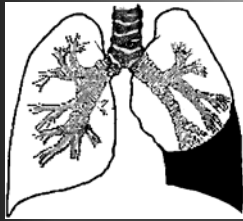


# International Pleural Newsletter



A Publication of the International Pleural Network

Volume 6 Issue 1  
January 2008

## Editors:

Richard W. Light Nashville, TN, USA  
Y.C. Gary Lee Oxford, UK

## Co-Editors:

Michael H. Baumann Jackson, MS, USA  
Robert J.O. Davies Oxford, UK  
John E. Heffner Portland, OR, USA

## International Advisors:

P Astoul France	D Bouros Greece
V C Broadus USA	T E Eaton New Zealand
A Ernst USA	F V Gleeson UK
G Hillerdal Sweden	S Idell USA
Y Kalomenidis Greece	T K Lim Singapore
R Loddenkemper Germany	S E Mutsaers Australia
M Noppen Belgium	J Porcel Spain
F Rodriguez-Panadero Spain	S Romero Canderia Spain
S A Sahn USA	G F Tassi Italy
L R Teixeira Brazil	F S Vargas Brazil
C Xie China	A P C Yim Hong Kong

Administrator: Emma Hedley Oxford, UK  
[emmahedley@orh.nhs.uk](mailto:emmahedley@orh.nhs.uk)

The *International Pleural Newsletter* is distributed or web-posted by the:

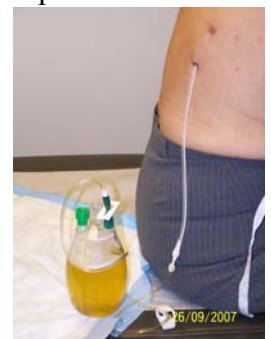
American College of Chest Physicians  
Asian Pacific Society of Respiriology  
Asociacio n Latino Americana del Torax  
Belgian Society of Pulmonology  
Brazilian Thoracic Society  
British Thoracic Society  
Costa Rican Thoracic Society  
European Respiratory Society  
International Mesothelioma Interest Group  
Italian Association of Hospital Pulmonologists  
Singapore Thoracic Society  
South African Thoracic Society  
Thoracic Society of Australia & New Zealand  
Turkish Thoracic Society

The *Newsletter* is on line:  
[www.musc.edu/pleuralnews](http://www.musc.edu/pleuralnews)

## Tunneled Indwelling Pleural Catheters for Malignant Pleural Effusions

David R Stather MD FCCPC  
Alain Tremblay MDCM FCCPC  
University of Calgary, Alberta, Canada  
[alain.tremblay@ucalgary.ca](mailto:alain.tremblay@ucalgary.ca)

Malignant pleural effusion (MPE) is a common complication in advanced malignancy that causes debilitating symptoms. Tunneled pleural catheters (TPC) represent a safe, effective outpatient treatment option for these patients, with no reported mortality and minimal morbidity<sup>1,2</sup>. TPCs allow intermittent home drainage of pleural fluid into vacuum bottles (Fig). TPCs are usually inserted in an outpatient setting under local anesthesia<sup>1,2</sup> and then drained every 2-3 days by a home care nurse.



**Pros of TPC:** TPCs are an effective method of controlling MPE on an outpatient basis. The lack of requirement for inpatient admission is certainly one of the most significant advantages both from the patients' point of view and with regards to costs.

The effectiveness of TPC in MPE was documented in a multi-center randomized control trial comparing TPCs and doxycycline pleurodesis where symptomatic improvement in dyspnea, quality of life and survival were comparable in both groups<sup>3</sup>. Several other studies have corroborated these results including a study of 250 sequential TPC insertions<sup>1</sup> showing symptomatic improvement in 89% of patients at two weeks and long lasting control with <10% of patients requiring any further ipsilateral procedures. Spontaneous pleurodesis is seen following approximately 40% of all TPC insertions<sup>1</sup>,

but is not necessary for palliation of dyspnea nor is it the primary goal of treatment.

TPCs can be used successfully in patients with trapped lung as well as in those with poor performance status - two common findings in this patient population for which few other treatment options exist<sup>1,4</sup>. When TPCs are used in patients otherwise fit for pleurodesis procedures, higher spontaneous pleurodesis rates are seen (70%) and symptomatic improvement occurs in all patients<sup>2</sup>.

**Cons of TPC:** Although reports of safety and efficacy of TPC use in MPE are growing, no study has yet compared this technique with talc pleurodesis, arguably the current gold standard.

The most common complication associated with TPCs is symptomatic loculation of fluid seen in 8.4% of patients<sup>1</sup>. Empyema is seen in 3.2% of cases<sup>1</sup> usually after prolonged drainage, although this is similar to the rates reported for thoroscopic talc poudrage<sup>5,6</sup>. A theoretical concern regarding the potential negative impact of chronic drainage of protein-rich fluid on nutritional status has been raised, but has not been well documented.

Length of drainage of 2-3 months is often seen as an undue burden imposed on patients and families by detractors of this approach, although in our experience patients accept this with ease. Strategies to reduce the length of TPC drainage while minimizing side effects could be of benefit.

A TPC insertion program requires specific resources such as adequate home care support and catheter supplies, as well as a dedicated team of health care providers. While the cost of the initial catheter insertion is low, the cost of supplies is not insignificant and a long-term cost effectiveness study has not been performed.

In conclusion, a growing body of evidence confirms that long-term palliation of MPE can be achieved by using TPCs in relatively unselected patients on an outpatient basis. While the high success rates, low complication rates and efficacy in patients with a wide range of performance status support the use of TPCs as a first line treatment for symptomatic MPE, there is still a need for cost effectiveness studies with talc pleurodesis as the benchmark, and for the development of further treatment modalities for this condition.

1. Tremblay A, Michaud G. Chest 2006;129: 362-8.
2. Tremblay A, et al. Eur Respir J 2007; 30:759-62.
3. Putnam JB Jr., et al. Cancer 1999; 86:1992-9.

4. Pien GW, et al. Chest 2001; 119:1641-6.
5. de Campos JRM, et al. Chest 2001; 119:801-6.
6. Viallat JR, et al. Chest 1996; 110:1387-93.

## Research Update: Mesothelioma

### Ongoing Clinical Trials in Mesothelioma

**Paul Baas MD**

Netherlands Cancer Institute, Amsterdam, The Netherlands  
[p.baas@nki.nl](mailto:p.baas@nki.nl)

Malignant pleural mesothelioma (MPM) remains a challenge for the oncologist to treat. This paper summarizes the current status of clinical studies on MPM. From the available literature it is clear that the folate pathway has been found to be (one of) the Achilles heel in this disease. The combination of cisplatin and pemetrexed or raltitrexed have resulted in significant survival benefits in this disease<sup>1,2</sup>. However, most patients suffer from tumor relapse within two years. Hence, development of new drugs and combinations of different treatment modalities are needed.

As first-line treatment, a multimodality approach, including cisplatin/pemetrexed treatment, has been tested by two groups. Krug *et al.* have tested the combination of four courses of induction chemotherapy, extra-pleural pneumonectomy and postoperative irradiation of the treated side. During the American Society of Clinical Oncology (ASCO) meeting in 2007, they reported a complete pathologic response rate of 5.3% in 72 patients after induction chemotherapy, which underscores the importance of chemotherapy in MPM. The toxicity of this approach is acceptable but strongly depends on the selection of patients. A similar approach has been performed by the EORTC Lung Cancer Group in which 59 patients were evaluated for feasibility and toxicity. Since these studies have not yet been published, patients should only be treated with this combination as part of a study.

Most patients are not eligible candidates for this multimodality approach but can be entered in different first line phase II studies. The EORTC 8052 study tests the effect of cisplatin in combination with bortezomib, a proteasome inhibitor. Preclinical experience in cell lines indicate that the pathway of blocking protein degradation could be another way of

killing mesothelioma cells selectively. A single agent study of bortezomib is currently ongoing.

For second line therapy in MPM several studies are available. The use of a single agent bortezomib in a phase II setting has finished accrual recently and it is expected to be reported on in the second quarter of 2008. Currently there are two ongoing phase III studies. The first study is a placebo-controlled, double-blind study of an oral agent Vorinostat (suberoylanilide hydroxamic acid). Recruitment of the 220 patients required is expected to be completed in the first quarter of 2008. The second study compares doxorubicin with or without Onconase (Ranpirnase). It has accrued over 425 patients and is expected to be closed in late 2007 for analysis.

A noteworthy presentation in MPM was given at ASCO 2007 by Karrison<sup>4</sup>. He reported on a randomized, double-blind study of the addition of bevacizumab or placebo to cisplatin with gemcitabine. The survival and responses in both groups (total number of patients 110) was similar with a staggering median survival of 15.6 months. This unexpected result might be explained by patient selection. This study emphasizes the need for randomized studies, preferably in phase II settings.

1. Vogelzang et al. JCO 2003;21::2636-44

2. van Meerbeeck JCO 2005;23:6881-9

3. Krug et al. pASCO 2007;25:18S:abstr 7561

4. Karrison et al. JCO 2007; vol 25 (18S): abstract

### ***Potential Novel Immunotherapy Agents for Mesothelioma***

**Anil Vachani MD**

**Steven M. Albelda MD**

University of Pennsylvania, Philadelphia, PA, USA

[albelda@mail.med.upenn.edu](mailto:albelda@mail.med.upenn.edu)

The treatment of malignant pleural mesothelioma remains generally ineffective despite the application of surgery, radiation therapy, and chemotherapy individually or in combination. New treatment approaches for mesothelioma are urgently needed. One exciting approach is immunotherapy. Among the strategies currently in pre-clinical and early clinical development are cytokine gene therapy, transforming growth factor (TGF)- $\beta$  blockade, CD40 activation, and anti-mesothelin therapy.

The basis for cytokine gene therapy in

mesothelioma results from direct antiproliferative effects on tumor cells and the ability of certain cytokines to activate systemic, intrapleural, and intratumoral immune effector cells. One such approach is the use of an adenoviral vector encoding interferon- $\beta$  (Ad.IFN- $\beta$ ), which is directly instilled into the pleural space. Preclinical studies of Ad.IFN- $\beta$  have demonstrated dramatic therapeutic efficacy in animal models of mesothelioma<sup>1</sup>. A Phase I study demonstrated that intrapleural Ad.IFN- $\beta$  was well tolerated, generated anti-tumor immune response in almost all of the patients, and resulted in encouraging anti-tumor activity<sup>2</sup>. More recent pre-clinical studies have shown the utility of tumor debulking, adjuvant COX-2 inhibitors, and immunomodulatory chemotherapy (with drugs such as gemcitabine) when combined with Ad.IFN- $\beta$  gene transfer.

An alternative method for the activation of cytotoxic T-lymphocytes (CTL) is via stimulation of CD40 on antigen presenting cells. The use of an activating anti-CD40 antibody drives the process of T-cell priming and expansion of CTLs and induces these cells to leave lymph nodes and circulate. These CTLs have strong tumor killing capacity and can destroy established tumors. In mice, therapy with an agonistic anti-CD40 antibody with gemcitabine was very effective in mesothelioma models<sup>3,4</sup>.

Mesotheliomas make high levels of TGF- $\beta$ . This cytokine is an important mechanism of suppression of anti-tumor immune responses. Neutralization of TGF- $\beta$  (using monoclonal antibodies, antisense oligonucleotides, etc.) has shown promise in a variety of solid tumors. Small-molecule inhibitors of TGF- $\beta$  type I receptor kinase have been recently developed; these agents are especially attractive for clinical development given their increased flexibility in dosing and oral route of administration. One such small molecule inhibitor, SM16, has been shown to effectively reduce the growth of mesothelioma tumors in a murine model<sup>5</sup>. SM16 was also effective when used in an "adjuvant" setting in combination with tumor debulking.

Mesothelin, a tumor associated antigen present at high levels on the cell surface of virtually all mesotheliomas, is being actively evaluated as an immunotherapy target. A strain of live-attenuated *Listeria monocytogenes* (*Lm*) has recently been engineered to express mesothelin and is being used as a vaccine (CRS-207)<sup>6</sup>. Pre-clinical studies have shown mesothelin-specific cellular immunity and

therapeutic efficacy in tumor-bearing mice. A Phase I study will be initiated shortly to explore the safety profile and immune responses to this strain.

Mesothelin is also being used in other immunotherapy strategies: 1) as a target for ‘designer T-cells’ by transfecting CD-8 T-cells with an artificial T-cell receptor designed to bind to mesothelin on tumor cells; 2) SS1P, a recombinant immunotoxin consisting of an anti-mesothelin Fv linked to a truncated Pseudomonas exotoxin that mediates cell killing<sup>6</sup>; and 3) MORAb-009, a chimeric monoclonal antibody with high affinity and specificity for mesothelin<sup>6</sup>.

These and other approaches are being actively investigated in animal models and in clinical trials. Hopefully, over the next few years, many of these approaches will show clinical efficacy and become a part of standard therapy for mesothelioma.

1. Odaka M, et al. *Cancer Res* 2001; 61:6201-12.
2. Sterman DH, et al. *Clin Cancer Res* 2007; 13:4456-66.
3. Nowak AK, et al. *Cancer Res* 2003; 63:4490-6.
4. Stumbles PA, et al. *J Immunol* 2004; 173:5923-8.
5. Suzuki E, et al. *Cancer Res* 2007; 67:2351-9.
6. Hassan R, Ho M. *Eur J Cancer* 2008; 44:46-53.

The 2008 Congress of the International Mesothelioma Interest Group will be held in Amsterdam from Sept 25th to 27th. For details, see [www.imig.org](http://www.imig.org)

## CASE REPORT

### *A Caveat in Empyema Diagnosis*

A 72 year old female was admitted with severe community acquired pneumonia and a small right pleural effusion on CXR. Pleural aspirate revealed a straw color fluid of pH 7.38 and 7.39 at the time of diagnostic and therapeutic thoracentesis respectively (DPA1&2). Despite antibiotics, the patient remained



unwell with ongoing elevated inflammatory markers, and a CT scan (left) showed bilateral loculated pleural collections and liver abscesses.

On day 9 the patient deteriorated further and CXR now showed a large left sided effusion. An intercostal drain was inserted (DPA3) and the pH remained non-

acidic (7.46). The patient subsequently required intubation and ICU admission. Blood culture subsequently grew *Proteus vulgaris*. The patient was ventilated for two days and had initial improvements in inflammatory and clinical indices over the next 30 days before suffering an acute deterioration and died.

	DPA 1	DPA 2	DPA 3
Effusion Protein g/L	17	15	21
Glucose	6.3	5.3	1.0
Pleural LDH IU	364	392	957
pH	7.38	7.39	7.46
Serum LDH IU	216	224	288
Serum Protein	N/D	47	N/D
Pleural fluid culture	No Growth	No Growth	<i>Proteus vulgaris</i>

**Discussion:** It is recommended that a pleural fluid pH of 7.2 is useful to distinguish between a simple parapneumonic effusion and empyema/complicated parapneumonic effusion (PPE). Our patient never developed an acidic effusion and had no other evidence to suggest complicated PPE/empyema initially. Pleural aspirates 1 and 2 suggest a discordant exudate, the results likely complicated by the low protein state of the patient (due to poor nutrition and sepsis) and a degree of fluid overload. Of note, application of Light’s criteria to the LDH values does give a ratio of >0.6. The results of Aspirate 3 illustrated the development of an empyema with low glucose and high LDH; however the fluid remained non-acidic, even though *Proteus vulgaris* was later cultured.

This case demonstrates an important exception to using pleural pH as a diagnostic tool. Both *Proteus mirabilis* and *Proteus vulgaris* have been reported as causing non-acidic empyemas. *Proteus mirabilis* has been shown to cause pH’s of >8.0, whereas *Pr. vulgaris* has been reported as giving pH values much nearer to that of our patient’s (7.61). *Proteus vulgaris* is a gram negative enteric bacterium containing the enzyme urease which cleaves urea to produce ammonia as a breakdown product. This produces an elevated pH not usually seen in empyema, hence leading to diagnostic confusion.

1. Pine RJ, et al. *Chest* 1983; 84:109-111.
2. Eisenstein D & Honig E. *Chest* 1990; 97: 511

**Lynne Curry MRCP & Andrew Stanton MRCP**  
Oxford Centre for Respiratory Medicine, UK  
[andrewstanton@hotmail.com](mailto:andrewstanton@hotmail.com)

## Highlighted Pleural Research Papers from 2007

### Clinical Research

**Ioannis Kalomenidis MD**  
University of Athens, Athens, Greece  
[ikalom@med.uoa.gr](mailto:ikalom@med.uoa.gr)

Many of the landmark publications on pleural disease in 2007 focused on advances in malignant pleural disease. Three studies showed that serum or pleural fluid content of soluble mesothelin related proteins may be helpful in differentiating between malignant pleural mesothelioma (MPM) and benign pleural disease but they can also be elevated in some patients with metastatic pleural carcinomas<sup>1-3</sup>. A randomized-controlled study on MPM patients who underwent an invasive procedure<sup>4</sup> disclosed that prophylactic radiotherapy (21 Gy over 3 consecutive days) at sites of pleural biopsy or chest drain insertion did not decrease the risk of tumor seeding thereby challenging the current recommendations of prophylactic radiotherapy. A multi-center trial reported no case of ARDS or any fatal complication among 558 patients with malignant pleural effusions (MPE) treated with large-particle talc poudrage<sup>5</sup>, suggesting that large-particle talc pleurodesis is a safe method to control symptomatic MPE. Tunneled pleural catheters (TPC) are the method of choice for selected MPE patients which are not eligible for pleurodesis. A retrospective analysis showed that TPC was effective in ~ 70% of patients who otherwise could be candidates for pleurodesis<sup>6</sup>.

Regarding benign pleural diseases, an analysis of TB surveillance data in the USA revealed that multi-drug resistance is extremely rare in patients with TB pleural effusion<sup>7</sup>. This finding refutes the necessity for pleural biopsy to isolate mycobacteria and the need to perform routine drug-resistance studies.

1. Grigoriu BD, et al. *Clin Cancer Res* 2007; 13:2928-35.
2. Cristaudo A, et al. *Clin Cancer Res* 2007; 13:5076-81.
3. Creaney J, et al. *Thorax* 2007; 62:569-76.
4. O'Rourke N, et al. *Radiother Oncol.* 2007; 84:18-22.
5. Janssen JP, et al. *Lancet.* 2007; 369:1535-9.
6. Tremblay A, et al. *Eur Respir J* 2007; 30:759-62.
7. Baumann MH, et al. *Chest.* 2007; 131:1125-32.

**If you have any comments on the Newsletter or interesting cases of pleural disease, contact:  
Ms Emma Hedley [emma.hedley@orh.nhs.uk](mailto:emma.hedley@orh.nhs.uk)**

### Laboratory Research

**Georgios T. Stathopoulos MD PhD**  
University of Athens, Athens, Greece  
[gstathop@med.uoa.gr](mailto:gstathop@med.uoa.gr)

In 2007, several important advances in basic scientific research of pleural diseases were accomplished. To begin with, a new animal model of pleurodesis was established in mice<sup>1</sup>. As a multitude of genetically engineered mice are available, the model may facilitate studies on the involvement of specific gene products in the mechanisms of pleural fibrosis. Another elegant morphologic study identified and characterized visceral pleural sensory receptors in the rat<sup>2</sup>. These findings may facilitate new understanding of pleural nociception and development of specific treatments for pleural-based pain.

Another interesting paper reported that resident pleural myeloid and mesothelial cells possess the capability of taking up acid-prepared mesoporous spheres, measuring 1-2  $\mu\text{m}$  in diameter and having a 40  $\text{\AA}$  pore size<sup>3</sup>. This new finding expands the possibilities of pleural-based drug or gene delivery, a key for the local therapy of pleural diseases, including mesothelioma.

Work from Brazil showed that eosinophilia associated with pleural BCG infection of mice is dependent on toll-like receptor 2 signaling via the eotaxin/chemokine receptor 3 axis<sup>4</sup>.

In another report, our group showed how tumor necrosis factor (TNF)- $\alpha$  promotes malignant effusion formation and intrapleural tumor dissemination in the mouse via nuclear factor- $\kappa\text{B}$ - and ceramide-dependent effects, setting a rational framework for clinical trials of anti-TNF- $\alpha$  agents against malignant pleural disease<sup>5</sup>.

Finally, a mesothelioma-inhibiting role for TNF-related apoptosis-inducing ligand (TRAIL) was discovered; mesothelioma cells were sensitized to TRAIL-induced apoptosis by heat stress via inhibition of the 3-phosphoinositide-dependent kinase 1/Akt pathway<sup>6</sup>. These results may contribute to future therapies for the disease.

In conclusion, the year 2007 was very productive in terms of high-impact pleural basic research publications and of advancing the current understanding of pleural pathobiology.

1. Marchi E, et al. *Respirology* 2007; 12:500-4.
2. Pintelon I, et al. *Am J Respir Cell Mol Biol* 2007; 36:541-51.
3. Blumen SR, et al. *Am J Respir Cell Mol Biol* 2007; 36:333-42.
4. D'Avila H, et al. *Infect Immun* 2007; 75:1507-11.
5. Stathopoulos GT, et al. *Cancer Res* 2007; 67:9825-34.
6. Pespeni MH, et al. *Cancer Res* 2007; 67:2865-71.