Response to Spray Cryotherapy in a Patient with Adenocarcinoma in the Parietal Pleura

Gordon Downie^a William Krinsky^b

^aDivision of Interventional Pulmonology, Titus Regional Medical Center, Mount Pleasant, Tex., and ^bDivision of Pulmonary Medicine, Franklin Square Hospital Center, Baltimore, Md., USA

Established Facts

- Malignancies of the parietal pleura, whether primary or metastatic, are a therapeutic challenge; current therapies target their symptoms not their tumor burden. Therefore, alternatives to standard approaches seem warranted.

Novel Insights

- A patient with a parietal pleura-based adenocarcinoma was treated with low-pressure spray cryotherapy after failing more traditional approaches in the treatment of this disease.

Key Words

Adenocarcinoma · Cryotherapy · Lung cancer · Neoplasm · Parietal pleura · Thoracic surgery

Abstract

Malignancies of the parietal pleura, whether primary or metastatic, are a therapeutic challenge, and current therapies target their symptoms and not their tumor burden. Therefore, alternatives to standard approaches seem warranted. A patient with a parietal pleura-based adenocarcinoma was treated with low-pressure spray cryotherapy after failing

more traditional approaches. The patient underwent therapeutic pleuroscopy with moderate sedation and local analgesia of the right chest. She was treated with the CSA Medical spray cryotherapy system, which was introduced into the chest via the working channel of a semi-rigid pleuroscope. Pleuroscopic examination 3 days after spray cryotherapy revealed >50% reduction in tumor size. No adverse events or complications occurred as a result of treatment. At the 3-month follow-up, a slightly raised mound of tissue was noted at the treatment site. This area was biopsied and found to be negative for tumor, containing only chronic inflammatory tissue. No evidence of residual cancer was observed. Ini-

tial observations include lack of a bystander effect on lung and pleura; no significant side effects or symptoms; a 50% tumoricidal response 3 days after treatment, and a complete tumoricidal response 90 days after treatment without evidence of tumor on the parietal pleura.

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Introduction

Malignancies of the parietal pleura, whether primary or metastatic, are a therapeutic challenge; current local therapies largely target the symptoms rather than their tumor burden. Therefore, alternatives to these standard approaches would seem to be warranted. We present a novel cryo-based technology to treat pleural disease and describe the first use of spray cryotherapy for malignant pleural disease.

Cancer within the thorax is the most frequently diagnosed non-skin cancer in both men and women, and the leading cause of cancer death in the United States. The National Cancer Institute estimated that >230,000 Americans would be diagnosed with lung cancer in 2007 [1]. Pleural-based cancers are not specifically recorded in the American Cancer Society's 2007 new diagnosis estimates. However, pleural mesothelioma, often caused by exposure to asbestos, accounts for 2,000–3,000 new cases of mesothelioma diagnosed in the USA each year [2].

The historical 5-year survival rate for lung cancer is approximately 14%. The 5-year survival rate for pleural-based cancer is even lower. Prolonged survival is often limited to asymptomatic patients whose disease is detected serendipitously either in the lung or on the pleural surface. Strong clinical data indicate that the survival of lung cancer dramatically improves with the diagnosis and treatment of early-stage disease; this has also been suggested by treatment of stage 1–2 mesothelioma. Current standard of care treatment for pleural metastasis is targeted at symptom attenuation via pleurodesis associated with pleural decortication in some cases. A less invasive, more tolerable method of reducing symptoms would represent a substantive improvement relative to current approaches. In addition, it remains unknown whether decreasing tumor burden would potentially have other salutary effects [3].

Oncologic clinical research for pleural metastasis over the last 20 years has included locoregional application of novel chemotherapeutics, phototherapy, cryotherapies, radiation and immunotherapies with limited success. Specifically cryo-based applications have included pain

reduction after thoracotomy, biopsies, ablation and combination therapies, including chemotherapy with cryotherapy [4–11].

Standard, slow-energy transfer cryotherapy or cryosurgery has been used in the thorax for many decades, and there is a large body of literature examining the biologic principles governing these slow-energy transfer devices [12–16]. Slow cooling favors dehydration [12] and is the basis of currently available cryotherapy/cryosurgery instruments. Cryosurgery with a probe device has been reported in the medical literature since its development by Cooper and Lee in the 1960s, and Neel et al. [13] over-viewed its use within the thorax in a series of two papers in 1973, using dogs and a cryoprobe to assess thorax structure susceptibility to freezing. Rubinsky [14] discussed the standard theory and application of cryotherapy in an exhaustive review in 2000. Baust and Gage [15] examined modes to optimize the therapeutic effects of standard cryotherapy as well as more exact imaging to assess real-time response to cryotreatments. Slow-energy transfer devices utilize the Joule-Thomson effect, which is the expansion of gas resulting in thermal cooling. Among the limitations with this approach have been a narrow field of effect, obligatory mechanical contact with the target, and inconsistent depth of injury as thermal transfer rates are limited by lowest attainable temperature.

Spray cryotherapy using low-pressure (<4 PSI) delivery of liquid nitrogen at nearly –200°C addresses many of these deficiencies. It is a rapid energy transfer platform using liquid nitrogen and is significantly more efficient regarding energy transfer. This Food and Drug Association-certified, low-pressure spray cryotherapy device (K072651) may be used to destroy unwanted tissues and was initially introduced in the gastrointestinal tract; with thousands of procedures completed to date, it has not only proven to be safe, but also reproducible with durable results [17–25]. Further, spray cryotherapy had been applied in animal models not only in the chest and esophagus but also in other organ systems [unpubl. data] with consistent results. After completing safety and feasibility work in animals, a pilot study in the airways of humans demonstrated findings similar to those seen in these models [22, 23].

Given the safety and efficacy from this prior work, spray cryotherapy was performed in the pleural space during pleuroscopy in a patient with diffuse metastatic melanoma including extensive disease in the parietal pleura. The treatment was delivered without complication or any observed side effects to a relatively small area

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Fig. 1. A metastatic adenocarcinoma of the right parietal pleural surface, located slightly posterior of the midaxillary line, just above the fourth intercostal space.

Fig. 2. The patient was treated with 3 cycles of 10-second sprays of liquid nitrogen, resulting in a white frost (or 'cryofrost') on the targeted mucosa.

Fig. 3. Multiple biopsies of the right pleura, taken 3 months after spray cryotherapy, were found to be negative for tumor.

on the pleural surface. Radiographically and clinically, there appeared to be improved pleurodesis. As a result, the spray cryotherapy technique was performed on a patient with biopsy-proven cancer on the parietal pleural surface, and the outcome reported herein is encouraging.

Case Report

A 49-year-old woman with pleuroscopic biopsy-proven adenocarcinoma of the right parietal pleural surface, located slightly posterior of the midaxillary line, just above the fourth intercostal space, was admitted to the ward service. Presented at a multidisciplinary tumor board, she was initially treated as a stage IIIB lung cancer, despite no evidence of distant disease on positron emission tomography scan, demonstrable parenchymal lesions or lymphadenopathy. The patient began treatment with a platinum-based 2-drug chemotherapy regimen and this continued over a 3-month period.

Pleuroscopy, performed 3 months after chemotherapy, revealed that the tumor was relatively unaffected visually (fig. 1). The tumor was biopsied again, confirming the presence of active disease. Because no documented disease outside the single pleural lesion could be found by imaging studies including positron emission tomography scanning, aggressive local treatment strategies were reconsidered. This particular patient was extremely debilitated as a result of multiple traumas, especially on the tumor side. While surgical approaches with wide excision were considered in addition to external beam radiation, her prior injuries and degree of deconditioning were considered and she was felt to be an appropriate candidate for spray cryotherapy. Informed consent was obtained from the patient prior to participation and treatment. A waiver from the institutional review board was obtained, too.

The patient was then treated with the CryoSpray Ablation™ 'CSA' System (model CC2-NAM; CSA Medical). It is used as a cryosurgical tool for the destruction of unwanted tissue in the field of general surgery, specifically for endoscopic applications. The system enables the physician to control the start and stop of cryogen flow and the duration of the cryogen spray to the selected site.

Our patient was treated in a specialized procedure room, employing only moderate sedation, local subcutaneous analgesia and oxygen via a nasal cannula at 3-liter flow. The patient was placed in a left lateral decubitus position exposing her right midaxillary line; subsequently, she was prepped and draped in a standard sterile fashion. The CSA system was introduced into the chest via the working channel of a semi-rigid pleuroscope through a standard mid-right axillary line incision with placement of a trocar. A cryo-decompression tube, situated no more than 1 cm beyond the distal tip of the scope, was placed into the right pleural space to evacuate nitrogen gas. Freezing and thawing techniques were monitored by direct visualization. Spray cryotherapy dosimetry is based on the duration of the tissue freeze time in seconds, and the number of cycles a predefined target area or site was frozen and thawed. The patient was treated with 3 cycles of 10-second sprays of liquid nitrogen, which causes a white frost (or 'cryofrost') to appear on the targeted mucosa (fig. 2). A 20-french chest tube was put in place to reinflate the right lung, and no obvious air leak was noted. This dosimetry was chosen based on the prior work described above [17–25].

The treatment site contained a long, raised area of malignant tissue without adhesions, which was biopsied after chemotherapy as an active disease focus; however, the initial diagnostic pleuroscopy with multiple biopsies promoted adhesions in this area that were lysed prior to spray cryotherapy. The right pleural cavity was reentered on day 3 to assess initial response and potential need for retreatment; the cavity was again reentered 3 months after treatment to assess long-term response of spray cryotherapy and the

overall pleural status. The patient received narcotic analgesics and sedation, as needed, during the procedures, according to institutional standards. Additionally, technical ease of treatment deployment was noted, with near-immediate change in the treatment site, suggesting tumoricidal events. A pleuroscopic examination, taken 3 days after spray cryotherapy to check for mucosal sloughing and to reassess tumor burden, revealed >50% reduction in the tumor size. No adverse events or complications occurred as a result of treatment, including zero bystander effect on the areas of the lung or pleura not targeted by the cryospray, as well as absence of adhesions after treatment.

An examination performed at the 3-month follow-up revealed a slightly raised linear mound of tissue (fig. 3) at the treatment site. This area was biopsied multiple times, along the length of the mound, and found to be negative for tumor, containing only chronic inflammatory deposits of the previous tumor bed. Surprisingly, there was little in the way of adhesions, and two focal areas of tethering were easily taken down between the parietal pleura and lung. No gross evidence of parietal pleural cancer was observed.

Study personnel contacted the patient by telephone 30 days following spray cryotherapy to assess any complications (using a side effect questionnaire, CRF 3, St. Georges Respiratory Questionnaire, and Borg Dyspnea Index), and the patient demonstrated symptomatic improvement and had little in the way of any discomfort over the next 30 days.

Discussion

We present the use of spray cryotherapy in the treatment of a patient with cancer in the pleural space. This is an investigation of safety and feasibility that, combined with observations about tissue response, is intended to be used to inform other work. Eliminating symptoms via pleurodesis and, when necessary, decortication of the affected pleural space are the current standard of care for wet-stage IIIB non-small cell cancer. This process is, therefore, often fairly invasive and typically requires extended hospital stays and convalescence. Further, barriers for direct tumor treatment options within the pleura are costs, complex dosimetry, and potential futile interventions if survival is unaffected. Novel strategies to mitigate symptoms while at the same time defining and reducing the pleural tumor burden may be of value.

It is impossible to deduce that the degree of clinical response seen in this one patient is entirely the consequence of spray cryotherapy. Other factors include the limited extent of disease, previous oncologic treatments, and the possibility of inaccurate staging. Whether spray cryotherapy might be consistently employed in this clinical setting awaits further work. However, this initial response is encouraging. In specific, we are intrigued by

several parameters of this treatment including feasibility, safety, costs, tumor response, and lack of patient discomfort.

Cryobiologic therapies – whether they are diagnostically or therapeutically centered – are attractive for the pleural space. To date, these approaches employed the slow-energy transfer platforms to achieve the desired effect. In their recent review of cryotherapy for the airways, Vergnon et al. [11] pointed out the positive properties of this treatment including an abundance of important cryoresistant support structures that help attenuate bystander side effects. Additionally, the vascular effects of cryotherapy promote thrombosis and infarction of tumors, and support the principles of combining cryotherapy with chemotherapy for a synergistic response, as demonstrated by Forest et al. [9, 10]. Pain is another prominent feature of pleura-based malignancies, and although pleuritic pain was not a significant finding in this case there are decades of reported positive outcomes from cryoanalgesia in patients after thoracotomy [4–7]. Additionally, well-documented immunoregulatory effects have been described with cryotherapy, raising the possibility of a systemic immune response from this local therapy [16, 26, 27].

To summarize, the initial observations from this case include: lack of a bystander effect on normal lung and pleura; no significant treatment or 30-day post-treatment side effects or symptoms, and ease of treatment. There was an observed immediate 50% tumoricidal response 3 days after treatment, and a complete visual and histologically proven tumoricidal response 90 days after treatment.

This case illustrates the potential of addressing malignant pleural disease with a low-cost, low-complexity technology with the potential to affect parameters influencing survival. We believe that spray cryotherapy represents a viable opportunity for further study within the pleura. The degree of tumor necrosis in multiple clinical presentations (e.g. bulky, flat, or studding) awaits definition, as does the rate and timing of pleurodesis after treatment and the possibility of an immunoregulatory effect.

References

- 1 American Cancer Society: Cancer Facts and Figures, 2007. <http://www.cancer.org/downloads/STT/CAFF2007PWSecured.pdf> (accessed on Nov 24, 2008).
- 2 American Cancer Society: Cancer Reference Information. Detailed guide: malignant mesothelioma; what are the key statistics about malignant mesothelioma? http://www.cancer.org/docroot/CRI/content/CRI_2_4_1X_What_are_the_key_statistics_for_malignant_mesothelioma_29.asp?sitearea= (accessed on Oct 16, 2007).
- 3 Hnizdo E, Sullivan PA, Bang KM, et al: Association between COPD and employment by industry and occupation in the US population: a study of data from the Third National Health and Nutrition Examination Survey. *Am J Epidemiol* 2002;156:738–746.
- 4 Glynn CJ, Lloyd JW, Barnard JD: Cryoanalgesia in the management of pain after thoracotomy. *Thorax* 1980;35:325–327.
- 5 Moorjani N, Zhao F, Tian Y, et al: Effects of cryoanalgesia on post-thoracotomy pain and on the structure of intercostal nerves. *Eur J Cardiothorac Surg* 2001;20:502–507.
- 6 Roberts D, Pizzarelli G, Lepore V, et al: Reduction of post-thoracotomy pain by cryotherapy of intercostal nerves. *Scand J Thorac Surg* 1988;22:127–130.
- 7 Ju H, Feng Y, Yang BX, Wang J: Comparison of epidural analgesia and intercostal nerve cryoanalgesia for post-thoracotomy pain. *Eur J Pain* 2008;12:378–384.
- 8 Bonnoit JP, Homasson JP, Roden SL, et al: Pleural and lung cryobiopsies during thoracoscopy. *Chest* 1989;95:492–493.
- 9 Forest V, Peoc'h M, Ardiet C, et al: In vivo cryochemotherapy of a human lung cancer model. *Cryobiology* 2005;51:92–101.
- 10 Forest V, Hadjeres R, Bertrand R, Jean-Francois R: Optimization and molecular signaling of apoptosis in sequential cryotherapy and chemotherapy combinations in human lung cancer xenographs in SCID mice. *Br J Cancer* 2009;100:1896–1902.
- 11 Vergnon J-M, Huber RM, Moghissi K: Place of cryotherapy, brachytherapy and photodynamic therapy in the therapeutic bronchoscopy of lung cancer. *Eur Respir J* 2006;28:200–218.
- 12 Mazur P: Cryobiology: the freezing of biological systems. *Science* 1970;168:939–949.
- 13 Neel HB, Farrell KH, DeSanto LW, et al: Cryosurgery of respiratory structures. I. Cryonecrosis of trachea and bronchus. *Laryngoscope* 1973;83:1062–1071.
- 14 Rubinsky B: Cryosurgery. *Annu Rev Biomed Eng* 2000;2:157–187.
- 15 Baust JG, Gage AA: Progress toward optimization of cryosurgery. *Technol Cancer Res Treat* 2004;3:95–101.
- 16 Sable MS: Cryo-immunology: a review of the literature and proposed mechanisms for stimulatory versus suppressive immune responses. *Cryobiology* 2009;58:1–11.
- 17 Johnston MH, Eastone JA, Horwhat JD, et al: Cryotherapy of Barrett's esophagus: a pilot study. *Gastrointest Endosc* 2005;62:842–848.
- 18 Cash BD, Johnston LR, Johnston MH: Cryospray ablation (CSA) in the palliative treatment of squamous cell carcinoma of the esophagus. *World J Surg Oncol* 2007;5:34.
- 19 Dumot JA, Greenwald BD: Argon plasma coagulation, bipolar cautery and cryotherapy: ABCs of ablative techniques. *Endoscopy* 2008;40:1026–1032.
- 20 Johnston MH: Cryotherapy and other newer techniques. *Gastrointest Endosc* 2003;13:491–504.
- 21 Johnston MH, Schoenfeld LP, Mysore JV, et al: Endoscopic spray cryotherapy: a new technique for mucosal ablation in the esophagus. *Gastrointest Endosc* 1999;50:86–92.
- 22 Krimsky W, Sarkar S, McKenzie K, et al: Failure mode effects analysis (FMEA) of cryospray ablation in the airways of swine (abstract). *FASEB J* 2008;22:1220.1.
- 23 Krimsky W, Sarkar S, McKenzie K, et al: Safety and efficacy of cryospray ablation in the airways of healthy swine (abstract). *Am J Respir Crit Care Med* 2008;177:A893.
- 24 Krimsky W, McKenzie K, Broussard J, et al: A study of cryospray ablation using surgical resection specimen to determine safety and histological effect in the human lung (abstract). *Chest* 2008;134:96001S.
- 25 Krimsky WS, Broussard JN, Sarkar SA, et al: Safety and histology of spray cryotherapy in the human lung, submitted.
- 26 den Brok MGMH, Suttmuller RPM, Nierkens S, et al: Efficient loading of dendritic cells following cryo and radiofrequency ablation in combination with immune modulation induces anti-tumour immunity. *Br J Cancer* 2006;95:896–905.
- 27 Allison RR, Bagnato VS, Cuenca R, et al: The future of photodynamic therapy in oncology. *Future Oncol* 2006;2:53–71.