Issue 4

Clydeside Action on Asbestos

Mesothelioma: Medical News November 2007

A compilation of articles by medical professionals on the treatment and care for those diagnosed with Mesothelioma.

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Foreword

At the launch of this newsletter in 2004, the stated aim was to exchange information and encourage debate about the management of mesothelioma. Previous editions focused primarily on diagnosis and presentation of mesothelioma, management of symptoms and clinical trials. In this edition the emphasis shifts to the consideration of the practical applications of immunotherapy to potentially manage and treat mesothelioma. The articles of Doctor Rudd, Doctor Tabi and Doctor McSharry discuss the role of immunotherapy in the diagnosis, staging, monitoring and treatment of mesothelioma and broadens the scope of the debate to new possibilities for the future. This is particularly relevant given that the incidence of mesothelioma continues to rise and continues to affect people from a broad occupational background. This is highlighted in the contribution from Doctor Telfer, a retired anaesthetist who was exposed to asbestos during the course of his work within Glasgow hospitals.

Whilst Doctor Telfer examines the patients perspective, Doctor Ferguson's article highlights the many issues that arise following a diagnosis from the experience of pain to coping with social security and legal matters. Establishing entitlement to social security benefits and submitting applications causes additional stress following a diagnosis and can lead to considerable anxiety and frustration. Our welfare rights team provide practical support, advice and assistance throughout this process.

In May 2006, Clydeside Action on Asbestos hosted a conference in London chaired by Professor Julian Peto, which focused on clinical trials for the management of mesothelioma, surgical procedures, asbestos related lung cancer, palliative medicine and patient care. The conference was well attended and generated a lively discussion with the panel of speakers.

A further evening conference will be held on 27 March 2008 in the Western General Hospital in Edinburgh, with the focus on novel therapies for mesothelioma, asbestos related lung cancer and current clinical trials. The conference is aimed at medical professionals and will be free of charge for those who wish to attend. Booking forms can be obtained by contacting Clydeside Action on Asbestos on 0141 552 8852

On 27 February 2007, Clydeside Action on Asbestos hosted a morning seminar in Glasgow City Chambers in support of the second National Mesothelioma Day. The event was attended by consultants of respiratory medicine, radiology, thoracic surgery, oncology, palliative medicine and pathology with the aim of producing a document of best practice and treatment of mesothelioma and lung cancer. The document will be distributed in Scotland initially and will be distributed to all junior doctors via university Deans. The afternoon seminar was hosted by the respected chest physician Doctor Robin Rudd. A question and answer session generated much debate amongst a selected audience and his contribution to the day was most valuable and greatly appreciated.

It is anticipated that future editions will contain a comments page to encourage debate of the many issues raised in the newsletter. Comments and suggestions for articles in future editions should be forwarded to Clydeside Action on Asbestos in writing by January 2008.

Clydeside Action on Asbestos would like to extend thanks to the authors who kindly submitted articles to this edition. We would also like to express sincere thanks, on behalf of those with an asbestos related disease, to Doctor Rudd for his continued support of this charity .

ASBESTOS RELATED LUNG CANCER + MESOTHELIOMA CONFERENCE 2008

Clydeside Action on Asbestos will host a Medical Conference on

Thursday 27th March 2008 at the
Fettes Suite in the Western General Hospital, Edinburgh, between 5.30pm - 8.30pm.
Registration : 4.45pm
A hot Buffet Supper will be provided between 5.00 - 5.30pm

Speakers / Topics :

Dr Robin Rudd	-	**Asbestos Related Lung Cancer**
Dr Dean Fennell	-	**Novel Therapies**
Professor Price	-	**Current Clinical Trials**
TBC	-	**Surgical Procedures**
Dr Marie Fallon	-	**Palliative Medicine**
TBC	-	**Psychological Effects of Diagnosis**

All interested medical professionals are invited to attend FREE of charge. Due to the demand, attendees must book their seat in advance.

For further information or to obtain a booking form, please contact Phyllis Craig at CAA on 0141 552 8852

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NICE MAKES LANDMARK DECISION TO ALLOW ACCESS TO TREATMENT FOR PATIENTS WITH ASBESTOS-INDUCED LUNG CANCER

Eli Lilly and Company Limited, Lilly House, Priestley Road, Basingstoke, Hampshire, RG24 9NL

The National Institute for Health and Clinical Excellence (NICE) made a landmark decision today to overturn their original recommendation to deny patient access to the only licensed treatment for this asbestos-induced form of lung cancer. After appealing the initial NICE recommendation, this positive decision now means that hundreds of patients with malignant pleural mesothelioma (MPM) will have access to Alimta (pemetrexed disodium), which could potentially give them an extra year of life and a better quality of life. (1)

Following an extensive and lengthy review process (which began in July 2005 and included a formal appeal by both patient groups and the manufacturer, Lilly) NICE has changed its position and approved Alimta for the treatment of malignant pleural mesothelioma. (2) In the Final Appraisal Determination (FAD) NICE states the reasoning behind the recommendation as follows: 'Having considered the likelihood of lower numbers of treatment cycles in clinical practice, the potential availability of a 100-mg pemetrexed vial and the likelihood of greater quality of life benefits than assumed by the cost-effectiveness analyses, the Committee agreed that the incremental cost-effectiveness ratio (ICER) for pemetrexed/cisplatin in the fully supplemented subgroup with advanced disease and good performance status was likely to fall within acceptable levels. The Committee also noted that MPM is a rare and aggressive malignancy caused by occupational exposure to asbestos and was mindful that this disease has a very poor prognosis.(3)

This decision means that Alimta, in combination with cisplatin, will be available on the NHS which in turn means that Primary Care Trusts (PCTs) should be able to prescribe this important treatment in the future. After a review of efficacy and safety data, Alimta (+ cisplatin) received a licence in the UK in November 2004 and it was accepted for use by the Scottish Medicines Consortium in July 2005.

This decision by NICE comes at a time when the number of cases of mesothelioma is on the increase. It takes between 20 and 40 years after exposure to asbestos for mesothelioma to develop, so people exposed to asbestos before its gradual withdrawal from the 1970s onwards are only now beginning to show symptoms of the disease. In 2004 over 1,600 people died from mesothelioma in the UK (4) but the peak in numbers won't be reached until around 2015 when 2,500 new cases are expected. (5)

Dr Gary Middleton, a Consultant Medical Oncologist at Royal Surrey County Hospital commented, "I am simply delighted for all of those distressed patients and their families and carers who so deserved this decision. I have a hope, borne out of the success of this appeal, that this moment will come to be seen as the point at which NICE transformed itself from the force that legitimised arbitrary budgetary restriction at the expense of individual suffering into the agency that facilitates excellence in patient care."

People affected by mesothelioma in the UK are primarily those who have worked in manufacturing industries such as shipbuilding, construction work and railway engineering. Incidence of the disease is therefore concentrated in areas such as Glasgow, the North East, the North West, Belfast, Plymouth and Hampshire. Asbestos affects not only those who are directly exposed to it but other family members who have come into contact with the deadly fibres on clothing worn at the place of work. e.g a number of teachers working in schools built using asbestos have also contracted the disease.

"At last NICE has stood up for these neglected patients and acknowledged that we have a duty of care to these people that cannot be defined by cost effectiveness alone. We are thrilled they will get the support and treatment they deserve. This is thanks to the patient groups particularly in Greater Manchester, the North West, the North East and in Scotland who have worked so hard to turn this decision around." said Tony Whitston, Chair of The Asbestos Support Groups' Forum."

Andrew Hotchkiss, General Manager of Lilly UK, makers of Alimta, comments; "This is good news for malignant pleural mesothelioma patients and their families in the UK and shows that NICE has recognised the benefits Alimta can offer in terms of survival and quality of life. The challenge now is to remove the current postcode lottery of care in England and Wales and make Alimta available to all patients who clinicians believe can benefit from it as soon as possible."

ENDS

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Notes:

The guidance published by NICE is the final appraisal determination (FAD), which sets out the Appraisal Committee's final recommendations subject to any appeal. The FAD will form NICE's final guidance on the use of the appraised technologies. Subject to appeals, final guidance from NICE is anticipated in September 2007.

Anyone wishing to submit comments regarding this decision may write to NICE at the following address:

National Institute for Health and Clinical Excellence
Technology Appraisal Manager/Alimta (pemetrexed disodium) in Malignant Pleural Mesothelioma
MidCity Place
71 High Holborn
London
WC1V 6NA

1. Data on File. Eli Lilly and Company Limited. 2007.
2. NICE has recommended pemetrexed (Alimta) as a treatment option for malignant pleural mesothelioma only in people who have a World Health Organization (WHO) performance status of 0 or 1, who are considered to have advanced disease and for whom surgical intervention is considered inappropriate. Patients currently receiving pemetrexed who do not fall into the patient population defined in section 1.1 should have the option to continue therapy until they and their clinicians consider it appropriate to stop.
3. Scottish Medicines Consortium. Detailed advice document. Pemetrexed 500mg infusion (Alimta®) Drug No (192/05) July 2005
4. Cancer Research UK. http://info.cancerresearchuk.org/images/excel/cs_mort_t6.1.xls.
5. Health & Safety Executive. Mesothelioma mortality in Great Britain: estimating the future burden. National Statistics 2003.
http://www.hse.gov.uk/statistics/causdis/meso.htm

MESOTHELIOMA: NEW POSSIBILITIES FOR TREATMENT

Introduction

Although there is now chemotherapy available for mesothelioma which can prolong survival to a modest extent and alleviate symptoms in a majority of patients, [1] the benefits of currently available agents are limited. While new chemotherapeutic agents will probably emerge, they will continue to share the limitations of chemotherapy, i.e. they damage normal cells as well as malignant cells and consequently give rise to substantial toxicity. Moreover some mesotheliomas are profoundly resistant to all forms of chemotherapy.

Chemotherapy owes its efficacy to induction of programmed cell death known as apoptosis. Tumours that efficiently engage their cellular apoptotic machinery, such as germ-cell cancers, commonly respond well to chemotherapy, resulting in marked reduction in tumour bulk, and often complete eradication of the tumour. The limited effectiveness of cytotoxic drugs and radiotherapy in mesothelioma reflects an important functional defect in apoptosis signalling. Failure of intrinsic apoptosis signalling is characteristic of many solid tumours, and is associated with resistance to conventional cytotoxic drugs. Increased understanding of the molecular blocks in the apoptosis pathway in mesothelioma is needed if new effective treatments are to develop.

Apoptosis resistance can arise from inhibition of mitochondrial permeabilisation, or suppression of enzymes known as caspases. Several mechanisms of natural inhibition of apoptosis have been discovered in mesothelioma, including stabilisation of the mitochondrial membrane, and direct inhibition of caspases by the inhibitor of apoptosis protein (IAP) family. [2] These have been found to regulate apoptosis in several malignant tumours. Agents which interfere with their activity, thereby increasing susceptibility of the mesothelioma cell to apoptosis, are under investigation.

There is interest in the possible role of new targeted agents which may selectively damage mesothelioma cells whilst not harming normal cells. One approach to treatment of tumours which has proved to be of value in several tumour types is the use of agents which inhibit growth of new blood vessels which are needed by tumours in order to grow and spread. These are called angiogenesis inhibitors and they may work by several different mechanisms.

Bevacizumab (Avastin®)

Bevacizumab (Avastin®) is a monoclonal antibody which acts as a vascular endothelial growth factor receptor anatagonist. It is an angiogenesis inhibitor with proven anti-tumour properties in several types of cancer including lung, colon and breast. A multicentre randomised trial is currently examining whether the addition of bevacizumab to chemotherapy with gemcitabine and cisplatin is beneficial in mesothelioma. So far there appears to be no unacceptable toxicity. [3] Other angiogenesis inhibitors, including thalidomide, are currently under trial in mesothelioma.

Ranpirnase (Onconase®)

Ranpirnase (Onconase®) is a ribonuclease enzyme which breaks down the genetic material ribonucleic acid (RNA) into smaller components and thereby renders the cell dysfunctional. Ranpirnase has some activity against mesothelioma. In a phase II trial of 81 patients assessable for response there were four partial responses, two minor responses and in 35 patients there was stabilisation of previously progressive disease. [4] A phase III trial of doxorubicin with or without ranpirnase is nearing completion.

Many mesotheliomas express P-glycoprotein and multidrug resistance-associated protein which are associated with resistance to chemotherapeutic agents, including doxorubicin and cisplatin, older chemotherapeutic agents with some activity against mesothelioma.

An important mechanism appears to be active extrusion of drugs. In the laboratory statins including simvastatin potentiate the

intracellular accumulation and extrusion of drugs. In the laboratory statins including simvastatin potentiate the intracellular accumulation and the cytotoxicity of doxorubicin. Their potential role as adjuvant agents to chemotherapy in treatment of mesothelioma merits exploration [5] (Riganti et al 2006).

Proteasomes are enzymes which have an important role in controlling cell function and growth. Agents which interfere with the function of Proteasomes may prevent growth of the cancer or eveu cause cancer cells to die. [6] Bortezomib (Velcade®) is a proteasome inhibitor to which cancer cells are more susceptible than normal cells. It has proven clinical value in multiple myeloma. A randomised phase II clinical trial in mesothelioma has recently started recruiting in the UK.

Arginine is an amino acid which is a precursor for several molecules which have important roles in tumorigenesis, including nitric oxide, nucleotides, proline and polyamines. Arginine may be important in mediating free radical damage that accompanies asbestos induced inflammation. In normal cells arginine is designated a non-essential amino acid because it can be synthesised. Argininosuccinate synthetase is a rate-limiting enzyme in arginine production which is reduced or deficient in more than half of mesotheliomas, so that they cannot synthesis arginine. This observation offers the possibility of treating mesothelioma by arginine depletion which normal cells but not tumour cells will be able to survive. [7] A phase II clinical trial in mesothelioma is expected to start in the UK later this year. Immunotherapy with agents including interleukin-2 and interferon has proved disappointing [8] and appears less likely to be valuable with the emergence of newer targeted biological agents. Gene therapy remains an attractive concept but so far has no practical use outside small clinical trials. [9] It seems clear that a single transgene is never likely to be able to eradicate a solid tumour like mesothelioma which is diagnosed late in its natural history and any role is likely to be as part of multi-modality therapy.

In conclusion, while further advances in chemotherapy are hoped for, increasing knowledge of the metabolic pathways that underlie resistance of mesothelioma cells to apoptosis are more likely to lead to the development of more effective and less toxic targeted agents for the treatment of mesothelioma over the next few years.

[illegible]

RESEARCH INTO THE IMMUNOLOGICAL PROFILING OF MALIGNANT PLEURAL MESOTHELIOMA (MPM)

Background

MPM is usually discovered at an advanced stage, when patients develop symptoms. As with all malignancies, earlier detection is crucially important for more successful applications of conventional and novel treatments. New biomarkers for the early detection of MPM emerged recently: soluble mesothelin-related protein (SMRP, MesoMark) (Robinson, 2003) and osteopontin (Pass, 2005).

They are presently undergoing validation tests to confirm their sensitivity and specificity in high risk groups with known exposure to asbestos, in unexposed controls, and in patients diagnosed with MPM. Thus it seems especially timely to study the feasibility of vaccines or combined immunotherapeutic interventions in MPM as in cases of earlier diagnosis these new therapeutic approaches can deliver real benefits for the patients.

My research group at Cardiff University received a research grant this year from the BLF's June Hancock Foundation for the immunological characterisation of mesothelioma.

Immune protection against cancer

Immunosurveillance means the continuous patrol of the body by immune cells in order to discover and destroy infected, foreign or transformed cells. In healthy people it is an ongoing, very effective way to protect the body from viruses and bacteria as well as emerging malignancies.

However, just as some viruses are able to avoid immune destruction and establish persistent infections (e.g. EBV or cytomegalovirus), tumour cells can also escape immune recognition and elimination; more so as they do not always have easily recognizable, immunogenic markers on the cell surface. It has been observed that in people who experienced a period of immune suppression, due to certain treatments or diseases, there is a dramatic increase in the incidence of certain types of cancer, emphasizing the importance of immunosurveillance.

By the time a tumour becomes symptomatic, it has not only evaded the immune system but can be actively suppressing it. The accumulating evidence compels even non-immunologists to accept that, together with the well-known intrinsic factors, evasion of immunosurveillance is one of the hallmarks of cancer (Zitvogel, 2006).

Cancer vaccines and immunotherapy

Immunological approaches in cancer can be preventative or therapeutic. Preventative vaccines are designed to establish a strong immune response for certain antigens before a tumour can develop (e.g. HPV-vaccines in cervical cancer). These are practical only when there is a well-defined protective antigen and a high risk group for the development of a certain malignancy.

Immunotherapy of established tumours, on the other hand, tries to redress the balance lost earlier between the malignant cells and the immune system. This may involve non-specific treatments, such as the application of IL-2 or TNF, or antigen-specific interventions, when tumour-specific effector cells (mainly T cells) are generated ex vivo or stimulated in situ to enable them to selectively target and destroy tumour cells.

The potential benefits and the advantages of antigen-specific immune therapy are immense. Unlike non-specific therapies, it is non-toxic for healthy cells and it causes none or minimal side effects. More importantly, tumour-antigen-specific immune cells can track down and destroy cancer cells in the entire body and, a feature of adaptive immune responses, the developing long-lasting immune memory ensures continued protection against the given tumour antigen(s).

Antigen-specific immunotherapy itself is extremely challenging and complex, and, given the potential combinations with conventional therapies, there is still some way to go before we can see it as a routine treatment of advanced cancer.

Immunotherapy and MPM

Beside impressive pre-clinical models there are several lines of evidence confirming that human MPM is an immunogenic cancer and thus a promising candidate for immunotherapy. There are examples of rare spontaneous recoveries in patients with improved immune function, but also well-documented studies demonstrating significantly elevated levels of antibodies specific for mesothelioma-associated antigens in MPM patients. Furthermore, Phase I and II clinical trials with promising outcomes, employing different aspects of immune therapy, such as combination chemo-IL-2 therapy (Lucchi, 2007) or therapy with GMCSF+ autologous tumour cell lysate (Powell, 2006) also confirm that this field deserves further investigation.

With the help of this research grant, we aim to characterize systemic and tumour-associated immune responses to identify (a) potential antigenic targets, and (b) immune evasion mechanisms which may interfere with immunotherapy.

(a) Potential target-antigens on mesothelioma cells

Mesothelin, a differentiation antigen, is overexpressed on mesotheliomal, ovarian and pancreatic cancer cells, while its expression on normal cells is low. The presence of mesothelin-specific antibodies in mesothelioma patients confirms the immunogenic nature of this antigen. Mesothelin-specific T cell responses have also been demonstrated in cancer patients and it is the choice antigen in immunotherapy clinical trials of pancreatic cancer.

Although CD4 and CD8 T cell epitopes have been identified for several HLA types, they have not been tested in mesothelioma. Mesothelin was highly expressed on all our mesothelioma lines tested. These lines were established from pleural fluid (PF) and from solid tumours. The tumour cell lines (22 and more in progress) will serve as target cells for testing T cell-mediated cytotoxicity as part of the project. Further potential tumour-associated antigens, such as survivin, WT-1, and others, will also be analysed as potential T cell target antigens.

These are well-characterised and ubiquitous tumour anigens, but their immunogenicity has not been studied in mesothelioma. Our preliminary experiments have proved very promising, as autologous tumour-cell killing was observed following stimulation of lymphocytes, isolated from the PF of an MPM patient, either by TCR cross-linking or with HLA class-I restricted survivin-peptides.

These findings will be validated in a large number of samples and extended to the other candidate antigens.

(b) Potential immune-escape mechanisms in MPM

Mesothelioma cells and other cells in the tumour such as matrix fibroblasts and macrophages are able to produce growth factors (HGF and VEGF) and cytokines (TGFβ, IL-6) which not only promote cancer cell growth but also generate an environment which impairs the function of infiltrating lymphocytes. Some of these soluble factors may convert the infiltrating T cells into T regulatory cells which then actively suppress the function of other effector lymphocytes. Ongoing experiments in our group have established that HGF has a Th2-polarizing effect by regulating normal dendritic cell (DC) development. Severe impairment of T cell proliferation due to TGFβ,
- expressing subcellular particles (exosomes) derived from mesothelioma cells has also recently been identified by us (Clayton, 2007, in press). Interestingly, osteopontin, a potential biomarker of MPM, a chemokine-like extracellular matrix-associated protein with roles in cancer cell migration and tumour progression, has the opposite immunological effect: it is able to induce DC maturation and has a Th1-polarizing effect.

The regulation of the expression of these factors and their combined immunological effect has not been studied

before and is one of the projects we are currently working on.

Summary

Mesothelioma research finally includes the immunological profiling of the disease. Our work focuses on the characterisation of systemic and tumour-associated immune responses in MPM, including tumour-related immune escape mechanisms, and aims to identify tumour antigens which are potential targets for immune effector cells. The results will aid the design of a new treatment for mesothelioma.

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Wales Institute of Immunology
Cardiff University

AN INTRODUCTION TO NEW DEVELOPMENTS IN THE DIAGNOSIS AND TUMOUR IMMUNOBIOLOGY OF MALIGNANT MESOTHELIOMA

Introduction

Malignant mesothelioma is an aggressive tumour of cells derived from the mesothelium which is composed of epithelial cells originating in the embryonic mesoderm; the middle of the three germ layers in the early embryo, from which the muscular, skeletal, vascular, and connective tissues develop. The cells are located in a layer of specialized pavement-like cells forming a thin membrane that lines the body's serous cavities and internal organs.

Firstly, where it covers the lungs and the inner surfaces of the chest wall, it is known as the pleura.

Secondly, where it covers the organs of the abdominal cavity and the inner surfaces of that cavity, called the peritoneum.

Thirdly, where it constitutes the sac (the pericardium) that surrounds the heart. The functions of these cells are primarily as a mechanical barrier that produces a lubricant fluid that helps protect organs and allows them to move.

It is also a metabolically and immunologically responsive membrane, for example, when cells migrate and proliferate in response to injury or growth factors, contributing to inflammation and tissue repair, coagulation and fibrinolysis. Neoplastic transformation of these cells gives rise to malignant mesothelioma most often of the pleura (and less commonly of peritoneum) as a consequence of deposition of asbestos fibres. It is generally accepted that malignant mesothelioma is of poor prognosis and has no standard treatment.

The National Cancer Institute has recently published on the changing trend in incidence of mesothelioma since 1973 in the USA [1] reporting that the male incidence has peaked at 2 per 100,000 of the population per year in 1990 and has declined since. Industrial asbestos exposure peaked in the 1960s therefore demonstrating a clear latency period for tumour development.

On the basis of this we can anticipate global incidences of mesothelioma in relation to amount and exposure to asbestos. For example, the expected burden of mesothelioma mortality in Great Britain from 2002 to 2050 has been studied by JT Hodgson in 2005 [2].

Using the British Mesothelioma Register he examined the deaths from 1968 to 2001 and used the data to predict burden of mortality in GB. The peak of derived asbestos exposure index was in the late 1960s, and the observed and fitted mesothelioma deaths by year of death is estimated to peak between 2011-13, and between 1968 and 2050, there will have been approx 90,000 deaths from mesothelioma in GB (65,000 of these after 2001). Similar worldwide trends in the epidemiology of malignant mesothelioma have been reported by Robinson and colleagues in 2005 [3], and summarized on **Table 1.**

New aids to diagnosis, staging and monitoring.

Recent developments include new applications of antibodies for immuno-histochemical staining of tissue sections, and

Country	Incidence Cases/million population	Predicted peak year	Predicted no. of deaths in the next 40 years	Predicted costs $ Billion
USA	15	2004	72,000	200
Europe	18	2010-2020	250,000	80
Japan	7	2025	103,000	-
Australia	40	2015	30,000	5-10

Table 1 (see reference 3)

new serum markers particularly mesothelin-related protein and osteopontin. The histological diagnosis of malignant mesothelioma remains complex. Despite early promise, no specific antibodies are yet available which exclusively support this diagnosis [4, 5].

The use of antibody panels can, in most cases, discriminate malignant tumours of mesothelial origin from metastatic tumour. These panels should include antibody which would usually react with mesothelium - Wilms tumour antigen (WT-1), CK 5/6, calretinin, and HBME-1, as well as those which usually are non reactive - CEA, MOC31, BerEP4, and CD15.

The distinction between reactive or hyperplastic mesothelium and malignant proliferation remains difficult and still relies heavily on morphological features, particularly of stromal invasion. Immunohistochemistry has proven less beneficial although the pattern of expression of EMA can be helpful.

Diagnostic serum proteins

Mesothelin

Mesothelin is a glycosyl-phosphatidyl-inositol-linked cell-surface glycoprotein which is expressed on normal mesothelium and over-expressed in ovarian cancer and mesothelioma. Mesothelin monoclonal antibody McAb OV569 shows intense staining of tumour cells.

Mesothelin is also found in serum and appears to be specifically increased in mesothelioma, and may have some screening value since serum mesothelin concentration correlates with tumour size and it can be found in higher than normal concentrations in some healthy asbestos-exposed individuals [6].

Osteopontin (OPN)

This is a protein first recognized as an early T lymphocyte activation-1 (Eta-1) antigen which is involved in inflammation and repair. It is expressed on fibroblasts and is the most upregulated gene in pulmonary fibrosis and continues to increase during fibrosis after inflammation has receded. Tumour-cell-derived osteopontin is increased in mesothelioma.

High expression levels and serum levels are associated with poor survival of patients with mesothelioma, as well as stage I non-small cell lung cancer and prostate cancer. Serum osteopontin may therefore be a diagnostic and disease progression marker.

In a study of asbestos exposure, mesothelioma and serum osteopontin levels by Pass and colleagues [7] they found that increased concentrations were associated with pulmonary plaques and fibrosis, and with asbestos exposure and mesothelioma but not with normal radiographic findings, plaques alone or fibrosis alone (summarized on table 2).

Serum osteopontin and mesothelin may therefore be useful markers that are convenient for diagnosis and to monitor disease progression. These markers might be best used in combination for screening asbestos-exposed subjects for early evidence of disease.

This earlier diagnosis would enable research into treatment at a less advanced phase, and also perhaps explain why some individuals do not develop disease despite similar work exposures.

	Study Group		
	1	2	3
Number	69	45	76
Asbestos exposure	No	Yes	Yes
Mesothelioma	No	No	Yes
Osteopontin (ng/ml)	20+/-4	30+/-3	133+/-10

Table 2. (see reference 5)

Potential new treatment - immunotherapy

Patients with mesothelioma have no evidence of impaired cellular immunity therefore the proliferation of mesothelioma cells is more likely caused by these tumour cells evading the protective immune response.

The normal response to self tissue is immune tolerance, but when self tissue is abnormal, for example in the case of tumours, the immune system kills these cells by cytotoxic NK cells or CD8 T lymphocytes. Cytotoxicity is against "newly expressed" antigens on the tumour cells, but sometimes the tumour cells evade this immune response by secreting high concentrations of immunosuppressive cytokines for example TGFß.

There have been immunotherapy (or immunostimulatory) trials using molecules such as interferon-α, IL-2, and GM-CSF which have shown some measurable but not curative response. As an alternative strategy, better tumour antigen recognition could be achieved by dendritic cell-directed immunotherapy to promote efficient cross-priming and activating expansion of tumour-specific T cells.

This is demonstrated by experimental immunizing mice with mesothelioma cells plus the anti-tumour cytokine interleukin (IL)-12 which induces a potent anti-mesothelioma cell immune response. [8].

Gene therapy

A novel extension of this work is gene therapy for malignant mesothelioma. This was first explored in mouse models of disease in which adenovirus vectors were used alone or in conjunction with genes for the cytokine IFNß or IFNß and COX-2 inhibitors, or mesothelioma cells transfected with TGFßR to mop up TGFß.

There are a range of experimental models and specific molecules recruited to stimulate a response (see table 3).

Alternatively there are some novel therapeutic agents that prevent some of the biochemical pathways needed by the tumour cells, or indeed directly toxic for the tumour, which have reached early clinical trials.

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Mesothelioma patients	Vaccinia vector plus IL-2	lymphocytic infiltrate and persistent IL-2 expression.	No major tumor regression. Ref.9
Human mesothelioma cell lines	Herpes simples virus vector plus thymidine kinase	Renders the cell sensitive to ganciclovir	Induced modest responses. Ref.10
Human mesothelioma cell lines	Adenovirus plus Adp16INK4A (p53 signal molecule)	p53 normal but p16 reduced. Causes cell cycle G1 arrest and susceptibility to cytotoxic drugs.	May be effective in the treatment of mesothelioma. Pilot studies underway.

Table 3. Virus vectors for gene therapy

DIFFUSE ASBESTOS-RELATED PLEURAL THICKENING

Introduction

Diffuse asbestos-related pleural thickening (DAPT), also referred to as diffuse pleural fibrosis, is one of the less sinister consequences of asbestos inhalation and although rarely fatal, it can cause major respiratory disability. Whilst pleural plaque and mesothelioma are almost invariably due to asbestos, diffuse pleural thickening (like bronchial carcinoma) is not specific to asbestos and other aetiologies must be considered and excluded by a careful history or perusal of medical records. Unlike plaque, DAPT is a disorder of the visceral as opposed to parietal pleura and hence involves the fissures. Typically there develops fusion of the visceral and parietal membranes leading to an "industrial pleurodesis".

Differential diagnosis

Pleural fibrosis is a common outcome of a number of inflammatory disease processes including infective pleurisy (particularly tuberculous), empyema, trauma with haemothorax, radiotherapy and autoimmune diseases. It can occur in the pre-arthritic phase of rheumatoid disease but here the blood rheumatoid factor is usually strongly positive. There is no evidence that the autoimmune diseases predispose to fibrotic pleural reactions in asbestos workers.

Difficulties can sometimes be encountered in differentiating a benign reaction from a slowly growing epithelioid mesothelioma where the histology is either non-diagnostic or unavailable. This may result in uncertainty amongst medical attendants or, worse, a change in diagnosis some months down the line, and inevitable distress for patient and relatives with loss of confidence in the clinical team. Junior doctors must be aware that a pleural biopsy which does not show malignancy does not exclude malignancy.

Anatomy and Radiology

Whilst DAPT can affect all zones of the pleura including extensive apical fibrosis and distortion, the hallmark of this problem is involvement of the costophrenic recesses. This is the most important feature in distinguishing DAPT from plaque, the latter having been described as affecting the areas of maximum friction between the pleura the domes of the diaphragms, the thoracic midzones and the left mid-pericardium. Plaque does not occur, or at least does not occur early, in the apices, the costophrenic angles or the fissures.

DAPT is usually asymmetrical on the two sides whereas plaque tends to be relatively symmetrical. However in order for plaque to develop, there must be a pleural cavity; if a patient has previously had an infective pleurisy obliterating the cavity, plaque will not appear on that side. Other features of DAPT on the plain chest radiograph are distortion and thickening of fissures, and horizontal linear shadows known as "tidemarks".

Plaque and DAPT are both causes of thickening of the pleura and it is important to be specific when reporting radiographs as to the exact nature of the abnormality because casual unqualified mention of "thickening" may trigger unsupportable claims for damages if only plaque is present. Of course the presence of plaque is evidence of asbestos exposure and will support the attribution of diffuse fibrosis to an industrial origin.

One common feature associated with DAPT is the appearance of one or more areas of "enfolded lung", also known as rounded atelectasis and Blesovsky's syndrome. These are tumour-like masses of fibrotic tissue invaginating the lung tissue from the pleura.

They have a characteristic pattern on the CT scan of linear shadows extending out from the mass likened to a comet's tail. Where the appearances are typical there will be no need to investigate the patient for cancer. Enfolded lung should

be taken as a part of the DAPT spectrum. Although it has been described in non-asbestos related pleural conditions it is in general a strong indicator of an asbestos aetiology.

The appearances of diffuse thickening can be mimicked by extra-pleural fat but this typically is highly symmetrical, maximal at the apices and wanes inferiorly.

Occasionally it may be justifiable to carry out a CT scan to measure the Hounsfield number of the shadowing in order to distinguish fibrosis from fat.

Mechanism and progress

Clinically significant DAPT is much less common than plaque, amounting to a few percent of the exposed. The onset may be earlier than other asbestos related disorders and the Australian experience suggests that some cases may occur within five years of first exposure. There is no clear reason why some workers are susceptible to DAPT and there is a wide and unaccountable range in extent of the fibrosis. All asbestos fibre types can be responsible although there is an impression that the amphiboles (blue and brown asbestos) are more hazardous than chrysotile (white).

It is apparent that in some cases there is a preceding acute exudative pleural reaction but this is the exception rather than the rule. Most cases present with no identifiable account of an acute pleural episode.

It was previously considered that a heavy exposure was a prerequisite for the development of DAPT - the sort of fibre burden necessary to cause an industrial lung cancer. For this reason DAPT was accepted by the Benefits Agency for the attribution of a lung cancer to asbestos as opposed to tobacco consumption. However research on records of workers from the Devonport Naval Base indicates that DAPT arises from a wide range of fibre burdens and cannot be accepted as a marker of heavy exposure. The Industrial Injuries Advisory Council has therefore recommended removal of DAPT as a pointer to industrial cancer. It does however seem that heavy exposure is more likely than light to give bilateral thickening.

Once DAPT has formed, it may remain static, but it may also progress to cause increasing respiratory handicap. Classically the progress is described as taking place in a stepwise fashion but 'creeping' detioration can occur. It is not possible with any confidence to predict whether or when change will take place, nor the extent of the resulting handicap.

DAPT is not in itself a premalignant condition.

Physiological Impairment and Disability

Clinically there will be signs of pleural thickening which can to the unwary mimic pleural effusion; however there will also be evidence of loss of thoracic volume and possibly mediastinal deviation towards the more affected side. Crackles may be heard under the area of pleural fibrosis and must not be taken to indicate pulmonary fibrosis (asbestosis).

In pure pleural fibrosis there will be loss of the capacity of healthy lung tissue to expand. Physiologically this results in reduced lung volumes without airflow obstruction but reduced gas transferring capacity (DLCO) and raised transfer coefficient (KCO).

The resultant breathlessness varies from trivial to severe according to the extent of the respiratory impairment. The presence of pain should alert the clinician to the possibility of an alternative diagnosis.

Management

There is no effective treatment. Corticosteroids have no role and attempts at surgical removal of fibrous tissue, analogous to pericardectomy for constrictive pericarditis, are to be avoided. Patients should be told that whilst their disorder is disabling, it is not precancerous, and advised that exercise is not harmful.

Industrial Pension and Compensation

DAPT is a prescribed disease and asbestos workers with this diagnosis should be advised to apply for the appropriate pension from the Benefits Agency.

Editors note : It is not always in the financial interest of those with an asbestos related disease to apply for Industrial Disablement Benefit from the Benefits Agency. This is due to the United Kingdom social security system having means tested benefits and non-means tested benefits. Someone on a means tested benefit e.g. council tax benefit, housing benefit, income support or pension credit can lose their entitlement if they are awarded industrial injuries benefit, which is non means tested. It is therefore advisable for those diagnosed with an asbestos related disease to seek specialist advice regarding these matters before applying for any state benfits.

It may also be possible to pursue a claim for industrial injury from a negligent employer through the Civil Courts.

It is most unwise for a clinician to advise the patient that he has a case against the previous employer: it is more prudent to state that a claim might be successful and the patient may wish to take advice from a lawyer with expertise in personal litigation, or to consult his Trades Union.

A Trades Union may well be sympathetic to supporting a claim even if the man is no longer a member.

Conclusion

Diffuse asbestos-related pleural thickening is not uncommon and is an important cause of anxiety and breathlessness, particularly if extensive and severe.

Problems with litigation can arise because pleural fibrosis is not specific to asbestos and because of uncertainty about progress in the disease process.

Doctor Clive McGavin MD FRC P
Chest Physician,
Nuffield Hospital, Plymouth

ASBESTOS RELATED LUNG CANCER + MESOTHELIOMA CONFERENCE 2008

Clydeside Action on Asbestos will host a Medical Conference on Thursday 27th March 2008 at the Fettes Suite in the Western General Hospital, Edinburgh, between 5.30pm - 8.30pm.

Registration : 4.45pm

A hot Buffet Supper will be provided between 5.00 - 5.30pm

All interested medical professionals are invited to attend FREE of charge. Due to the demand, attendees must book their seat in advance.

For further information or to obtain a booking form, please contact Phyllis Craig at CAA on 0141 552 8852

MESOTHELIOMA: A PATIENTS PERSPECTIVE

In over thirty years of Anaesthesia and Intensive Care, Mesothelioma was never a feature in one's life either professionally or socially. Then suddenly, in early February 2006, you are told you have got it. An incurable malignancy without any clear cut line of management, and with terrible survival figures.

This is probably the most traumatic piece of news anyone can be given, comparable to the loss of a wife or child. So how to deal with it?

During the first month or so we gave a great deal of thought as to the principles we thought we should follow in the future and we were able to discuss these at the Respiratory Clinic on our next visit.

Following earlier discussions we had already rejected the surgical option which seemed to us to be just too heroic. That left chemotherapy plus of course treatment of any symptoms as they arose, for example chest pain or increasing breathlessness. At this time (Feb 2006) I felt extremely well apart from the exertional dyspnoea which had been the presenting symptom, and I certainly did not feel that I needed chemotherapy or indeed any other treatment

Medicine is not an exact science: it never was and it never will be. So no-one can say how any one individual's disease will progress. This, coupled with uncertainty about the possible effects of chemotherapy on both myself and the tumour made us opt for the status quo, i.e. do nothing meantime.

The Consultant Physician and the Oncologist both readily agreed. I write this in early November 2006, some nine months after that decision was made, and while my quality of life is significantly reduced I have not required to take a single pill of any sort so far, nor have we had to cancel any social engagements.

A positive attitude from everyone in the family unit seemed to us to be essential and is not easy for some. The most difficult thing was to put the survival figures right out of one's head. This probably took about three months.

Now we keep looking forward day by day, week by week and month by month. We make no secret about it and are entirely open but we now talk about it much less between ourselves,and try very hard to carry on as near normally as possible. We particularly try to ensure that my wife's normal routine of such things as Golf, Art Club, and the Music Club continues. You might say that we are in a state of denial, but it is our way of coping.

We were greatly influenced by Esther Rantzen's programme "How to have a Good Death" shown on BBC 2 in March this year, in which she makes the point about the number of people who are unable to gain access to palliative care facilties offered by Hospices.

In mid-summer we were referred to our local Marie Curie Hospice and we have had several visits there which we found immensely helpful, incorporating much lateral thinking and an explanation of the reassuring support services available for both myself and my wife. The consultant there also supported our policy of aiming for quality and not quantity, ie trying to maintain the best quality of life for the longest possible time. Hence no treatment at present till symptoms demanded it.

Of course everybody asks "How did you get it?" when they hear that it is related to asbestos. I believe that the most likely source was the asbestos covering on the steam heating pipes in the tunnels deep under the hospital.

I worked in Intensive Care and we frequently had to transfer patients on ventilators through these tunnels to other parts of the hospital. Although we did not bump into the pipes, people such as kitchen porters with large trolleys did, thus breaking the soft grey asbestos and leaving dust for themselves and others to breath in.

We are talking now about the late 60's and early 70's. I understand that one of the hospital tradesmen who had walked up and down the tunnels every day for thirty years has also contracted the disease.

In due course we discovered the non-medical support which is available. The hospital directed us to the social services for Attendance Allowance and gave us informative leaflets. But in the early months after diagnosis one is not interested in money and it was not until June 2006 that I telephoned Clydeside Action for Asbestos. They were extremely helpful and said that I was entitled to Industrial Injuries Benefit which I was subsequently granted. They also advised that in their opinion it was worth having lawyers look into the possibility of raising an action against the Health Board, and this is currently in progress.

So what about the more personal and domestic issues, both physical and mental, that have beset us during the last nine months?

Within days of the diagnosis becoming known and word spreading, we began to receive a flood of letters, each expressing sympathy in their own way. Several of the letters were so emotional that I had to stop reading them, and two of them would have had me dead the next day. I do not wish to appear ungrateful to the authors.

I appreciate their motives and I learned a lot about people from reading them, but at this time of domestic upheaval I must be honest and say that I did not find them supportive. They merely served to rub it in when we were trying to put it out of our minds.

Visitors too seemed to arrive on an almost daily basis, leading to endless repetition of the story and this was a bit of a trial for the larynx which from the beginning had been affected and too much talking would soon make it fail.

The physical symptoms experienced so far, include chest discomfort, breathlessness on exertion, lack of energy, gastric upsets, voice problems and significant weight loss.

Of these only the gastric upset makes you feel really unwell.

Distension, flatulence, hyperactive gut and no desire to eat are features.

Interestingly enough we found that if the smell in the kitchen was "right" before eating then one could face food, but if it was "wrong" one could not. Since my wife is a dietician and expert cook we soon got this under control. I had these problems for about four weeks recently but they have now resolved.

I have also gone completely off alcohol, which is a great pity, and it looks as if it will be permanent. This is an example of a topic I will return to later, namely the uncertainty of the timing and duration of symptoms and the realisation that one is not in control.

Chest discomfort has not been a problem. It comes and goes and may be absent for days and has not been severe enough to require analgesics.

Too much talking is bad for the larynx and my voice may give out completely only to recover in about half an hour. This can be extremely embarrassing, especially if one is speaking on the phone. It feels like a bad laryngotracheitis and is probably related to reduced movement of the left diaphragm which thus fails to generate enough pressure for good phonation. It also means that you can't blow your nose very well!

The lack of energy goes with the breathlessness and these show the greatest variability of all. There are good days, when one feels remarkably well, and there are less good days (we don't call them bad days) when one really doesn't want to go too far from the nearest well padded armchair. I mention this because with the loss of body mass sitting on a hard chair or one with a hard back is not to be recommended. This weight loss also makes one feel the cold much more readily.

But generally it is the available energy which governs one's activity rather than the breathlessness.

On a good day what can I do ? (Nov 06)

I can drive the car and the Disabled Drivers Badge is a great help. This is a good occupation since one is seated and it keeps the brain active.

I can use the computer and respond to requests to write articles like this. Nevertheless even quite small administrative

tasks take longer than before and it takes very little before they become a "hassle".

Today is a good day and I should be out in the fresh air.

I can do short slow walks on the level, but gradients are very difficult.

Unfortunately I have not been able to enjoy a game of golf since the summer although I have been out a few times on the buggy with my wife and others.

I can still do light jobs in my workshop, including some small scale wood-turning, but trimming the lawn edges is about my limit in the garden.
A degree of the initial gross disinterest still remains, and this leads me on to say a word about the mental effects that this disease has had on me.

Frustration at not being able to do things is a major problem, and watching your wife doing some of it makes it worse.

While one will never really get over the shock, and the knowledge is always subliminally in one's mind, at the beginning the key word was disinterest. One just was not interested in anything at all.

As time went on this improved to be replaced by the realisation that the timing and severity of the symptoms was very variable, the day to day future was unpredictable and perhaps the most difficult thing to accept is that you are not in control. Your disease is in control. As a Type A personality with over 20 years experience running an Intensive Care Unit you will understand that this did not come easily to me.

However we have now reached a state of mental equilibrium where we don't ask ourselves why we find it difficult to climb these stairs, or why we need a taxi right to the door of the theatre or will there be a lift in this building?

We just accept it.

So far this has all been about me, but what about all the other people who are affected? We are very fortunate in that we have a huge amount of support from Family, Friends, Minister, General Practioners and the Consultants at the Respiratory Clinic and the Marie Curie Centre. The knowledge that we have direct access to the latter is a great comfort.

I dread to think how I would manage without my wife of 49 years, who has risen to the challenge with a huge amount of courage and determination and displays enormous strength of character in coping with it. I wish I could do the same.
Our son lives at home and has become the man of the house, taking on all the heavier tasks, such as grasscutting, which I am now unable to do.

Our daughters live some distance away but are regularly on the telephone, and cheap air fares facilitate quick day or overnight visits.

Both are physiotherapists so there is plenty of advice about such things as diaphragmatic breathing, etc.

Then there is the church. I am the Property Convener, so I have had close contact with the minister over the years. It used to be about boilers, central heating and leaking roofs. Now it is about anything that comes to mind ranging from air traffic control to the problems of teenagers. Anyway much two-way chat passes over numerous cups of coffee and this form of support is also very much appreciated.

I am eternally grateful to all of them.

For the moment I remain independent. I can get up, have a shower, get dressed and make the bed without assistance. I am not as well from the energy point of view as I was in the summer, and I realise this can only get worse.

So what does the future hold?

I don't know.

I said before that Medicine is not an exact science. It never was and it never will be. That is what keeps you going.

You just hope you are going to be one of the luckier ones.

"Green buds for the hope of tomorrow,
Fair flowers for the joy of today,
Sweet memory, the fragrance they leave us,
As time gently flows on its way"
(Anon.)

THE LEGAL POSTION IN ENGLAND AS OPPOSED TO SCOTLAND

Introduction

Families affected by a death from mesothelioma experience unusually severe grief and an enduring sense of loss. That is often exacerbated by having witnessed the extreme pain, suffering and death of a loved one and knowing that it was caused by the negligence of a previous employer.

Most mesothelioma deaths are needless and avoidable if employers in the past had only taken more care to protect workers from exposure to asbestos. The heavy emotional burden of losing a close relative to mesothelioma is borne by the whole family.

This article seeks to review the differences between the legal systems in the separate jurisdictions of England & Wales and in Scotland. It considers how the system ends up with mesothelioma patients and their families having very different civil compensation rights for damages for personal injury and death depending on which side of the border they bring their claim.

The deciding factor as to which legal system has jurisdiction to deal with a claim is determined by where the asbestos exposure took place. Only if the asbestos exposure occurred both in Scotland and in England or Wales may a claim be brought in either jurisdiction.

Where there is a choice about which jurisdiction to bring the claim it is in the vast majority of cases currently in the patient's interest and their family to do so in Scotland. This applies whether the claim is pursued during lifetime or posthumously.

This article also considers the need for reform in relation to particular aspects of the way mesothelioma compensation claims are dealt with in England & Wales and the importance of taking a compassionate and pragmatic view of the interests of the family when considering compensation for bereavement.

England & Wales - Lifetime claims

In England & Wales the settlement of a claim for damages for mesothelioma during the patient's lifetime extinguishes the right of any family member to pursue a claim after death. If the claim is commenced but not finalised within lifetime it will survive for the benefit of the deceased's dependants and Estate.

This means patients have to make the cruel and invidious choice between something now (and die in the knowledge that the family is provided for) or something later which will be significantly greater in value. Paradoxically, those who decide not to settle during lifetime, in order that their family may derive the benefit of inheriting a claim of greater value, will die without the certainty of knowing if their family will be financially secure.

Fatal claims

The statutory framework which governs entitlement to, and assessment of, damages in fatal cases in the jurisdiction of England & Wales determines that on death there are two claims that can arise;

(a) *a claim on behalf of the Estate of the deceased under the Law Reform (Miscellaneous Provisions) Act 1934, as amended by the Administration of Justice Act 1982 (the LRA claim);*

(b) *a claim by certain persons, in their own right, under the Fatal Accidents Act 1976, as amended by the Administration of Justice Act 1982 (the FAA claim).*

The LRA Claim

The claim for the Estate under the LRA provides for recovery of damages for the deceased is pain and suffering, pre-death financial losses and expenses together with the costs of nursing care, assistance and domestic services etc.

Sections 1(1) and (2) of the Fatal Accidents Act 1976 provide for compensation relating to the post death period as follows:

(1) *If death is caused by any wrongful act, neglect or default which is such as would (if death had not ensued) have entitled the person injured to maintain an action and recover damages in respect thereof, the person who would have been liable if death had not ensued shall be liable to an action for damages, notwithstanding the death of the person injured;*

(2) *Subject to Section 1A(2) (see below), every such action shall be for the benefit of the dependants of the deceased.*

The FAA Claim

Usually the most substantial claim under the FAA relates to financial dependency. An exhaustive definition of who is entitled to pursue a dependency claim is contained in section 1(3) of the Fatal Accidents Act. The prescribed categories of dependents include;

a) *The wife or husband or former wife or husband (or civil partner) of the deceased*

b) *Common law partners who had co-habited with the deceased for at least two years before death and were treated as living as husband and wife during the whole of that period.*

c) *Any parent or other ascendant of the deceased.*

d) *Any dependent person who was treated by the deceased as a parent.*

e) *Any dependent child or other descendent of the deceased.*

f) *Any person (not being a child of the deceased) who in the case of any marriage to which the deceased was at any time a party, was treated by the deceased as a child of the family in relation to that marriage.*

g) *Any person who is, or is the issue of a brother, sister, uncle or aunt of the deceased, i.e. the extended family.*

All claims under sections 1(3)(a)-(g) require proof of actual financial dependency on the deceased.

Dependency claims can also be advanced not only on the basis of income but may also take into account the value of the services the deceased provided to the dependent relative. This may include the costs of decorating, gardening, DIY and house/car maintenance etc.

Bereavement claims

Section 1A(1) Fatal Accidents Act 1976 provides that an action under the Act may consist of or include a claim for damages for bereavement. The statutory list of persons entitled to an award for bereavement is very limited:

Fatal Accidents Act section 1A(2):

A claim for damages for bereavement shall only be for the benefit of:

(a) *the wife or husband (or civil partner) of the deceased*

(b) *where the deceased was a minor who was never married*

(i) *his parents, if he was legitimate and*

(ii) *his mother, if he was illegitimate.*

The statutory bereavement award is currently fixed at

£10,000 for deaths occurring on or after 1 April 2002 and £7,500 for deaths before then. The court has no discretion to depart from those figures or to make the award to anyone other than the narrowly defined category of relatives

Scotland

In Scotland the approach towards assessing pre-death losses and post-death dependency claims in mesothelioma cases is broadly similar to that in England & Wales. However there are two important differences: the entitlement of family members to bring a claim in their own right for compensation for "non-patrimonial loss" and the consequences for the family if the patient brings the claim to settlement during lifetime.

Non-Patrimonial loss

The nearest equivalent in Scotland to a bereavement claim is the concept of non-patrimonial loss.

Section 1(4) of the Damages (Scotland) Act 1976 provides that a claim for non-patrimonial loss may be brought by an immediate family member for the distress and anxiety they endure in contemplation of the patient's pain and suffering, for the grief and sorrow caused by death, and for the loss of the deceased's companionship and guidance. The definition of the immediate family members entitled to bring such a claim is set out in a Schedule and has recently been extended by Section 35(5)(b) of the Family Law (Scotland) Act 2006, so that it now includes the husband or wife, parents, siblings, children (adults and minors) and grandchildren of the deceased.

The levels of compensation presently awarded for bereavement range from £30,000 for widows and widowers (£10,000 each for the parents, siblings and children of the deceased). No court has yet determined the appropriate level of the award for grandchildren.

Rights of relatives

The Rights of Relatives (Mesothelioma) (Scotland) Act 2007 was introduced following a Petition by Clydeside Action on Asbestos to the Scottish Parliament and a campaign supported by other asbestos victim support groups in Scotland and Solicitor Advocate, Frank Maguire from Thompsons who gave evidence to the Justice Committee on the need for legislative reform. The Act received Royal Assent in April 2007 and now entitles mesothelioma patients in Scotland to settle their claims during lifetime while preserving their relatives entitlement to bring their own claim after the patientís death.

The effect of this legislation is to bring some comfort and relief to the patient and their family, allowing them to pursue their claims and be compensated fully without prejudicing each other's entitlement to claim.

Department of Constitutional Affairs consultation

On 4 May 2007 the DCA published a consultation paper on The Law on Damages which in part considers recommendations made by the Law Commission as long ago as the late 1990's in their report Claims for Wrongful Death.

Whilst a DCA proposal to amend the FFA so as to extend the statutory list of claimants able to make claims as dependants is welcome, it is far from clear that other proposals in the paper go far enough to bridge the widening gap between the way mesothelioma compensation claims are dealt with in Scotland and the way in which they are dealt with in England & Wales

Justice for Asbestos Families

On both sides of the border the families of mesothelioma patients regard bereavement damages and non-patrimonial loss as compensation for the same thing. They feel only cynical politicians or pedantic lawyers would attempt to draw a distinction to justify treating their suffering differently. We believe they are right.

The divergence of approach between the two legal systems, in terms of who is eligible to claim and the level of the award they are entitled to means that families in England & Wales are receiving tens of thousands of pounds less in compensation than the equivalent family in Scotland. This distinction exists despite the fact that in many cases the patient who was exposed to asbestos in England may have contracted mesothelioma as a consequence of doing exactly the same job, at exactly the same time, for exactly the same company as someone who was exposed to asbestos in Scotland.

Thompsons also believe that mesothelioma sufferers and their families throughout the UK should have the same opportunity to bring claims independently of each other. For the families it is not just about the compensation : they have all suffered harm in very similar circumstances and should therefore all have the legal right to be compensated for a shared sense of grievous injustice.

Thompsons has launched a campaign for Justice for Asbestos Families calling for changes in the law in England & Wales to achieve parity with, and build upon, the more favourable treatment of compensation claims for mesothelioma patients and their families in Scotland. Anyone wishing to support the campaign may do so by signing the online petition at

www.thompsons.law.co.uk

Ian McFall
Head of Asbestos Policy
Thompsons Solicitors

THE LIVED EXPERIENCE OF PAIN IN PATIENTS WITH MALIGNANT MESOTHELIOMA

The goal of palliative medicine is the relief of physical, psychological, social and spiritual suffering experienced by patients with incurable illness. Patients diagnosed with malignant mesothelioma usually have a poor prognosis and limited treatment options. For most patients the focus of treatment will be palliative.
The population of patients living with malignant mesothelioma in the West of Scotland is predominantly male gender and working class. The majority of them will have had occupational exposure to asbestos as younger men. In Glasgow the thriving ship building industry has resulted in a substantially higher incidence of mesothelioma than elsewhere in the UK.

Pain is the most common symptom and can prove difficult to control. In a study adapting the Lung Cancer Symptom Scale (LCSS) to measure quality of life in mesothelioma, pain was reported in over 85% of patients [1]. In these 495 patients, the presence of pain was predictive of symptom distress, reduced activity level and reduced global quality of life.

Whilst working as a specialist registrar in palliative medicine, I have found pain control in malignant mesothelioma complex and challenging. Physically the tumour may invade the chest wall through muscle, bone and nerves resulting in severe pain. There are also psychological, spiritual and social factors, which may contribute to the pain experience.

In contrast to many other cancer patients, those with mesothelioma know that their disease is attributable to asbestos exposure during their working lives. Whilst this allows opportunity for financial compensation it also introduces the additional stress of legal proceedings and paperwork. If there is any doubt regarding tissue diagnosis a post mortem is necessary where compensation is being sought.

Pain is a multidimensional phenomenon and the influence of non-physical factors on pain is well recognised [2]. The founder of the hospice movement, Dame Cicely Saunders, introduced the concept of "total pain" [3]. This describes the all-encompassing nature of pain. She recognised that cancer pain is not a purely nociceptive phenomenon but involves complex aspects of human functioning including behaviour, affect, cognition, personality and social relations. "Total pain" is also referred to as "spiritual pain" in the literature. Her definition of total or spiritual pain reads: "bitter anger at the unfairness of what is happening (at the end of life) and above all a desolate feeling of meaningless. Here lies, I believe, the essence of spiritual pain."[4]

The meaning of pain for a patient can intensify the experience of cancer pain. Cancer patients who attribute a new pain to an unrelated benign cause report less interference with activity and pleasure than those who believe that their pain represents progressive disease [5]. Therefore the appraised meaning of pain can influence pain intensity. The meaning of cancer pain is based on the past and implications for the future.

This research will look at the experience of pain felt by patients with malignant mesothelioma. By providing this insight into their lifeworld it aims to inform future palliative care for patients with mesothelioma.

Aims

- To describe the lived experience of mesothelioma and pain.
- To understand what meaning pain holds for these patients.
- To explore the psychosocial factors which may influence pain
- To identify areas for further research

Methods

A literature search identified the lack of evidence regarding the pain experience of mesothelioma patients. A qualitative approach was selected. Patients were recruited through oncology, respiratory and palliative medicine doctors and nurse specialists. Patients with pain relating to their mesothelioma were invited for interview. Ten patients participated, nine men and one woman.

All were interviewed at home. Five had partners or other family members present who contributed to the interview. An open interview technique allowed patients to tell their stories. These were recorded on tape and transcribed verbatim. The transcripts were then analysed and common themes identified. Initially I had planned to interview the participants one month later however this was only possible in one case.

Unfortunately over half of the patients had died and the remainder were too frail to be interviewed. This indicates the aggression of malignant mesothelioma.

Results

These are interim results as analysis is ongoing. For the majority of patients their stories begin up to forty years ago when they were working with asbestos. The scene was set as they told me about their working lives.

The story moved onto when they first became unwell, were diagnosed and finally to their current situation. They then spoke in depth about their experience of pain and day-to-day life with mesothelioma.

Asbestos exposure and attitude towards previous employers

The men and woman had given a lot of thought to their previous places of employment. For some it was difficult to remember as they had had so many different jobs. There was divided opinion as to whether employers were aware of the dangers of asbestos at that time. Whilst most patients saw no point in feeling anger towards previous employers, two did express anger and resentment. The majority felt that anger would not change the situation. It was of little point given how much time had elapsed.

Several had received compensation and admitted they had never been so well off financially. Whilst a number commented that money could not give them back their lives, they saw this as justice for their families rather than themselves. One man did not have a tissue diagnosis of mesothelioma and this prevented him from taking legal proceedings further whilst alive.

Editors Note : Those who have been informed that they may be suffering from mesothelioma, even if there is no biopsy to absolutlely confirm this, should still seek specialist advice at the earliest opportunity. State benefit/compensation can be awarded without a tissue diagnosis. Further, with a view to any future litigation, it is important for solicitors to get a statement as early as possible of where and when exposure occured.

His doctor had discussed the possibility of a post mortem to allow pursuit of compensation. He saw this as a means to provide for his younger wife following his death.

Diagnosis

Reaching a definitive diagnosis of mesothelioma can be a protracted journey. Patients often require chest drain insertion or video-assisted thoracoscopic biopsies.

For some of the participants, the diagnosis was not unexpected however for others it was as a shock.

One patient had a particularly stressful experience. He was found to have pleural plaques and was immediately alarmed. It was long after his symptoms of chest pain presented that he was finally diagnosed with mesothelioma.

He was dismissed on numerous occasions by his GP and made to feel like a malingerer.

Pain experience

All patients recruited to the study had pain related to their mesothelioma. They each discussed the individual nature of the pain of which their were common features. The pain was likened to a sharp object or in three cases

"like somebody sticking a knife in".

The involvement of intercostal nerves was also suggested with pain described as numb, burning or red hot.

Others described a dull, gripping ache or tightness eased by changing position.

"you feel as if there is something just standing punching into you, you know, and other times it can be like muscles all just gripping, you know . It is all under here. Sometimes I feel as if my breast is going to explode. You are holding it up and you are actually holding yourself and find I if I sit with my arms up, stretch it. "

Through their descriptions of pain not only do the patients convey the severity of their pain "excruciating", "very acute", "horrendous", "absolutely dreadful" , "really really sore" . They also commented on how important analgesia is in controlling their pain.

Painkillers were considered essential in managing the pain. The participants talked about how much worse pain was before painkillers were titrated. One man stated that he would be unable to make it through a day without them.

Meaning of pain

A shared opinion was that pain acted as a reminder of their illness. For some this was a source of worry, a feeling of something being there. In addition to signifying the presence of their cancer, patients were aware that their pain may be worsening and wondered if this was a sign of disease progression.

"I feel now as if this pain has reached a crescendo..... Where does it go from there? My body you know."

"Sometime I feel as if could it get worse? "

"I think now the pain is getting a bit worse than what it was. In fact I know it's getting worse. "

Pain as a herald of death

One patient described an episode of severe uncontrolled pain to the extent where she wondered if she was dying.

"To have the pain, oh I can't do anything when I've got this.....I've had pain but nothing, nothing like that because I just couldn't speak to anyone. One day it was pretty bad, I was lying here and I just couldn't speak, I burst out crying. I said I can't speak, you know, it was so horrendous, it was dreadful. It was absolutely dreadful and that was before it was increased (painkillers). "

L: Was that quite frightening for you?

P: Oh yes. You know because I'm saying 'what's happening' is it going to happen now, you know?

L: Because the pain was so bad?

P: Yes.

L: Did you actually think that...?

P: Yeh I thought I was...(crying)

(later)

Sometimes when it is really bad I say is this it? You know because if it is really severe, what is it doing, what is going on inside? You know when it is really bad. Maybe I shouldn't think that way, maybe I should think positive about it but as you know the old brain does funny things.

Psychological impact of illness and pain

Depression and anxiety were common amongst those interviewed. Low mood was reported in the context of fatigue, loss of independence and social isolation. Pain and breathlessness worsened anxiety. Others felt irritable and gave examples of being "crabbit" with those closest to them. Guilt was confessed about the impact their illness had on family and the burden they perceived themselves to be.

Support

Clydeside Action on Abestos

All patients who had been in contact with Clydeside Action on Asbestos had found them universally helpful taking much of the strain from them, explaining the process involved in claiming compensation and helping with practicalities like form-filling.

" We were falling out with each other trying to fill in forms... Phyllis was like a lifesaver. When you look at these forms it's like jumping into a world of mystery. You haven't got a clue – its as if they have made them as difficult as they possibly can."

Health care professionals

The feeling of constantly needing to phone / ask for help was a common theme. One family spoke at length about how they needed to 'fight' for everything since their father became unwell. Others provided examples where information had not been communicated between various health care professionals involved leading to confusion.

Patients and families appreciated those who had kept them informed and been frank with them about their illness.

Whilst support was valuable a few patients felt overwhelmed as different services were involved in their care.

"I was getting a bit taken over by everybody, telling you what to do, doing this and doing that. Changing your tablets and doing that. I just thought wait a minute here it's me, it's my life but you've just got to go with the flow. Everybody is trying to help but nobody knows everything."

Future

The majority of men had a stoical attitude to the fact that their disease was incurable. They had a shared feeling of acceptance, several stating "there is nothing I can do". A smaller number appeared to be struggling with their diagnosis and the impact this had on their lives. They could see nothing to look forward to. Two expressed a desire for hastened death. Both commented that had they been animals they would have been put down. Uncontrolled pain, breathlessness and overwhelming fatigue contributed to their suffering.

Conclusion

These are preliminary results of main themes arising from interviews with patients living with pain related to mesothelioma. This was a qualitative study therefore findings are not necessarily transferable to all with malignant mesothelioma. However the potential severity of this pain and need for early assessment and management is suggested. Pain experienced held meaning of worsening illness and death. Psychological consequences of mesothelioma included depression, frustration, anxiety and guilt.

The importance of good communication between doctors, nurses and patients from the point of investigation and diagnosis is highlighted. Support for those issues unique to mesothelioma patients through Clydeside Action on Asbestos is also essential. Other support may need to be assessed on an individual case basis so as not to overwhelm nor abandon these patients. Full results from this study will be submitted for presentation and publication later this year.

Acknowledgements

I am grateful to the patients and families who contributed to this research by sharing their stories. I am also grateful to those who helped recruit participants.

Finally I am grateful to my supervisors Professor John Atkinson and Elaine Stevens from the University of Paisley for their continued support.

ASBESTOS EXPOSURE AND LUNG CANCER

Introduction

Asbestos has been recognised as a potential cause of lung cancer since the 1940s and 1950s, long before the link with mesothelioma was described in 1960, but the nature of the carcinogenic effect of asbestos has been the subject of considerable discussion.

Of the disorders associated with asbestos (table) pleural plaque and mesothelioma are effectively only caused by asbestos exposure whilst basal pulmonary fibrosis and diffuse pleural thickening invite a differential diagnosis. The much more usual aetiology of lung cancer - tobacco smoke – has tended to eclipse other factors and it has been difficult to disentangle the industrial causes.

This article looks at various aspects of asbestos-related lung cancer with particular relation to attributability. Although asbestos has been implicated anecdotally in lymphoma and cancers of larynx, oropharyngx and oesophagus, in this article "cancer" should be taken as "lung cancer" unless otherwise indicated.

The size of the problem

The epidemiological study of the incidence of cancers caused by asbestos is made difficult by a number of factors which include the "noise" generated by smoking- related tumours, the lack of specific features of the industrial tumour and the problems of retrospective assessment of asbestos fibre type and total fibre burden.

There are estimates of numbers of asbestos related cancers and a range of 4-12% of tumours has been suggested as being due to asbestos (1). Alberg and Samet consider that about 90% of cancers are attributable to tobacco, 9-15% to occupation and 10% to radon (some having multiple aetiology). In Sweden it has been suggested that over 25% are occupational. Overall the impression is that there has in the past been a gross underestimation of the contribution of asbestos to the development of cancer.

Recent studies in the UK indicate that there are between 0.7 and 1.0 cases of cancer per cases of mesothelioma, i.e. between 1400 and 2000 per annum attributable in whole or part to asbestos. However the relative risk of developing cancer after heavy exposure is only about five-fold compared with the one thousand-fold risk of mesothelioma.

Types of lung cancer

One of the main difficulties in attribution of cancer to asbestos is that there is no anatomical or histological way of distinguishing between an industrial and non-industrial tumour. There is no recognised association between industrial exposure and either pulmonary carcinoid or bronchoalveolar carcinoma. All of the other usual histological types are equally represented and there appears to be no differences in tumour distribution in the lung – central versus peripheral or upper versus lower zone.

Where a cancer has been removed at surgery in a previously exposed subject, the surrounding lung tissue must be examined histologically for asbestos fibres and bodies, as this may provide evidence of attributability. Lung tissue should also be retained for fibre analysis.

Fibre Type

In general with asbestos related disorders the amphiboles (crocidolite/blue and amosite/brown) are more dangerous than the serpentine (chrysotile/white). This difference is most marked in the case of mesothelioma but the principle is thought to hold true for lung cancer. Some evidence suggests that the dose of white asbestos necessary to double the cancer risk may be100-1000 fibre/ml years, well above the burden for amphibole exposure of 25 fibre/ml years. There are reports widely differing rates of cancer after white asbestos exposure, some workers even suggesting that chrysotile is entirely safe, but chrysotile tends to be contaminated with another mineral fibre tremolite and/or amphibole, and one cannot dismiss exposure to white asbestos as irrelevant.

Interaction between Tobacco and Asbestos

There is no doubt that there is an interaction between these two important causes of cancer. The exact nature of the interaction is unclear from the epidemiological work. Evidence from the 1970s suggested that the risk of cancer was increased by 5 to 10 fold by asbestos exposure whatever the individual's baseline risk from smoking. It is not certain whether the two causes of tobacco smoke and asbestos interact in a multiplicative or additive manner and the overall impression is that it is "submultiplicative". As Rudd points out, the proportion of risk of lung cancer attributable to asbestos is independent of tobacco consumption. However the message for the clinician is that continuing smoking is particularly hazardous for the person with previous asbestos exposure and is grounds for strong encouragement and support for quitting.

Cancer Latency

The time lag between industrial exposure and increased cancer risk is not established, but the "Helsinki Criteria" (2) state that the time interval between exposure and presentation should be at least 10 years for attribution of a cancer to asbestos, and this seems widely accepted.

Relationship of disease to asbestos burden

Whilst mesothelioma, plaque and diffuse pleural thickening can occur after low exposure, asbestosis and cancer require a higher fibre burden. It is thought that cases of asbestosis can be encountered after cumulative exposures to mixed asbestos of 25 fibre/ml years and this is the level of burden which is considered to double the risk of cancer (1). Increasing burdens cause increasing risk.

Is Asbestosis Necessary?

It is accepted that where a cancer occurs in the presence of asbestosis the tumour is directly attributable to that exposure. There has been discussion as to whether asbestosis is a prerequisite for the designation of a tumour as industrial and the epidemiological evidence is inconclusive. It has been argued that both are diseases of high dust burden and that the asbestosis may simply be a marker of that burden as opposed to a tumour-initiator in its own right. It has become increasingly accepted that asbestos can induce cancer in the absence of asbestosis. The subject is discussed in detail by Henderson et al (1).

The Helsinki Criteria for Attribution of Lung Cancer to Asbestos.

These criteria (2) were proposed by a group of experts and published in 1997 under the title "Consensus report: asbestos, asbestosis and cancer: the Helsinki Criteria for diagnosis and attribution", and have been the basis for discussion and legislation ever since. In brief their criteria for attribution of a cancer to asbestos include the following:

1. Coexistent asbestosis.

2. A minimum number of asbestos bodies or equivalent uncoated amphibole fibres per gram of dry lung tissue. The exact figures are not included here but are discussed by Henderson (1). One difficulty which arises is that whilst amphibole fibres persist in the body, white asbestos tends to be cleared from the lung and late analysis gives an invalid assessment of previous fibre burden. Hence an occupational history taken carefully by someone knowledgeable in asbestos fibre levels in various occupational situations and at various periods of time is considered more reliable than lung fibre levels.

3. An estimated cumulative exposure of 25 fibre/ml years or more, or

4. An occupational history of at least one year of heavy unprotected exposure or 5-10 years of moderate exposure. Heavy exposure may have resulted from insulation work, demolition, asbestos spraying and work in the asbestos manufacturing industry: moderate exposure is said to include work in construction or shipbuilding. High intensity exposure sufficient to double the cancer risk may have been acquired in less than one year under exceptional circumstances.

5. Latency of at least 10 years between exposure and symptoms.

Table: Disorders Associated With Asbestos Exposure

1. Anxiety
2. Benign Pleural Plaque
3. Diffuse Pleural Fibrosis (Thickening)
4. Asbestosis
5. Malignant Mesothelioma of the Pleura or Peritoneum

It must be stressed that the fibre burden required for attribution is high and neither pleural plaque nor diffuse pleural thickening can be regarded as surrogates for heavy exposure.

UK State Occupational Compensation

The UK Industrial Injuries Advisory Council accepts that asbestosis is not a prerequisite for the designation of a lung cancer as industrial and has recently rejected diffuse pleural thickening as a marker of sufficient exposure for attribution. The acceptance of a claim relies on the history of unprotected work in selected industries where cumulative dust levels are likely to have at least doubled the cancer risk.

Civil Claims

It will be apparent from the above that the clinician and nurse specialist must be alert to the possibility that occupation has caused or contributed to a lung cancer, and hence the necessity of a thorough occupational history. The chest specialist without particular expertise in asbestos disorders must not feel it is his/her role to decide whether a given tumour is industrial because this has little effect on management. One should however raise the possibility with the patient and indicate that he may wish to seek legal advice. It is unwise to tell the patient that a claim is likely to succeed unless the clinician is very sure of his ground.

Conclusions

1. 9-14% of lung cancers may be caused by occupational exposure with a predicted 1400-2000 cases annually in the UK attributable to asbestos.

2. This attribution requires the demonstration of a relatively high asbestos burden.

3. Whilst the coexistence of asbestosis is accepted as evidence that a given lung cancer is industrial, the history of high exposure 10 or more years previously may also allow the designation of a cancer as industrial.

Editors note:The Benefits Agency accepts two forms of lung cancer as having occupational causation. Firstly, lung cancer with accompanying evidence of asbestosis is classified as prescribed disease PDD8. The second prescribed disease PDD8 (a) is primary lung cancer where there is evidence of occupational exposure to asbestos within a prescribed duration of years and only within a very few designated occupations

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CLYDESIDE ACTION ON ASBESTOS

MESOTHELIOMA CONFERENCE 2008

Thursday 27th March 2008 at the
Fettes Suite in the Western General Hospital, Edinburgh,
between 5.30pm - 8.30pm.
Registration : 4.45pm
A hot Buffet Supper will be provided between 5.00 - 5.30pm

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The following publications can be obtained by contacting Clydeside Action on Asbestos directly.

- "Have you been diagnosed with an asbestos related disease" - general information leaflet providing information about Clydeside Action on Asbestos - available in A4 gatefold format. Information can also be supplied in Welsh.

- "Have you been diagnosed with an asbestos related disease" - display poster - available in A3 format. Information can also be supplied in Welsh.

- "Have you been diagnosed with mesothelioma" - provides information about the services that may be available at all levels of care - available in A5 format. Information can also be supplied in Welsh.

- " Have you been Diagnosed with an Asbestos Related Lung Cancer" - available as an A3 Display Poster.

- Mesothelioma: Medical news - a compilation of articles by medical professionals on the treatment and care for those diagnosed with mesothelioma.

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