Optimizing the study of tunneled intrapleural catheters for malignant pleural effusions

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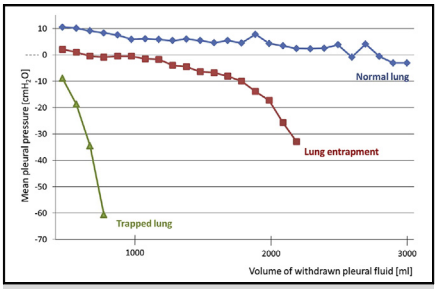

Pleural compliance curves useful for categorizing effusions.

Central Message

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

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 ''thoracoscopic 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 were more pneumonias for those who underwent a general anesthetic, the former became more popular.[6] However, surgeons today still will opt for a thoracoscopic 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 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

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