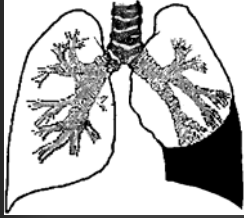


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Recently Published Multi-Center Clinical Trials in Pleural Diseases

Randomized Trial of Talc Slurry vs Talc Insufflation for Malignant Pleural Effusion

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Controversy has existed concerning the most efficacious method of treating malignant pleural effusion (MPE). To resolve this question, 501 patients with MPE were randomized to either talc slurry as a bedside procedure or talc insufflation through thoracoscopy (standard or VATS). The trial involved >100 surgeons throughout North America, all credentialed for proficiency with VATS. The study was powered as an equivalency trial for the primary endpoint: efficacy of sclerosis with prevention of recurrence measured at 30 days. Patients were required to have a diagnosis of malignancy with a pleural effusion that necessitated sclerosis, an ECOG status of 0-2 to increase the probability of a 30-day survival, life expectancy as judged by the surgeon of >2 months and able to tolerate general anesthesia.

Once randomized, patients received 4-5g of talc either as a slurry via a percutaneously placed chest tube (≥ 28 Fr), or by insufflation via a thoracoscope. For either procedure, the pleural effusion had to be completely drained and there was >90% lung re-expansion. In the insufflation arm, drainage and expansion was assessed at surgery. For the slurry arm, drainage and re-expansion was assessed by x-ray and talc slurry given within 24-36 hours of chest tube placement. At the time of this trial, only one talc spray product was commercially available and was

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used by some of the surgeons. Most talc was sterilized at each institution.

501 patients were randomized (19 patients excluded due to ineligibility or withdrawal of consent): 250 in the slurry arm and 251 in the insufflation arm. Age, gender, race and performance status were well matched in both arms. Cancer types were equally represented in both arms, with lung (38%), breast (24%) and gastrointestinal (9%) cancers being the most common. Approximately 70% of the patients in both arms met the criteria for >90% lung re-expansion. 20% of the patients in the slurry arm and 14% in the insufflation arm died within 30 days of treatment (suggesting that assessment of two-month survival was overly optimistic).

For the primary endpoint, there was no difference between the two methods ($p=0.169$). However, for all patients (whether they lived 30 days or not) who had >90% lung re-expansion, there was a statistical difference ($p=0.045$) favoring insufflation (78% vs 71% slurry). If the two most common etiology (breast and lung cancer) for MPE were examined, there was also a statistical difference favoring insufflation ($p=0.022$) in patients living 30 days with >90% re-expansion.

Fever and pain were the most frequent toxicities (grade 3 toxicity \cong 30%). Respiratory failure caused 11 deaths (five in slurry and six in insufflation arm).

In summary, no difference in efficacy was found between the two methodologies for the primary endpoint. However, prevention of recurrence of MPE from breast or lung cancers can be achieved with a success rate of 82% with insufflation (vs 67% with slurry). Respiratory toxicities do occur and patients require monitoring for hypoxemia.

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Progress from Chemotherapy Trials for Malignant Pleural Mesothelioma

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Malignant pleural mesothelioma (MPM) is a challenging disease with an incidence that is increasing in most West-European countries. The median survival after diagnosis is <1 year, and most patients are not amenable to any kind of radical treatment. Independent prognostic factors are performance status, extent at presentation, histological subtype and white blood cell count. Numerous phase II trials have been conducted in the past looking at the activity and toxicity of different compounds and combinations for treatment of mesothelioma. The “least inactive” regimens consisted of cisplatin, an anthracycline, methotrexate or gemcitabine, either as single agents or in combination. The intent of chemotherapy is palliative and symptomatic relief¹.

The promising response rate observed with high-dose methotrexate provided support for further testing of novel antifolates in the treatment of this disease. Pemetrexed and raltitrexed both target multiple enzymes involved in folate metabolism and pyrimidine/purine synthesis. Both drugs enter the cell via the reduced folate carrier and bind to the α -folate receptor with very high affinity. They both inhibit thymidylate synthase, an enzyme involved in pyrimidine metabolism, but are 30- to 200-times more potent than other antifolates².

In addition to single agent activity, responses were seen in 32-45% of patients in two phase I trials of pemetrexed combined with platinum analogs. A phase II study with single agent raltitrexed in naive patients showed a promising response rate³. Further studies with raltitrexed combined with oxaliplatin have demonstrated response rates varying from 20 to 35%. These studies led to the conduct of two large multi-national randomized trials^{4,5}.

The phase III study by Vogelzang et al⁴ showed response rates of 41.3% in the pemetrexed/cisplatin arm vs 16.7% in the control arm. The median survival was better in the pemetrexed/cisplatin arm (12.1 vs 9.3 months) as was the median time to progression (5.7 vs 3.9 months). There was also an improvement

in vital capacity with pemetrexed/cisplatin, as well as in overall quality of life (QOL), dyspnea and pain using the adapted Lung Cancer Symptom Scale.

The EORTC Lung Cancer Group investigated if the addition of raltitrexed to cisplatin, compared with cisplatin alone, improved outcome⁵. In this study, median survival was 8.8 months in the cisplatin arm vs 11.4 months in the combination arm; and the respective response rates were 13.6% vs 23.6%. The one year survival rates were 40% and 46% respectively. No deterioration of QOL was observed with the addition of raltitrexed. As in the pemetrexed study, a significant improvement in dyspnea and a trend to improvement in pain was observed with combined use of raltitrexed and cisplatin⁶.

We conclude that the combination of cisplatin and a novel antifolate (pemetrexed or raltitrexed) should be the new standard first line systemic therapy for selected patients with mesothelioma. In the absence of formal comparative data, the choice of regimen is dependent on issues as availability, compliance, toxicity and cost.

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Advances in Translational Research in Pleural Diseases

Single-Chain Urokinase in Pleural Fibrosis Management

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Ever since the 1950s, fibrinolytics have commonly been used to treat intrapleural loculations associated with parapneumonic effusions or hemothoraces. The literature has provided broad support for the continued use of these agents. That support was based on a number of clinical trials, many small and uncontrolled, with a few exceptions¹. In a recent multicenter, landmark trial, the fibrinolytic strategy for intrapleural loculation was seriously challenged². In that large, randomized, double-blind study, the

authors reported that there were no clinically relevant benefits of intrapleural streptokinase treatment of organizing pleural disease associated with parapneumonic effusions. The outcomes included mortality, length of hospital stay, radiographic improvement and rate of surgery and all were unchanged. Largely predicated on these findings, many (but not all) authorities have adopted a more conservative approach to the use of intrapleural fibrinolytics, reserving their use for patients who are deemed unfit for more invasive treatment.

While the place of fibrinolytic therapy for pleural loculations remains to be resolved, the search for more effective medical therapy is timely. All of the currently used fibrinolytics have a common limitation as they are rapidly inhibited within biologic fluids. Streptokinase, low molecular weight two chain urokinase (the form most commonly used for pleural applications) and tissue plasminogen activator (tPA) are all subject to rapid inhibition within pleural fluids. Both uPA and tPA are inhibited by plasminogen activator inhibitors, particularly PAI-1. Plasmin generated by streptokinase, uPA or tPA-mediated cleavage of plasminogen substrate in pleural fluids is likewise subject to downstream inhibition by antiplasmins that are likewise elaborated in the injured pleural space³.

Based on its biochemical characteristics, we inferred that the proenzyme form of uPA; single chain urokinase (scuPA, otherwise called prourokinase) could be a more effective intrapleural fibrinolytic. First, the urokinase receptor (uPAR) is expressed by pleural mesothelial cells⁴ and scuPA, when bound to uPAR, becomes a more active fibrinolytic. Second, scuPA exhibits fibrin selectivity and, when bound to uPAR, more effectively resists inactivation by PAI-1 than the active, two chain form or uPA⁵. Lastly, bound scuPA provides better fibrinolytic capacity than 'active' two chain uPA (tcuPA) in pleural fluids *in vitro*⁶.

We previously reported that scuPA, otherwise known as the proenzyme prourokinase, effectively prevents pleurodesis induced by tetracycline in rabbits⁶. More recently, we found that a single dose of scuPA effectively blocks tetracycline-induced pleurodesis in rabbits when given either before or after formation of overt pleural adhesions. scuPA is activated *in vivo* to two chain uPA and is detectable in pleural fluids for at least 24h after intrapleural injection (manuscript submitted). These observations

suggest that scuPA merits further evaluation and is a potential candidate for eventual clinical application. Several issues remain to be resolved, as uPA-mediated cellular signaling apart from or in addition to proteolysis could contribute to the overall effects in evolving pleurodesis. Direct comparison of scuPA's efficacy as an intrapleural fibrinolytic versus alternative agents will likely be informative as will studies to determine if scuPA actually offers anticipated dosing and safety advantages.

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Mesothelin as a Mesothelioma Marker

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Malignant pleural mesothelioma (MPM) is a cancer with poor survival and with a rising incidence¹. The diagnosis of MPM is often difficult and only established when the disease is too advanced for aggressive treatment. This prompted an ongoing search for biological markers that can provide early and reliable diagnosis of MPM. Soluble mesothelin-related peptides (SMRP)² and osteopontin³ have recently been proposed as markers for MPM.

Mesothelin is a glycoprotein expressed on the surface of normal mesothelial cells, but is over-expressed in mesothelioma and various carcinomas⁴. Evaluated by ELISA, serum SMRP level was significantly raised in patients with MPM or ovarian tumors. A first report of serum SMRP suggested it was a sensitive (84%) and specific ($\approx 100\%$) diagnostic marker of MPM. SMRP level was low in patients with various other pleuro-pulmonary diseases and in healthy asbestos-exposed subjects².

Our study compared blood and pleural fluid SMRP levels from patients with MPM, benign asbestos pleural effusions or metastatic pleural carcinomas⁵. We confirmed that serum SMRP level is significantly higher in patients with MPM, but at its optimal cut-off (0.93 μ M/L), SMRP only yielded a sensitivity of 80% and specificity of 83%. To reach

sensitivity of $>90\%$, the specificity falls below 50%. One reason is that SMRP levels are increased only in epithelioid but not in sarcomatoid MPM^{2,5}.

Pleural fluid SMRP was a marker at least as interesting as serum SMRP, and potentially better for differentiating MPM from metastatic carcinomas. Our data do not support a role for osteopontin, but suggest serum SMRP as a prognostic marker in patients with MPM. SMRP may also be helpful in monitoring patient response to therapy⁶.

In our opinion, asbestos-exposed subjects with high SMRP levels and pleural abnormalities should be 'aggressively' investigated to exclude MPM or metastases, though such strategy needs validation. Serum SMRP alone has insufficient specificity and sensitivity for MPM screening, but may act as an aid in tumor diagnosis and in monitoring patient outcome.

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Dendritic Cell-Based Immunotherapy of Malignant Mesothelioma (MM)

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Exploiting the immunostimulatory capacities of dendritic cells (DCs) holds great promise for cancer immunotherapy. Currently, dendritic cell-based immunotherapy is being evaluated clinically in a number of malignancies including melanoma, urogenital and lung cancer, showing variable but promising results¹. DCs are extremely potent antigen presenting cells specialized for inducing activation and proliferation of CD8⁺ cytotoxic T-lymphocytes (CTL) and helper CD4⁺ lymphocytes. DCs can be generated in large amounts *in vitro*, in the absence of the suppressive tumor environment, and subsequently injected in a mature state to induce anti-tumor responses². The possibility to harness the potency and

specificity of the immune system underlies the growing interest in cancer immunotherapy.

MM arises primarily from the serosal surfaces in body cavities and there is no universally accepted curative approach for MM. Most of the commonly used treatments are complicated by a high local recurrence rate and questionable survival benefit.

We have demonstrated the potency of DC immunotherapy in the control of MM growth in a mouse model. Injection of asbestos induced AB1 mesothelioma cells into the peritoneal cavity of syngeneic mice provides a valid experimental model for human MM. First signs of terminal illness after i.p. injection of 0.5×10^6 AB1 cells occurred between 2 to 4 weeks, but mice pre-treated with tumor lysate-pulsed DCs were protected for months and even resisted a secondary challenge with tumor cells, illustrating the induction of long lived immunity³. DCs given after tumor challenge had the capacity to slow down tumor growth although tumor load played an important role in survival.

In 2006, we initiated a clinical trial to define the safety and toxicity of tumor lysate-pulsed DCs and their ability to induce tumor specific CTL responses in patients with MM. Ten patients will be treated with chemotherapy (pemetrexed/cisplatin) followed by 3 vaccinations of autologous tumor lysate-loaded monocytes-derived dendritic cells, each dose consisting of 50×10^6 cells. Secondary end-points include immune responses by skin delayed type hypersensitivity reactions on mesothelioma cell lysate and keyhole limpet hemocyanin. Read-out parameters are the side effects, immune responses, anti-tumor responses and survival of this DC-based immunotherapy both *in vivo* and *in vitro*. More information can be found at the following website: <http://clinicaltrials.gov/ct/show/NCT00280982?order=1>.

If immune responses can be established in this phase I clinical study, a randomized phase II study will be performed comparing DC treatment versus best supportive care. In the future, the effect of DC-immunotherapy as a post-operative therapy after radical surgery for MM will be investigated, to establish if DC-immunotherapy can replace adjuvant radiotherapy and its associated toxicities.

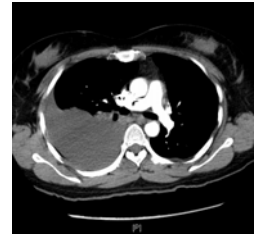
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IMAGES OF THE PLEURA

A 38-year old female presented with dyspnea and pleurisy 3 days after embryo transfer for *in vitro* fertilization. She had a moderate right pleural effusion. Pelvic ultrasound identified enlarged ovaries with multiple follicles, but minimal free fluid in the pelvis. Laboratory investigations showed a raised hematocrit (50.4%), leukocytosis and subclinical hypothyroidism. Thoracentesis yielded a serosanguineous exudate with a normal LDH (111 IU/L) level.



Our patient received therapeutic thoracentesis and eventually a pigtail catheter and drained 3.1L over 4 days. She subsequently developed a small contralateral effusion, moderate ascites and peripheral edema. Treatment included fluid support, thromboprophylaxis, albumin and thyroxine replacement. All symptoms and signs resolved by the eighth day of admission with no recurrence.

Diagnosis: Ovarian Hyperstimulation Syndrome (OHSS). The reported incidence of OHSS is 0.5-5% among patients undergoing ovulation-induction therapy. Predisposing factors include age <35 years, low BMI, polycystic ovarian disease, a high number of follicles, a high plasma estradiol level, pregnancy, hyperandrogenism and hypothyroidism. Exudative effusions are thought to be induced by increased vascular permeability from up-regulation of cytokines like vascular endothelial growth factor. The effusion is more often right-sided. OHSS usually resolves spontaneously. Management is supportive with avoidance of further hormonal therapy. Thoracentesis is reserved for symptom control.

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