PLEURAL MESOTHELIOMA

BACKGROUND

1. Overview

Mesothelioma is a rare cancer that typically originates in the pleura, and less commonly in the peritoneum, pericardium or the tunica vaginalis. Although some patients are believed to have a genetic predisposition to the disease, the large majority of mesothelioma cases are caused by exposure to asbestos. Few patients with mesothelioma survive beyond 2 years, with women surviving longer than men.

Accurate diagnosis of malignant pleural mesothelioma (MPM) can be challenging, as it is uncommon and often difficult to distinguish from benign conditions. Diagnosis requires appropriate clinical and radiographic investigations, ideally with analysis of adequate tissue samples.

To further establish whether MPM is epithelioid or biphasic requires identification of two positive and two negative immunohistochemistry (IHC) markers.

In terms of treatment, pemetrexed–cisplatin is the only recommended regimen for unresectable MPM that is categorised as being based on high-level evidence by the European Society for Medical Oncology (ESMO) guidelines. In addition to the lack of treatment options for advanced disease, there is a lack of tumour biomarkers to guide treatment selection and prognosis.

2. What is pleural mesothelioma?

Mesothelioma is a rare and aggressive cancer in which tumours develop in the mesothelial or sub-mesothelial cells of different tissues. The large majority of pleural mesothelioma cases are caused by exposure to asbestos or to similar mineral particles that occur naturally although recent studies have also identified a possible genetic predisposition in a minority of patients.

This disease is characterised by a long latency period (30–50 years) between asbestos exposure and the development of symptoms. Latency appears to be dependent on the degree of exposure to asbestos, with heavily exposed patients presenting earlier. Owing to the fact that many symptoms are difficult to distinguish from those of other benign conditions, mesothelioma is typically diagnosed when the disease has already reached an advanced stage, meaning that most patients have a poor prognosis.
Few patients with mesothelioma survive beyond 2 years. One retrospective analysis of 1,353 patients with MPM found that survival in the overall population was 47% after 1 year, 20% after 2 years, and 15% after 3 years. Overall survival has been found to be longer in women than in men. Analysis of data from the Surveillance, Epidemiology, and End Results Program (SEER) database in US which included 14,228 patients diagnosed between 1973–2009 found that the 5-year survival rate was 13.4% in women but only 4.5% in men (p<0.0001). Mesothelioma subtype and patient age at diagnosis also affects survival rate, with rates lower in the sarcomatoid subtype, and lower with increasing age.

Incidence of mesothelioma

The incidence of mesothelioma is difficult to access accurately due to variable reporting rates worldwide and the fact that mesothelioma is often not specified in global databases.

In most European countries and in Japan, the incidence of mesothelioma is still increasing, but it has peaked in the US and in Sweden. Once a country introduces asbestos control measures, the number of mesothelioma cases is expected to plateau and then fall. However, as many developing countries continue to use asbestos, it is predicted that mesothelioma prevalence in those countries will increase for many years.

Types of mesothelioma

The most common form of mesothelioma – accounting for >90% of cases – is pleural mesothelioma. Mesothelioma can also occur in the peritoneum, the pericardium, and in other tissues, including in the membrane that covers the testis.
Histological subtypes of MPM

The three main histological subtypes of MPM are:

- **Epithelioid (~60%)**\(^{15}\)
- **Sarcomatoid (10–20%)**\(^{1,15}\)
- **Biphasic (~30%)**\(^{1,15}\)

Epithelioid is the most common subtype and is associated with better outcomes than other histologies, with a median survival of up to 2 years.\(^{15}\) The sarcomatoid subtype is far less common, and has been found to be resistant to therapy. Patients with this subtype of MPM have a poor prognosis, with predicted survival often <1 year from diagnosis.\(^{5}\) The biphasic subtype is also associated with worse outcomes to therapy; it is characterised by the presence of a combination of mixed epithelioid and sarcomatoid histologies (≥10% epithelioid and ≥10% sarcomatoid areas).\(^1\)

3. What are the risk factors for pleural mesothelioma?

The main risk factor for MPM is occupational or indirect exposure to asbestos, which accounts for ~80% of cases.\(^8\) The term ‘asbestos’ includes six types of minerals used commercially that form fibres: cummingtonite-grunerite, chrysotile, actinolite, anthophyllite, riebeckite and tremolite.\(^9\) All types of asbestos are classified as Class I carcinogens.\(^{16}\) While the exact pathogenesis by which asbestos causes MPM has not yet been fully established, it is known that inhaled asbestos fibres enter the visceral pleura and the pleural space resulting in chronic inflammation, DNA damage, and cytotoxicity.\(^{16}\) Development of asbestosis, pleural plaques and, in some cases, mesothelioma may follow.\(^{16}\)

Exposure to other elongated mineral particles that occur naturally and are not categorised as ‘asbestos’ has also been associated with MPM.\(^9\)

Other less common risk factors include genetic factors, in particular a germline mutation in the BAP1 gene.\(^8\) Some studies have raised the possibility that infection with simian virus 40 (SV40) might increase the risk of developing mesothelioma.\(^{17}\)

This information is from an international website which is intended for healthcare professionals not located in the United States of America (US) and the United Kingdom (UK).
4. What are the clinical features of pleural mesothelioma?

**Symptoms of MPM**

In patients with MPM, symptoms may have developed over the course of many months; they often seek medical advice with a higher symptom burden than is typical of patients who present with other types of cancer.

*Weight loss¹*

*Fatigue¹*

*Cough*¹

*Insomnia¹*

**Dyspnoea due to:**¹
- Pleural effusion (in early stages)
- Lung encasement by pleural thickening (in later stages)

**Chest pain due to:**¹
- Parietal pleural irritation and/or compression
- Invasion of the intercostal nerves by tumour invading the chest wall

*A less prominent symptom.*

**Diagnosis of pleural mesothelioma**

A definitive primary diagnosis usually requires IHC assessment of tissue biopsies, using at least two ‘mesothelial’ markers and at least two ‘(adeno) carcinoma’ markers. The sarcomatoid subtype may not exhibit typical ‘mesothelial’ markers.

Note: cytological samples are often inconclusive or negative, even when patients have malignant mesothelioma.

- Occupational history to establish asbestos exposure
- Computed Tomography (CT) scan of the thorax

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- In patients who have a unilateral pleural thickening, with or without fluid and/or calcified asbestos plaques, a pathological specimen should be obtained if possible, as there are no specific clinical features of MPM

Disease staging is assessed according to depth of tumour invasion (T), extent of lymph nodal metastasis (N) and extent of distant metastases (M). 18

**Disease staging of malignant pleural mesothelioma** 18

<table>
<thead>
<tr>
<th>Stage</th>
<th>TNM stage</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>T1</td>
<td>N0 M0</td>
</tr>
<tr>
<td>IA</td>
<td>T1a</td>
<td>N0 M0</td>
</tr>
<tr>
<td>IB</td>
<td>T1b</td>
<td>N0 M0</td>
</tr>
<tr>
<td>II</td>
<td>T2</td>
<td>N0 M0</td>
</tr>
<tr>
<td>III</td>
<td>T3</td>
<td>N0, N1, N2 M0</td>
</tr>
<tr>
<td></td>
<td>T1, T2</td>
<td>N1 M0</td>
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<tr>
<td></td>
<td>T1, T2</td>
<td>N2 M0</td>
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<tr>
<td>IV</td>
<td>T4</td>
<td>Any N M0</td>
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<tr>
<td></td>
<td>Any T</td>
<td>N3 M0</td>
</tr>
<tr>
<td></td>
<td>Any T</td>
<td>Any N M1</td>
</tr>
</tbody>
</table>

**Biomarkers**

A number of biomarkers can be assessed in MPM to help ascertain subtype and prognosis. Epithelioid and biphasic MPM diagnosis requires a combination of two positive and two negative IHC markers: 7

- Calretinin, cytokeratins 5/6, D2-40, and Wilms' tumour-1 protein (WT-1) are mesothelioma markers 7,19 with sensitivities ranging from 70–100% in epithelioid MPM 21

- Mesothelin may be assessed in serum and pleural fluid, has a sensitivity of 68–90%, 7 and is elevated in 50% of MPM patients 7

- BAP1 mutations are potential predictive markers of mesothelioma 7,20 and may be potential markers of the epithelioid subtype 21

- p16/CDKN2A homozygous deletion may be found in 90–100% of sarcomatoid, 19 and 70% of epithelioid/biphasic mesotheliomas and is linked with poor prognosis 21
There is a need for biomarkers of malignancy that can be used to guide treatment selection and prognosis. In a study investigating the genetic landscape of MPM for biomarkers to inform future treatment, frequency and type of genetic alteration was analysed using next-generation sequencing in 23 patients with MPM. The most common gene alterations or losses were BAP1 (60.9%), CDKN2A/B (52.2%), and NF2 (34.8%). Research is also ongoing to assess whether analysing both BAP1 and p16INK4A (encoded by p16/CDKN2A) in samples increases their specificity and sensitivity.

Currently, there are a lack of accurate biomarkers to aid diagnosis, prognosis and treatment of MPM, but a number of other potential diagnostic biomarkers for MPM are also under investigation.

**Potential diagnostic biomarkers for MPM:**

<table>
<thead>
<tr>
<th>Category</th>
<th>Marker</th>
</tr>
</thead>
<tbody>
<tr>
<td>Immune checkpoints</td>
<td>PD-1/PD-L1 +/- TIL</td>
</tr>
<tr>
<td>DNA</td>
<td>Hyperacetylated HMGB1</td>
</tr>
<tr>
<td>RNA</td>
<td>miRNA (various assays)</td>
</tr>
<tr>
<td>Genomics</td>
<td>Gene panels</td>
</tr>
<tr>
<td>Proteomics</td>
<td>SOMAmers</td>
</tr>
<tr>
<td>Other</td>
<td>Col3A1</td>
</tr>
<tr>
<td></td>
<td>BDNF + fibulin 3</td>
</tr>
<tr>
<td></td>
<td>Circulating plasma C4d</td>
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<tr>
<td></td>
<td>Leucocyte count + fibrinogen</td>
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<td>EPHA2</td>
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<td>ENOX2</td>
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5. What are the treatment options for pleural mesothelioma?

Surgery may be an option where resection is possible. For unresectable MPM, cisplatin-based doublet chemotherapy is recommended. Pemetrexed–cisplatin is approved as a first-line regimen for unresectable MPM in both the EU and US. A summary of the ESMO recommendations for first-line treatment of unresectable MPM is as follows:

<table>
<thead>
<tr>
<th>Treatment</th>
<th>ESMO recommendation</th>
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<tbody>
<tr>
<td>Pemetrexed + cisplatin (Day 1 every 3 weeks)</td>
<td>Category 1A</td>
</tr>
<tr>
<td>Treatment</td>
<td>Category</td>
</tr>
<tr>
<td>-----------</td>
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</tr>
<tr>
<td>Raltitrexed + cisplatin (Day 1 every 3 weeks)</td>
<td>1A</td>
</tr>
<tr>
<td>Pemetrexed + cisplatin (Day 1 every 3 weeks for 6 cycles) + bevacizumab (Day 1 every 3 weeks until disease progression)</td>
<td>NR</td>
</tr>
<tr>
<td>Pemetrexed + carboplatin (Day 1 every 3 weeks)</td>
<td>Alternative to cisplatin in elderly patients</td>
</tr>
<tr>
<td>Gemcitabine (Days 1, 8 and 15) + cisplatin (Day 1) administered in 3- to 4-week cycles</td>
<td>NR</td>
</tr>
<tr>
<td>Pemetrexed (Day 1 every 3 weeks)</td>
<td>NR</td>
</tr>
<tr>
<td>Vinorelbine (weekly)</td>
<td>NR</td>
</tr>
</tbody>
</table>

NR, not recommended.

As yet, there is no standard of care for the second-line treatment of these patients, although studies of single-agent chemotherapy and novel agents are ongoing. Radiation therapy can be used for palliation, although it is not part of standard treatment in the adjuvant setting. As yet, there is no standard of care for the second-line treatment of these patients, although studies of single-agent chemotherapy and novel agents are ongoing. Radiation therapy can be used for palliation, although it is not part of standard treatment in the adjuvant setting.

**Emerging treatment options for MPM**

The role of targeted therapies in the treatment of MPM is likely to increase as therapeutic advances continue. Targets and therapies that are currently under investigation in a number of Phase III trials include:

- Angiogenesis, e.g. bevacizumab (Phase III results published), nintedanib (Phase III trial ongoing)
- Immune targets, e.g. nivolumab combined with ipilimumab (Phase III trial ongoing)

Targets and therapies that are currently under investigation in a number of Phase II trials include:

- Immune targets, e.g. pembrolizumab, atezolizumab, durvalumab
- Proliferative signalling, e.g. cetuximab, cixutumumab
- Mesothelin, e.g. anetumab rAVT, amatuximab
References


