

RECENT TRENDS IN THE MANAGEMENT OF MESOTHELIOMA – A RARE FORM OF CANCER: A REVIEW

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ABSTRACT

Mesothelioma is a rare form of cancer in which malignant (cancerous) cells are found in the mesothelium, a protective sac that covers most of the body's internal organs. Malignant mesothelioma is an aggressive cancer originating from the mesothelial lining of the pleural cavity. Malignant mesothelioma is associated with asbestos exposure and is characterized by a long latency period between exposure and disease onset. Chemotherapy can sometimes lead to improvement of overall survival but there is no cure for malignant mesothelioma and patients often succumb from the disease within a year of diagnosis. Cancer cells can also metastasize (spread) from their original site to other parts of the body. Smoking does not appear to increase the risk of mesothelioma. However, the combination of smoking and asbestos exposure significantly increases a person's risk of developing cancer of the air passageways in the lung. Symptoms of mesothelioma may not appear until 30 to 50 years after exposure to asbestos. Shortness of breath and pain in the chest due to an accumulation of fluid in the pleura are often symptoms of pleural mesothelioma. Symptoms of peritoneal mesothelioma include weight loss and abdominal pain and swelling due to a buildup of fluid in the abdomen. These symptoms may be caused by mesothelioma or by other, less serious conditions. Treatment for mesothelioma depends on the location of the cancer, the stage of the disease, and the patient's age and general health. Standard treatment options include surgery, radiation therapy, and chemotherapy. The aim of present article is to provide in depth knowledge about mesothelioma, its sign and symptoms, its etiology, causes, diagnosis, pathophysiology, treatment, as well as epidemiology. This article presents a brief review of mesothelioma with an emphasis on recent trends in the management of this disorder. Some researchers have demonstrated the safety of a potential vaccine against mesothelioma. The vaccine, which infuses a patient's own dendritic cells (DC) with antigen from the patient's tumour, was able to induce a T-cell response against mesothelioma tumours.

Keywords: Mesothelioma, malignant mesothelioma, cancer, pleural mesothelioma, peritoneal mesothelioma, asbestosis, serous carcinoma.

INTRODUCTION

Cancer is an imprecise term used to describe different kinds of malignant neoplasm, marked by uncontrolled growth and the spread of abnormal cells. Cancers may be lethal by invading adjacent normal tissues or by spread to sites distant from the place of origin. Cancers that arise in epithelial tissues are called carcinomas. Cancer cells are able to grow in parts of the body other than their site of origin. Mesothelioma, more precisely malignant mesothelioma, is a rare form of cancer that develops from the protective lining that covers many of the body's internal organs, the mesothelium. It is usually caused by exposure to asbestos¹.

Its most common site is the pleura (outer lining of the lungs and internal chest wall), but it may also occur in the peritoneum (the lining of the abdominal cavity), the heart², the pericardium (a sac that surrounds the heart) or tunica vaginalis. Most people who develop mesothelioma have worked on jobs where they inhaled asbestos particles, or they have been exposed to asbestos dust and fiber in other ways. It has also been suggested that washing the clothes of a family member who worked with asbestos can put a person at risk for developing mesothelioma. Unlike lung cancer, there is no association

between mesothelioma and smoking, but smoking greatly increases the risk of other asbestos-induced cancers³. Compensation via asbestos funds or lawsuits is an important issue in mesothelioma.

The symptoms of mesothelioma include shortness of breath due to pleural effusion (fluid between the lung and the chest wall) or chest wall pain, and general symptoms such as weight loss. The diagnosis may be suspected with chest X-ray and CT scan, and is confirmed with biopsy (tissue sample) and microscopic examination. A thoracoscopy (inserting a tube with a camera into the chest) can be used to take biopsies. It allows the introduction of substances such as talc to obliterate the pleural space (called pleurodesis), which prevents more fluid from accumulating and pressing on the lung. Despite treatment with chemotherapy, radiation therapy or sometimes surgery, the disease carries a poor prognosis. Research about screening tests for the early detection of mesothelioma is ongoing.

Signs and symptoms of mesothelioma

Symptoms or signs of may not appear until 20 to 50 years (or more) after exposure to asbestos. Shortness of breath, cough, and pain in the chest due to an accumulation of

fluid in the pleural space (pleural effusion) are often symptoms of pleural mesothelioma.

Symptoms of peritoneal mesothelioma include weight loss and cachexia, abdominal swelling and pain due to ascites (a build up of fluid in the abdominal cavity). Other symptoms of Peritoneal may include bowel obstruction, blood clotting abnormalities, anaemia, and fever. If the cancer has spread beyond the mesothelium to other parts of the body, symptoms may include pain, trouble swallowing, or swelling of the neck or face.

These symptoms may be caused by mesothelioma or by other, less serious conditions.

Mesothelioma that affects the pleura can cause these signs and symptoms:

- Chest wall pain
- Pleural effusion, or fluid surrounding the lung
- Shortness of breath
- Fatigue or anaemia
- Wheezing, hoarseness, or cough
- Blood in the sputum (fluid) coughed up (haemoptysis)

In severe cases, the person may have many tumour masses. The individual may develop a pneumothorax, or collapse of the lung. The disease may metastasize, or spread, to other parts of the body.

Tumours that affect the abdominal cavity often do not cause symptoms until they are at a late stage. Symptoms include:

- Abdominal pain
- Ascites, or an abnormal build up of fluid in the abdomen
- A mass in the abdomen
- Problems with bowel function
- Weight loss

In severe cases of the disease, the following signs and symptoms may be present:

- Blood clots in the veins, which may cause thrombophlebitis
- Disseminated intravascular coagulation, a disorder causing severe bleeding in many body organs
- Jaundice, or yellowing of the eyes and skin
- Low blood sugar level
- Pleural effusion
- Pulmonary emboli, or blood clots in the arteries of the lungs
- Severe ascites

A mesothelioma does not usually spread to the bone, brain, or adrenal glands. Pleural tumours are usually found only on one side of the lungs.

Etiology and causes of mesothelioma

Working with asbestos is the major risk factor for mesothelioma. In the United States, asbestos is the major cause of malignant mesothelioma and has been considered "indisputably"⁴ associated with the development of mesothelioma.

Indeed, the relationship between asbestos and mesothelioma is so strong that many consider mesothelioma a "signal" or "sentinel" tumour^{5,6}. A history of asbestos exposure exists in most cases. However, mesothelioma has been reported in some individuals without any known exposure to asbestos. In rare cases, mesothelioma has also been associated with irradiation, intrapleural thorium dioxide (Thorotrast), and inhalation of other fibrous silicates, such as erionite. Some studies suggest that simian virus 40 (SV40) may act as a cofactor in the development of mesothelioma⁷.

Asbestos was known in antiquity, but it wasn't mined and widely used commercially until the late 1800s. Its use greatly increased during World War II. Since the early 1940s, millions of American workers have been exposed to asbestos dust. Initially, the risks associated with asbestos exposure were not publicly known. However, an increased risk of developing mesothelioma was later found among shipyard workers, people who work in asbestos mines and mills, producers of asbestos products, workers in the heating and construction industries, and other trades people. Today, the official position of the U.S. Occupational Safety and Health Administration (OSHA) and the U.S. EPA is that protections and "permissible exposure limits" required by U.S. regulations, while adequate to prevent most asbestos-related non-malignant disease, they are not adequate to prevent or protect against asbestos-related cancers such as mesothelioma.

Likewise, the British Government's Health and Safety Executive (HSE) states formally that any threshold for mesothelioma must be at a very low level and it is widely agreed that if any such threshold does exist at all, then it cannot currently be quantified. For practical purposes, therefore, HSE assumes that no such "safe" threshold exists. Others have noted as well that there is no evidence of a threshold level below which there is no risk of mesothelioma⁸. There appears to be a linear, dose-response relationship, with increasing dose producing increasing disease⁹. Nevertheless, mesothelioma may be related to brief, low level or indirect exposures to asbestos. The dose necessary for effect appears to be lower for asbestos-induced mesothelioma than for pulmonary asbestosis or lung cancer. Again, there is no known safe level of asbestos to asbestos as it relates to increased risk of mesothelioma.

The duration of exposure to asbestos causing mesothelioma can be short. For example, cases of mesothelioma have been documented with only 1–3 months of exposure^{10, 11}. People who work with asbestos wear personal protective equipment to lower their risk of exposure.

Latency, the time from first exposure to manifestation of disease, is prolonged in the case of mesothelioma. It is

virtually never less than fifteen years and peaks at 30–40 years. In a review of occupationally related mesothelioma cases, the median latency was 32 years¹². Based upon the data from Peto et al, the risk of mesothelioma appears to increase to the third or fourth power from first exposure.

Environmental exposures

Incidence of mesothelioma had been found to be higher in populations living near naturally occurring asbestos. For example, in central Cappadocia, Turkey, mesothelioma was causing 50% of all deaths in three small villages — Tuzköy, Karain and Sarıhidir.

Initially, this was attributed to erionite, a zeolite mineral with similar properties to asbestos; however, recently, detailed epidemiological investigation showed that erionite causes mesothelioma mostly in families with genetic predisposition^{13, 14}. The documented presence of asbestos fibers in water supplies and food products has fostered concerns about the possible impact of long-term and, as yet, unknown exposure of the general population to these fibers.

Occupational

Exposure to asbestos fibers has been recognized as an occupational health hazard since the early 1900s. Numerous epidemiological studies have associated occupational exposure to asbestos with the development of pleural plaques, diffuse pleural thickening, asbestosis, carcinoma of the lung and larynx, gastrointestinal tumours, and diffuse malignant mesothelioma of the pleura and peritoneum. Asbestos has been widely used in many industrial products, including cement, brake linings, gaskets, roof shingles, flooring products, textiles, and insulation.

Paraoccupational secondary exposure

Family members and others living with asbestos workers have an increased risk of developing mesothelioma, and possibly other asbestos related diseases. This risk may be the result of exposure to asbestos dust brought home on the clothing and hair of asbestos workers. To reduce the chance of exposing family members to asbestos fibres, asbestos workers are usually required to shower and change their clothing before leaving the workplace.

Asbestos in buildings

Many building materials used in both public and domestic premises prior to the banning of asbestos may contain asbestos. Those performing renovation works or DIY activities may expose themselves to asbestos dust. In the UK use of Chrysotile asbestos was banned at the end of 1999. Brown and blue asbestos was banned in the UK around 1985. Buildings built or renovated prior to these dates may contain asbestos materials.

Diagnosis

Diagnosing mesothelioma is often difficult, because the symptoms are similar to those of a number of other conditions. Diagnosis begins with a review of the patient's medical history. A history of exposure to asbestos may increase clinical suspicion for mesothelioma. A physical examination is performed, followed by chest X-ray and

often lung function tests. The X-ray may reveal pleural thickening commonly seen after asbestos exposure and increases suspicion of mesothelioma. A CT (or CAT) scan or an MRI is usually performed. If a large amount of fluid is present, abnormal cells may be detected by cytopathology if this fluid is aspirated with a syringe. For pleural fluid, this is done by thoracentesis or tube thoracostomy (chest tube); for ascites, with paracentesis or ascitic drain; and for pericardial effusion with pericardiocentesis.

While absence of malignant cells on cytology does not completely exclude mesothelioma, it makes it much more unlikely, especially if an alternative diagnosis can be made (e.g. tuberculosis, heart failure). Unfortunately, the diagnosis of malignant mesothelioma by cytology alone is difficult, even with expert pathologists.

Generally, a biopsy is needed to confirm a diagnosis of malignant mesothelioma. A doctor removes a sample of tissue for examination under a microscope by a pathologist. A biopsy may be done in different ways, depending on where the abnormal area is located. If the cancer is in the chest, the doctor may perform a thoracoscopy. In this procedure, the doctor makes a small cut through the chest wall and puts a thin, lighted tube called a thoracoscope into the chest between two ribs. Thoracoscopy allows the doctor to look inside the chest and obtain tissue samples. Alternatively, the chest surgeon might directly open the chest (thoracotomy). If the cancer is in the abdomen, the doctor may perform a laparoscopy. To obtain tissue for examination, the doctor makes a small incision in the abdomen and inserts a special instrument into the abdominal cavity. If these procedures do not yield enough tissue, more extensive diagnostic surgery may be necessary.

Immunohistochemical studies play an important role for the pathologist in differentiating malignant mesothelioma from neoplastic mimics. There are numerous tests and panels available. No single test is perfect for distinguishing mesothelioma from carcinoma or even benign versus malignant. There are three histological types of malignant mesothelioma: (1) Epithelioid; (2) Sarcomatoid; and (3) Biphasic (Mixed). Epithelioid comprises about 50-60% of malignant mesothelioma cases and generally holds a better prognosis than the Sarcomatoid or Biphasic subtypes¹⁵.

Staging

Staging of mesothelioma is based on the recommendation by the International Mesothelioma Interest Group. TNM classification of the primary tumour, lymph node involvement, and distant metastasis is performed. Mesothelioma is staged Ia–IV (one-A to four) based on the TNM status^{16, 17}.

Screening

There is no universally agreed protocol for screening people who have been exposed to asbestos. Screening tests might diagnose mesothelioma earlier than conventional methods thus improving the survival prospects for patients. The serum osteopontin level might be useful in screening asbestos-exposed people for mesothelioma. The

level of soluble mesothelin-related protein is elevated in the serum of about 75% of patients at diagnosis and it has been suggested that it may be useful for screening¹⁸. Doctors have begun testing the assay which measures levels of soluble mesothelin-related proteins (SMRPs) released by diseased mesothelioma cells¹⁹.

Pathophysiology

The mesothelium consists of a single layer of flattened to cuboidal cells forming the epithelial lining of the serous cavities of the body including the peritoneal, pericardial and pleural cavities. Deposition of asbestos fibers in the parenchyma of the lung may result in the penetration of the visceral pleura from where the fiber can then be carried to the pleural surface, thus leading to the development of malignant mesothelial plaques. The processes leading to the development of peritoneal mesothelioma remain unresolved, although it has been proposed that asbestos fibers from the lung are transported to the abdomen and associated organs via the lymphatic system. Additionally, asbestos fibers may be deposited in the gut after ingestion of sputum contaminated with asbestos fibers.

Pleural contamination with asbestos or other mineral fibers has been shown to cause cancer. Long thin asbestos fibers (blue asbestos, amphibole fibers) are more potent carcinogens than "feathery fibers" (chrysotile or white asbestos fibers). However, there is now evidence that smaller particles may be more dangerous than the larger fibers. They remain suspended in the air where they can be inhaled, and may penetrate more easily and deeper into the lungs. Mesothelioma development in rats has been demonstrated following intra-pleural inoculation of phosphorylated chrysotile fibers. It has been suggested that in humans, transport of fibers to the pleura is critical to the pathogenesis of mesothelioma. This is supported by the observed recruitment of significant numbers of macrophages and other cells of the system to localized lesions of accumulated asbestos fibers in the pleural and peritoneal cavities of rats. These lesions continued to attract and accumulate macrophages as the disease progressed, and cellular changes within the lesion culminated in a morphologically malignant tumour.

Experimental evidence suggests that asbestos acts as a complete carcinogen with the development of mesothelioma occurring in sequential stages of initiation and promotion. The molecular mechanisms underlying the malignant transformation of normal mesothelial cells by asbestos fibers remain unclear despite the demonstration of its oncogenic capabilities. However, complete in vitro transformation of normal human mesothelial cells to malignant phenotype following exposure to asbestos fibers has not yet been achieved. In general, asbestos fibers are thought to act through direct physical interactions with the cells of the mesothelium in conjunction with indirect effects following interaction with inflammatory cells such as macrophages.

Analysis of the interactions between asbestos fibers and DNA has shown that phagocytosed fibers are able to make contact with chromosomes, often adhering to the chromatin fibers or becoming entangled within the

chromosome. This contact between the asbestos fiber and the chromosomes or structural proteins of the spindle apparatus can induce complex abnormalities. The most common abnormality is monosomy of chromosome 22. Other frequent abnormalities include structural rearrangement of 1p, 3p, 9p and 6q chromosome arms.

Common gene abnormalities in mesothelioma cell lines include deletion of the tumour suppressor genes:

- Neurofibromatosis type 2 at 22q12
- P16^{INK4A}
- P14^{ARF}

Asbestos has also been shown to mediate the entry of foreign DNA into target cells. Incorporation of this foreign DNA may lead to mutations and oncogenesis by several possible mechanisms:

- Inactivation of tumor suppressor genes
- Activation of oncogenes
- Activation of proto-oncogenes due to incorporation of foreign DNA containing a promoter region
- Activation of DNA repair enzymes, which may be prone to error
- Activation of telomerase
- Prevention of apoptosis

Asbestos fibers have been shown to alter the function and secretory properties of macrophages, ultimately creating conditions which favour the development of mesothelioma. Following asbestos phagocytosis, macrophages generate increased amounts of hydroxyl radicals, which are normal by-products of cellular anaerobic metabolism. However, these free radicals are also known clastogenic and membrane-active agents thought to promote asbestos carcinogenicity. These oxidants can participate in the oncogenic process by directly and indirectly interacting with DNA, modifying membrane-associated cellular events, including oncogene activation and perturbation of cellular antioxidant defences.

Asbestos also may possess immunosuppressive properties. For example, chrysotile fibres have been shown to depress the in vitro proliferation of phytohemagglutinin-stimulated peripheral blood lymphocytes, suppress natural killer cell lysis and significantly reduce lymphokine-activated killer cell viability and recovery. Furthermore, genetic alterations in asbestos-activated macrophages may result in the release of potent mesothelial cell mitogens such as platelet-derived growth factor (PDGF) and transforming growth factor- β (TGF- β) which in turn, may induce the chronic stimulation and proliferation of mesothelial cells after injury by asbestos fibres.

Treatment and Management

The prognosis for malignant mesothelioma remains disappointing, although there have been some modest improvements in prognosis from newer chemotherapies and multimodality treatments²⁰. Treatment of malignant

mesothelioma at earlier stages has a better prognosis, but cures are exceedingly rare.

Clinical behaviour of the malignancy is affected by several factors including the continuous mesothelial surface of the pleural cavity which favours local metastasis via exfoliated cells, invasion to underlying tissue and other organs within the pleural cavity, and the extremely long latency period between asbestos exposure and development of the disease. The histological subtype and the patient's age and health status also help predict prognosis.

Surgery

Surgery, by itself, has proved disappointing. In one large series, the median survival with surgery (including extra pleural pneumonectomy) was only 11.7 months. However, research indicates varied success when used in combination with radiation and chemotherapy. A pleurectomy is the most common surgery, in which the lining of the chest is removed. Less common is an extra pleural pneumonectomy (EPP), in which the lung, lining of the inside of the chest, the hemi-diaphragm and the pericardium are removed.

Radiation

For patients with localized disease, and who can tolerate a radical surgery, radiation is often given post-operatively as a consolidative treatment. The entire hemi-thorax is treated with radiation therapy, often given simultaneously with chemotherapy. This approach of using surgery followed by radiation with chemotherapy has been pioneered by the thoracic oncology team at Brigham & Women's Hospital in Boston²¹. Delivering radiation and chemotherapy after a radical surgery has led to extended life expectancy in selected patient populations with some patients surviving more than 5 years. As part of a curative approach to mesothelioma, radiotherapy is also commonly applied to the sites of chest drain insertion, in order to prevent growth of the tumor along the track in the chest wall.

Although mesothelioma is generally resistant to curative treatment with radiotherapy alone, palliative treatment regimens are sometimes used to relieve symptoms arising from tumor growth, such as obstruction of a major blood vessel. Radiation therapy when given alone with curative intent has never been shown to improve survival from mesothelioma. The necessary radiation dose to treat mesothelioma that has not been surgically removed would be very toxic.

Chemotherapy

Chemotherapy is the only treatment for mesothelioma that has been proven to improve survival in randomised and controlled trials. The landmark study published in 2003 by Vogelzang and colleagues compared cisplatin chemotherapy alone with a combination of cisplatin and pemetrexed (brand name Alimta) chemotherapy in patients who had not received chemotherapy for malignant pleural mesothelioma previously and were not candidates for more aggressive "curative" surgery²². This trial was the first to report a survival advantage from chemotherapy in malignant pleural mesothelioma, showing a statistically

significant improvement in median survival from 10 months in the patients treated with cisplatin alone to 13.3 months in the combination pemetrexed group in patients who received supplementation with folate and vitamin B₁₂. Vitamin supplementation was given to most patients in the trial and pemetrexed related side effects were significantly less in patients receiving pemetrexed when they also received daily oral folate 500mcg and intramuscular vitamin B₁₂ 1000mcg every 9 weeks compared with patients receiving pemetrexed without vitamin supplementation.

The objective response rate increased from 20% in the cisplatin group to 46% in the combination pemetrexed group. Some side effects such as nausea and vomiting, stomatitis, and diarrhoea were more common in the combination pemetrexed group but only affected a minority of patients and overall the combination of pemetrexed and cisplatin was well tolerated when patients received vitamin supplementation; both quality of life and lung function tests improved in the combination pemetrexed group. In February 2004, the United States Food and Drug Administration approved pemetrexed for treatment of malignant pleural mesothelioma. However, there are still unanswered questions about the optimal use of chemotherapy, including when to start treatment, and the optimal number of cycles to give.

Cisplatin in combination with raltitrexed has shown an improvement in survival similar to that reported for pemetrexed in combination with cisplatin, but raltitrexed is no longer commercially available for this indication. For patients unable to tolerate pemetrexed, cisplatin in combination with gemcitabine or vinorelbine is an alternative, or vinorelbine on its own, although a survival benefit has not been shown for these drugs. For patients in whom cisplatin cannot be used, carboplatin can be substituted but non-randomised data have shown lower response rates and high rates of haematological toxicity for carboplatin-based combinations, albeit with similar survival figures to patients receiving cisplatin²³.

In January 2009, the United States FDA approved using conventional therapies such as surgery in combination with radiation and or chemotherapy on stage I or II Mesothelioma after research conducted by a nationwide study by Duke University concluded an almost 50 point increase in remission rates.

Immunotherapy

Treatment regimens involving immunotherapy have yielded variable results. For example, intrapleural inoculation of Bacillus Calmette-Guérin (BCG) in an attempt to boost the immune response was found to be of no benefit to the patient (while it may benefit patients with bladder cancer). Mesothelioma cells proved susceptible to in vitro lysis by LAK cells following activation by interleukin-2 (IL-2), but patients undergoing this particular therapy experienced major side effects. Indeed, this trial was suspended in view of the unacceptably high levels of IL-2 toxicity and the severity of side effects such as fever and cachexia. Nonetheless, other trials involving interferon alpha have proved more

encouraging with 20% of patients experiencing a greater than 50% reduction in tumor mass combined with minimal side effects.

Heated Intraoperative Intraperitoneal Chemotherapy

A procedure known as heated intraoperative intraperitoneal chemotherapy was developed by Paul Sugarbaker at the Washington Cancer Institute²⁴. The surgeon removes as much of the tumor as possible followed by the direct administration of a chemotherapy agent, heated to between 40 and 48°C, in the abdomen. The fluid is perfused for 60 to 120 minutes and then drained.

This technique permits the administration of high concentrations of selected drugs into the abdominal and pelvic surfaces.

Heating the chemotherapy treatment increases the penetration of the drugs into tissues. Also, heating itself damages the malignant cells more than the normal cells. This technique is also used in patients with malignant pleural mesothelioma²⁵.

Multimodality Therapy

All of the standard approaches to treating solid tumours—radiation, chemotherapy, and surgery—have been investigated in patients with malignant pleural mesothelioma. Although surgery, by itself, is not very effective, surgery combined with adjuvant chemotherapy and radiation (trimodality therapy) has produced significant survival extension (3–14 years) among patients with favourable prognostic factors. However, other large series of examining multimodality treatment have only demonstrated modest improvement in survival (median survival 14.5 months and only 29.6% surviving 2 years). Reducing the bulk of the tumor with cytoreductive surgery is key to extending survival. Two surgeries have been developed: extra pleural pneumonectomy and pleurectomy/decortication.

The indications for performing these operations are unique. The choice of operation depends on the size of the patient's tumor. This is an important consideration because tumor volume has been identified as a prognostic factor in mesothelioma²⁶. Pleurectomy/decortication spares the underlying lung and is performed in patients with early stage disease when the intention is to remove all gross visible tumor (macroscopic complete resection), not simply palliation²⁷. Extra pleural pneumonectomy is a more extensive operation that involves resection of the parietal and visceral pleurae, underlying lung, ipsilateral diaphragm, and ipsilateral pericardium. This operation is indicated for a subset of patients with more advanced tumours, who can tolerate a pneumonectomy²⁸.

Possible Vaccine for Mesothelioma

Researchers have demonstrated the safety of a potential vaccine against mesothelioma, a rare cancer associated primarily with asbestos exposure. The vaccine, which infuses a patient's own dendritic cells (DC) with antigen from the patient's tumour, was able to induce a T-cell response against mesothelioma tumours.

The U.S. and other developed countries have prohibited the use of asbestos for decades, but the time between asbestos exposure and diagnosis of mesothelioma can be up to 50 years. The incidence of mesothelioma, therefore, is still on the rise and expected to continue to increase until 2020. Once diagnosed, mesothelioma has a median survival time of 12 months. The standard chemotherapeutic treatment only improves survival time by about three months.

The anticipated increase in the incidence of mesothelioma, together with the paucity of treatment options, has spurred considerable interest in the development of new therapies. Immunotherapy, which uses the body's own immune system to target and destroy cancer cells, has been shown to have some promise²⁹.

Mouse model for mesothelioma reproduces human disease

Scientists have established a mouse model³⁰ for human malignant mesothelioma that will provide valuable insight into cancer development and progression along with new directions for design of therapeutic strategies. The research, published by Cell Press in the March issue of *Cancer Cell*, may eventually lead to a substantially improved outlook for patients with this devastating disease.

"There is an urgent need for experimental models of malignant mesothelioma that can be used to not only study the onset and progression of the disease, but also to serve as a model to select new combination therapies and targeted agents," says study leader, Dr. Anton Berns, from The Netherlands Cancer Institute.

Epidemiology

Although reported incidence rates have increased in the past 20 years, mesothelioma is still a relatively rare cancer. The incidence rate is approximately one per 1,000,000. The highest incidence is found in Britain, Australia and Belgium: 30 per 1,000,000 per year³¹. For comparison, populations with high levels of smoking can have a lung cancer incidence of over 1,000 per 1,000,000. Incidence of malignant mesothelioma currently ranges from about 7 to 40 per 1,000,000 in industrialized Western nations, depending on the amount of asbestos exposure of the populations during the past several decades³². It has been estimated that incidence may have peaked at 15 per 1,000,000 in the United States in 2004. Incidence is expected to continue increasing in other parts of the world. Mesothelioma occurs more often in men than in women and risk increases with age, but this disease can appear in either men or women at any age. Approximately one fifth to one third of all mesotheliomas is peritoneal.

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