Trends and challenges in treatment of malignant pleural mesothelioma

Malignant pleural mesothelioma is a locally invasive carcinoma of the pleura. Eighty per cent of patients with malignant pleural mesothelioma have a history of asbestos exposure, in some cases many years ago. Media interest in malignant pleural mesothelioma, owing to the widespread use of asbestos during the 20th century, has created a high level of awareness of this neoplasm. The annual number of mesothelioma deaths in the UK increased from 153 in 1968 to 2037 in 2005. Over the next 40 years, compensation claims related to asbestos exposure are projected to reach around $80 billion and $200 billion in Europe and the USA respectively (Robinson and Lake, 2005).

The chrysotile and amphibole forms of asbestos are long thin fibres which are inhaled and travel freely to the smaller airways, penetrating the lung to reach the pleural cavity. The chronic irritation that ensues can result in the formation of pleural plaques and may predispose to mesothelioma. Asbestos fibres can also pierce intracellular mitotic spindles resulting in significant chromosomal damage. A proposed pathophysiological mechanism for mesothelioma is free radical-induced oncogenesis arising from asbestos-dependent cellular damage (Robinson et al, 2005). Simian virus 40 has also been implicated as a causative factor. Malignant pleural mesothelioma has an unusual genetic pattern. The loss of the p16INK4a, NF2 and p14ARF tumour suppressor genes can cause atypical mesothelial proliferation and increased susceptibility to asbestos-induced carcinogenesis (Gazdar and Carbone, 2003).

Current treatment regimens are either single modality (surgery or chemotherapy or radiotherapy), multimodality, or palliative or supportive care only, but only have limited success. New treatment strategies are needed because of the increasing prevalence of malignant pleural mesothelioma and the failure of current therapeutic regimens to offer long-term survival and improve quality of life.

Clinicopathological features and diagnosis

Malignant pleural mesothelioma is an insidious and uniformly fatal disease. Mean survival without treatment ranges from 4–12 months. Unremitting pleuritic pain, progressive exertional dyspnoea and recurrent pleural effusions are characteristic clinical features. Patients may also present with paraneoplastic fever, weight loss, fatigue and cough. Malignant pleural mesothelioma has a predisposition to the right hemithorax (60% right *vs* 35% left) and is bilateral at presentation in 5% of cases.

Plain chest radiograph and cross-sectional imaging may reveal diffuse pleural thickening or effusions indicative of the diagnosis. Computed tomography is the primary imaging modality used for the diagnosis and staging of malignant pleural mesothelioma. Magnetic resonance imaging and, more recently, positron emission tomography provide additional diagnostic and prognostic information to help further delineate the extent of disease, especially in surgical candidates.

Definitive diagnosis involves cytological analysis of pleural fluid or histopathological analysis of pleura. Tissue may be obtained through computed tomography-guided, video-assisted thoracoscopic surgical or open pleural biopsy. Distinguishing mesotheliomas from adenocarcinomas is challenging. Mesotheliomas are calretinin and epithelial membrane antigen positive. Additional immunocytochemical markers present on proliferative mesothelial cells are Wilms' tumour 1, cytokeratin and mesothelin (Whitaker, 2000).

There are four clinical histological subtypes of malignant pleural mesothelioma:

1. Epithelial (40%), which is more frequently associated with pleural effusions
2. Sarcomatoid (20%), also known as 'dry' tumours as they rarely cause effusions
3. Mixed tumours (35%)
4. Undifferentiated.

Staging of mesothelioma is difficult because there is limited surgical-pathological data from carefully staged patients. There are three staging systems which place different emphasis on primary tumour mass (Butchart), nodal/distant spread (tumour node metastasis) and operative resectability (Brigham).

Early studies attempting to prognosticate in this disease provided useful data. Prognostic factors associated with a better outcome include stage I or II disease, age <50 years, epithelial histological subtype, absence of pain and Karnofsky performance status 90–100 (Calavrezos et al, 1988).

Treatment

Treatment of malignant pleural mesothelioma involves single modalities or combinations of surgery, radiotherapy and chemotherapy. The aims of surgical intervention vary from symptom palliation to tumour eradication and prolongation of life. Problematic recurrent malignant pleural effusions causing dyspnoea can be palliated surgically. Video-assisted thoracoscopic surgical drainage of pleural effusion and talc insufflations is a simple and highly effective procedure. Talc causes an intense pleural inflammatory reaction (pleurodesis) which obliterates the pleural space. Other sclerosants used include tetracycline, bleomycin, doxycycline, quinacrine and even blood. Regardless of the sclerosant used, lung re-expansion is necessary for pleurodesis to be achieved.

In situations when a lung remains trapped, a long-term pleural catheter may be placed under either local or general anaesthetic. Prolonged drainage achieves pleurodesis and improves dyspnoea in these patients (Pien et al, 2001).

Surgery is also used to prolong and improve quality of life. Two surgical options are available: pleurectomy and decortication and extrapleural pneumonectomy. Extrapleural pneumonectomy is radical and aggressive, aiming for complete tumour removal. In pleurectomy and decortication resection is limited to the parietal and visceral pleura – this may be suitable for patients unfit to undergo extra-

pleural pneumonectomy or those unwilling to undergo such a massive operation. Over and above patient factors there is significant regional and surgeon variation as to whether extrapleural pneumonectomy is offered.

Mesothelial cells are poorly radiosensitive and evidence for the use of radiotherapy in a single modality regimen is lacking. Controversy surrounds the role of radical radiation in the treatment of malignant pleural mesothelioma. The dose of radiation in thoracic radiotherapy is complex and technically difficult because of the diffuse nature of the tumour. Avoiding serious toxicity is technically challenging, as adjacent vital structures are extremely radiosensitive (Ho et al, 2001). Radiotherapy is mainly used for palliation and symptomatic relief, prevention of malignant mesothelial cells seeding down tract sites after thoracoscopy and removal of chest drains, and to control local recurrences (especially in patients with positive resection margins). Adjuvant intensity modulated radiation therapy can prolong life and improve recurrence rates, but is associated with serious focal toxicity, predominantly fatal pneumonitis.

Chemotherapy is mainly used to improve survival length and quality of life. Over the years, many chemotherapeutic regimens have been suggested and then abandoned owing to comparatively poor responses and severe adverse effects. No single agent gives significant response rates. Platinum-based compounds and anthracyclines are the most active agents in the treatment of mesothelioma. Cisplatin and carboplatin have comparable response rates, but carboplatin is better tolerated (Baas, 2002). Neoadjuvant chemotherapy can be used for cytoreduction before extrapleural pneumonectomy and has been administered after extrapleural pneumonectomy and radiation to reduce distant recurrences.

A new anti-folate agent, pemetrexed (Alimta), is a major focus of international clinical trials. In an attempt to reduce systemic side effects, intrapleural chemotherapy has also been suggested. Results remain inconclusive, but intrapleural chemotherapy warrants further investigation.

Conclusions

Malignant pleural mesothelioma will become a more prominent problem in the next 10–20 years. The multimodality approach is the cornerstone of treatment for malignant pleural mesothelioma, demonstrating favourable outcomes compared with single modality treatments.

The British Thoracic Society Standards of Care Committee (2007) has emphasized the key role of a multidisciplinary team approach and suggested prompt involvement of a specialist nurse. Unfortunately there are few dedicated mesothelioma multidisciplinary teams in the UK, and it is estimated that 90% of malignant pleural mesothelioma cases are discussed at lung cancer meetings (Department of Health, 2007). Diagnosis, staging and treatment of malignant pleural mesothelioma is complex and the authors would question whether lung cancer multidisciplinary teams are appropriate and spend sufficient time discussing malignant pleural mesothelioma cases, especially in areas with a high prevalence of this neoplasm.

There are no randomized trials comparing different treatment regimens, and although current data suggest that the multimodality approach is superior, the optimum combination has yet to be defined. Guidance will be provided within the next 2 years from ongoing clinical trials.

If surgical resection is feasible then it should be the first-line treatment of malignant pleural mesothelioma. Early chemotherapy for non-resectable tumours is recommended as it improves survival, increases time to progression and provides adequate symptomatic relief. Platinum compounds and pemetrexed are most effective. Radical radiation alone should not be offered as a curative option. Radiotherapy after extrapleural pneumonectomy can decrease local recurrences. Procedure tract metastasis can be controlled with prophylactic radiation. Although there is no evidence for use of radiation alone, randomized trials of the curative role of radiotherapy and its impact on quality of life are needed. BJHM

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KEY POINTS

- Malignant pleural mesothelioma will remain an important social and epidemiological problem in the years to come.
- The role of surgery in the treatment of malignant pleural mesothelioma needs to be defined by controlled randomized trials.
- The effect of radiation on quality of life also needs to be appraised.
- Platinum compounds and pemetrexed alone or within the context of the trimodality regimen can stabilize symptoms and offer considerable survival benefit.
- Advances have been made but more targeted research in terms of the combination of treatments is warranted.