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Recent advances in mesothelioma

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Malignant mesothelioma is a highly aggressive cancer that arises from the surface serosal cells of the pleural, peritoneal and pericardial cavities; it is characterised by a long latency period from initial exposure to the development of disease. Exposure to asbestos fibres is the primary cause. Spread of the tumour is circumferential and longitudinal within the planes of the pleura, into the fissures and interlobular septa, and in places it focally invades the lung parenchyma. Regional lymph nodes can be affected in up to 70% of patients, with spread to the ipsilateral peribronchial and hilar lymph nodes, followed by the mediastinal, contralateral hilar and supraclavicular nodes. Haematogenous metastases are well documented, spreading to the liver, adrenal, bone and brain.

Experimental and epidemiological data support the view that asbestos, particularly amphibole asbestos, causes malignant mesothelioma. However, exposure to asbestos is usually not sufficient for the development of malignant mesothelioma; other factors, including radiation, genetic predisposition and simian virus 40 (SV40) infection, may render some individuals more susceptible to the carcinogenicity of asbestos. SV40 is present in most human malignant mesotheliomas. The virus appears to interfere with key cell cycle regulatory genes and may contribute with asbestos or alone (in nonasbestos-associated tumours) to the development of molecular genetic alterations that ultimately lead to a malignant phenotype. The local and systemic immunosuppressive activity of asbestos may also interfere with the ability of the immune system to attack and destroy cells expressing SV40 antigens, and thus favour tumour progression.[1]

Clinical features

Malignant pleural mesothelioma most commonly develops in the fifth to seventh decade (median age 60 years), typically 20–50 years or longer after the first documented exposure to asbestos. The risk appears to be proportional to both the intensity and duration of exposure. Latency periods between first exposure and diagnosis may vary according to occupation, with shorter latencies for insulators and dock workers and longer intervals for shipyard and maritime workers, as well as domestic exposures.[2] Men outnumber women by

Key Points

- **The management of mesothelioma requires a multidisciplinary and multimodality approach to therapy**
- **Chemotherapy offers an improvement in symptoms and quality of life**
- **Patients with poor performance status require careful assessment**
- **Age should not be a factor when deciding treatment**
- **Much of the research from clinical studies to date is heterogeneous and many of the trials underpowered to detect small differences**
- **Symptomatic benefit from anticancer treatment of mesothelioma is comparable with that of other tumours**

KEY WORDS: asbestos, mesothelioma, pemetrexed, simian virus 40 (SV40)

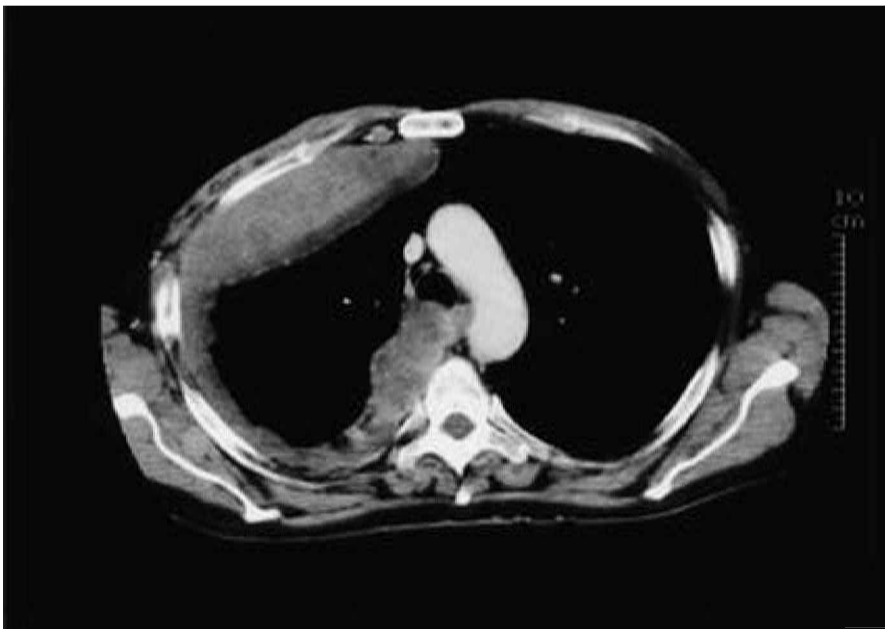

Fig 1. Computed tomography appearance of mesothelioma. A thickened rim of tumour arising from the pleura is beginning to encase the right lung. Characteristic findings are pleural thickening (92% of patients), thickening in the intralobar fissures (86%), effusions (74%) and pleural calcifications (20–50%).[3,4]

approximately 5 to 1. Initial misdiagnosis is frequent as a substantial proportion of patients present with no known exposure to asbestos.

Most patients present with intrathoracic symptoms of dyspnoea or non-pleuritic chest wall pain; more than 90% present with both. Rarely, features suggest involvement of the mediastinal pleura such as arrhythmias or dysphagia. Extrathoracic symptoms include anorexia, weight loss, malaise, lethargy and night sweats. Clinical examination usually reveals dullness at one lung base, and chest radiography shows a unilateral pleural effusion. Occasional patients are asymptomatic and an effusion is found incidentally on chest radiography. Tumours on the right side are found in 60% of patients, and fewer than 5% have bilateral involvement at the time of diagnosis.

Pulmonary function tests may show a restrictive lung pattern due to encasement of the lung, and any obstructive changes on spirometry are unrelated to mesothelioma or asbestosis. Laboratory evaluation is generally unremarkable except for an elevated platelet count and erythrocyte sedimentation rate. Computed tomography (CT) often shows a thickened rim of tumour arising from the pleura, often involving the mediastinal surfaces (Fig 1).[3,4] The factors that predict poor prognosis are listed in Table 1.[5–8]

Management of mesothelioma

The main treatment modalities are radiotherapy, surgery and chemotherapy, but other treatments may be given for symptomatic relief or to treat co-infections or other problems (Table 2).

Radiotherapy

The role of radiotherapy is not well defined. The doses required for reasonable control of mesothelioma can cause substantial pulmonary toxicity. External beam radiotherapy is an important palliative treatment for patients with chest wall pain, but its role in adjuvant treatment is not well established. It is also used for prophylaxis against regrowth for patients who have had a percutaneous biopsy. A randomised trial is currently evaluating the efficacy of this treatment. Intensity modulated radiotherapy has also been studied and appears feasible, although no survival advantage has yet been demonstrated.

Table 1. Prognostic factors predicting poorer survival.[5–8]

- Sarcomatous or mixed histology
- Poor performance status
- Positive lymph nodes
- Pleural primary tumour
- Weight loss
- Lactate dehydrogenase level >500 IU/l
- Older age
- Advanced stage
- Elevated platelet count
- Chest pain at diagnosis

Table 2. Other approaches to treatment.

- Analgesics
- Antibiotics for chest infections
- Codeine or methadone linctus for cough
- Medical treatment of breathlessness (opioids, anxiolytics)
- Treatment of biochemical abnormalities resulting from nonmetastatic manifestations
- Palliative radiotherapy to sites of metastatic disease
- Drainage of pleural or pericardial effusions and pleurodesis

Surgery

The role of surgery in the management of patients with diffuse pleural mesothelioma remains controversial, but an increasing number of thoracic surgeons operate for this disease. However, the combination of effusive disease and bulky tumour usually renders surgical eradication impossible.

Palliative surgery

The most common reason for a surgical procedure is either a diagnostic biopsy or a procedure to control or prevent an effusion that results in disabling dyspnoea.

Thoracoscopy with talc pleurodesis. The most efficacious and least invasive procedure is thoracoscopy with talc pleurodesis (success rates approach 90%). Failure of these techniques is usually associated with:

- mesothelioma with entrapped lung
- a large solid tumour mass
- a long history of effusion with multiple thoracenteses leading to loculations, or
- age older than 70 years.

Table 3 reviews the results of video-assisted thoracoscopic talc pleurodesis specifically for mesothelioma.[9–11] Patients whose pleurodesis was successful survived significantly longer than those in whom it was not. The likelihood of success was reduced in the presence of trapped lung or significant pleural invasion.

Pleurectomy. When performed routinely, pleurectomy for mesothelioma gives rise to few major complications. Pleurectomy plus decortication controls malignant pleural effusion in 88–98% of patients having decortication.[12,13] Median survival for patients having pleurectomy alone is approximately 13 months.

Radical surgery

A few tumours present as an encapsulated mass, not associated with pleural effusion. This may be amenable to surgical resection with negative margins of resection. In the largest series of extrapleural pneumonectomy (EPP) performed for mesothelioma, 36% of 183 patients had negative resection margins after EPP. Those with epithelial mesothelioma had 68% and 46% survival rates at two and five years, respectively, if the node dissection did not reveal tumour.[14] The preoperative quantitative bulk of disease may not only influence the choice of surgical approach but is also an important prognostic factor.[15]

EPP has significant morbidity: the major complication rate ranges from 20–40%, with arrhythmia requiring medical management the most frequent complication. In the early series the mortality following EPP was unacceptably high (31%), but there has been a steady decline in the operative mortality to less than 10% in series of 20 or more patients.[14,16] Mortality is greater in older patients due to respiratory failure, myocardial infarction, or pulmonary embolus.

EPP achieves local control, but distant recurrence is common. The site of first recurrence varies: local (35%), abdominal (26%), the contralateral thorax (17%) and other distant sites (8%).[17] Long-term survival rates after EPP remain disappointing, with median survival ranging from 9.3–17.0 months for most series. The impact of surgery on quality of life has neither been well studied nor reported.

In view of the predisposition for tumours to recur, multimodality protocols that incorporate surgery, radiotherapy and chemotherapy have been explored, but to date there has been no randomised phase III trial and therefore a survival advantage for surgery or radiotherapy has not been demonstrated.

Chemotherapy

Clinical trials involving chemotherapy and other anticancer therapies usually assess a new therapy on the basis of response rate and median survival. Response rates have until recently been poorly defined due to the methods of assessing changes in size, volume or area of tumour extent. This makes the assessment of new therapies difficult, and reported response rates may have been underestimated.

Most cytotoxic agents have been evaluated in mesothelioma and few drugs have consistently produced response rates over 20%. However, new cytotoxic agents with considerable activity in this disease have been developed and novel cytostatic agents that target the unique biology of this disease are under evaluation. Table 4 lists the response rates to different classes of agents.

For many years the gold standard treatment has been doxorubicin, with 14% response rates and median survival of 7.3 months.[18] A more recent phase III study compared cisplatin with cisplatin plus pemetrexed, a multitargeted antifolate. The response rate was 41.3% for the combination with median survival of 12.1 months versus 16.7% and 9.3 months for cisplatin alone.[19]

Despite the difficulties in assessing response rates, there is evidence of symp-

Table 3. Video-assisted thoracoscopy for malignant mesothelioma.

Author	Year	Ref.	No. of patients	*Success (%)	Median survival (months)
Viallat	1998	9	88	84	9.0
Canto	1997	10	46	80	9.4
Charvat	1998	11	13	100	6.8

*Success was defined as no further requirement for pleural aspiration after one month, with a normal radiographic result or less than 500 ml of residual fluid.

Table 4. Mesothelioma response rates according to chemotherapy drug class.

Class	No. of patients	Response rate (%)
Antimetabolites	247	18
Anthracyclines	267	13
Biological agents	94	13
Platinums	147	12
Alkylating agents	99	7
Vinca alkaloids	116	3

tomatic benefit to chemotherapy: although only 20–40% of patients demonstrate an objective response, 60–70% experience symptom improvement.[20] Vascular endothelial growth factor and epidermal growth factor appear important in the biology of this disease, and in recent years a number of biological agents that interfere with the response to growth factors have been developed. These agents can produce a response rate when used as single agents. The challenge will be how to combine conventional cytotoxic agents with these new biological therapies.

Conclusion

In the past chemotherapy had little impact on the natural history of mesothelioma, but there are now new active drugs with modest response rates that produce improvements in symptoms and quality of life. New insights into the biology of mesothelioma contribute to the development of biological agents that can exploit the unique characteristics of this aggressive disease. Several modalities of therapy can be used, emphasising the need for these patients to be managed by a multidisciplinary team with experience in this disease.

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