molecular profiles. Although it is beyond the scope of this article to cover all these confounding factors in detail, more nuanced clinical trial design addressing some of the following issues would likely yield better results.

We generally accept that lung entrapment impairs pleurodesis, and thus patients with suspected trapped lung probably are not referred to clinical trials offering pleurodesis. Unfortunately, despite the wide availability of reusable or

TABLE 1. Population diversity factors requiring better documentation or control in malignant pleural effusion trials

Predictors of pleurodesis
Pleural compliance
Imaging predictors of entrapment or success
Effusion biomarkers favoring pleurodesis
Existing chemotherapy use or infection
Technology factors
Catheter drainage frequency
Chest tube or tunneled catheter brands or types
Talc formulations
Tunnel catheters delivering or embedded with sclerosants
Technology-specific complications
Overall patient survival influenced by disease or treatment factors
Bilateral effusions
Tumor stage
Catheter tract metastases management
Tumor type including genomic prognosticators
Talc effect on metabolism
Nutrient loss from ongoing drainage
Sarcopenia and other causes of dyspnea
Complications from therapy
Surgical risk
Response to chemotherapy
Tumor microenvironment and immunocompetence
Socioeconomic
Cost
Patient anxiety and capacity for self-care
Caregiver support

disposable manometry equipment in hospital settings, quantifying pleural elastance is underused.¹³ Although certain cases of trapped lung are obvious by imaging, gradations of parenchymal stiffness or pleural entrapment remain underappreciated and not quantified or controlled well in pleurodesis trials (Figure 1). Other factors that impair patient survival and the success rate of pleurodesis include imaging findings such as large effusion size, unfavorable histologic types, delays from first presentation to catheter insertion, and effusion chemistry (low pH and high lactate dehydrogenase).¹⁴⁻¹⁷ Concerns with TIC drainage causing intercurrent infection in patients receiving chemotherapy have little support. In fact, infections may have a beneficial effect on pleurodesis and survival if they do occur.¹⁸⁻²¹

Related or competing technology factors can influence effusion trials. Although patients may choose to drain their TIC less frequently to reduce discomfort or cost, this has an adverse effect on achieving pleurodesis.²² Less-expensive catheter options including central venous catheters reduce patient cost but are not as well validated.²³⁻²⁵ Catheters fused with sclerosis agents such as silver nitrate or hybrid rapid pleurodesis protocols are becoming more popular to shorten the duration of TIC therapy.²⁶⁻²⁸ Finally, TIC-related pleural loculations are relatively common and

FIGURE 1. Pleural elastance curves that are useful to predict success with pleurodesis. “Lung entrapment” occurs along the spectrum from a normal organ to the final stage of “trapped lung,” which is generally irreversible without an intervention like decortication.¹³ “Lung entrapment” may be reversible depending on how effectively the process causing it (eg, parenchymal or pleural inflammation) can be treated. Reprinted with permission.¹³

managed safely with intrapleural fibrinolytics (some bleeding risk) but lack uniform guidelines between institutions.^{4,29}

Specific disease and survival factors correlated with pleural effusions require better control as well. Bilateral pleural effusions carry a 2.5 times higher risk of short-term death and thus often excluded from such trials; yet, they are common enough to deserve study.³⁰ Controlling for the totality of metastatic disease burden, which can differ between lung and other metastatic pleural tumors, is important.³¹ Although TIC tract metastases may occur (especially with mesothelioma), prospective randomized evidence does not support routine use of prophylactic radiotherapy.³²⁻³⁴ Likewise, although implanting devices has been a concern in patients with hematologic malignancy, this may be less of a concern for TIC.^{35,36} Talc, on the other hand, remains a relatively heterogeneous product that should be delivered with large particle gradation to prevent systemic distribution.³⁷ Talc creates acute and chronic increased metabolism in the mediastinal lymph nodes and pleura, and it is unknown to what extent this might usurp precious remaining metabolic capacity in patients dying of advanced malignancy.^{38,39} Furthermore, talc is distributed less well as a slurry despite rolling the patient.^{40,41} Homogeneous slurry dispersion might be achieved by its incorporation into a foaming product that is under development.⁴² Although the metabolic demand and protein malnutrition that go along with chronic pleural drainage are theoretic concerns, it has not been borne out in limited studies for TIC for malignant or benign disease.^{43,44}

Fit patients can be relatively asymptomatic with lung opacification, and patients dying of cancer often experience breathlessness with full pulmonary expansion. The latter results from a convergence of associated diseases such as

chronic obstructive pulmonary disease, sarcopenia with deconditioning, and wasting of respiratory muscles.⁴⁵ Unfortunately, these factors distort the dyspnea and reduced quality of life scales measured in pleural effusion studies. They need to be quantified better by functional testing and muscle imaging acceptable to participants so that the relative benefit of effusion drainage can be assessed. Effusion control–related adverse outcomes such as infections need better quantification by objective grading systems and validated surveys to assess their specific effects on quality of life. Serially linking the readily available biomarkers from the effusion microenvironment to outcomes is also critical. Finally, better overall classification of the metastatic patient needs consideration given the emergence of personalized targeted therapies, immunotherapy, totality of metastatic burden, and resistance to chemotherapy.³⁷

Because our methodologies fail to demonstrate effusion-control methods better in terms of survival or quality of life, idiosyncratic patient socioeconomic and behavioral factors become more important in decision process. Costs between pleurodesis and TIC break roughly even in multiple studies unless a short survival is predictable, and then TIC may be better.⁴⁶⁻⁵⁰ Patients who have difficulty affording drainage kits may reduce the aspiration frequency and paradoxically increase their expense by prolonging the time to pleurodesis. Less well documented but evident to those who counsel patients and their caregivers is the dichotomy of concerns regarding prolonged personal care of a transcutaneous device and avoidance of hospitalization.⁵¹ Desires for rapid resolutions, available support visits from nurses or family, previous medical or equivalent experiences, education levels, and abilities to adopt new skills (that may be impaired in older individuals) all influence patient decisions.

Going back to the AMPLE trial in which hospitalization served as a surrogate for reduced quality of life, the reader may wonder whether participants later perceived the extra 2 days of hospitalization for pleurodeses as value added because of the potential to avoid ongoing therapies or self-management of an external device. Instruments that capture this patient sentiment would be welcome.

The AMPLE trial article mentions AMPLE-2, which attempts to determine the optimal frequency of TIC drainage, and the recently published IPC-Plus study showing talc slurry instilled by an indwelling pleural catheter accelerates pleurodesis and catheter removal.^{1,4} An additional trial, OPTIMUM, is a randomized trial using quality of life as the primary end point comparing outpatient talc through an indwelling pleural catheter with inpatient management.⁵²

Although ongoing randomized pleurodesis clinical trials are useful, it is important to realize that many patients are not eligible or avoid them because of lung entrapment or the numerous reasons noted earlier. Our trials do not

adequately account for diversity of the population with this problem. We fail to adequately measure parameters such as pleural elastance or use biomarkers that predict rapid pleurodesis and prolonged survival. In addition, because patients often feel better immediately after fluid drainage, we often miss sarcopenia, comorbidities, and other manifestations of extensive malignancy that soon dominate to interfere with the long-term palliation goals that are primary end points in many of these studies. We need to add a more granular and holistic approach to symptom management and patient selection if we are to improve our understanding of this important problem. Arguably, a detailed prospective registry better capturing the items listed in Table 1 may be what we should be focusing on now to generate hypotheses that will yield more meaningful future trial results.

Conflict of Interest Statement

T.L.D. is a Medtronic consultant.

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APPENDIX E1

Supplemental citations in descending order of year published	
Tunneled pleural catheter original research studies	E1-E14
Tunneled pleural catheter reviews and meta-analyses	E15-E23

E-References

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