Palliative care for patients with mesothelioma

Mesothelioma is a highly symptomatic aggressive cancer affecting quantity and quality of life. Excellent palliative care is essential from diagnosis. This article discusses commonly encountered issues and management strategies including the rationale for early referral to specialist palliative care.

Mesothelioma is an aggressive cancer affecting serosal surfaces, most commonly the pleura. It is incurable and often rapidly progressive, with median survival just 14 months. Patients can be highly symptomatic, with multiple physical and psychological symptoms, impacting quality of life. This article outlines common palliative care issues and suggests management strategies. The specific evidence base for mesothelioma is limited, so this article often draws on literature from advanced malignancy. It will discuss:

- Rationale for palliative care
- Physical symptoms
- Psychological needs
- Care planning
- Legal issues
- Carer needs
- End of life care.

The rationale for palliative care

The high symptom burden in mesothelioma not only impacts quality of life but, if poorly controlled, may lead to unplanned, preventable hospital admissions (Moore et al, 2010). From diagnosis the focus of care must be on the individual needs of patients, supporting them in treatment decision making and establishing goals.

Patients often have palliative needs from diagnosis and early referral to specialist palliative care services can be beneficial. While the impact in mesothelioma has not yet been established, early specialist palliative care of patients with non-small cell lung cancer has been shown to increase survival by 2 months, improve quality of life, improve documentation of resuscitation preference and result in less aggressive care at the end of life (Temel et al, 2010). The RESPECT MESO multicentre randomized controlled trial is in recruitment to investigate the impact of early specialist palliative care on health-related quality of life in patients with newly diagnosed mesothelioma (Gunatilake et al, 2014).

Physical symptoms

In one study 92% of patients with mesothelioma reported three or more symptoms at diagnosis (Hollen et al, 2004). Fatigue was most prevalent (94%), but dyspnoea (89%), pain (85%), appetite loss (87%) and cough (75%) were common. These symptoms reduced global quality of life. The presence of constitutional symptoms can be a poor prognostic sign (Scott et al, 2000).

Pleural mesothelioma

Pain

Chest pain is a common symptom because of the location of the tumour (*Figures 1* and *2*). Patients may experience several different types of pain including localized somatic pain from chest wall invasion, neuropathic pain from intercostal nerve or vertebral invasion, and diffuse visceral pain from lung invasion (Lee et al, 2002). Pain can be complex and difficult to control, as it may respond poorly to pharmacological approaches alone. Some patients have severe intractable chest pain – costopleural syndrome. Early involvement of specialist palliative care should be sought in cases with complex pain.

Pharmacological management: The principles of cancer pain management using the World Health Organization analgesic ladder should be followed, as this is an effective method to ensure systematic titration of therapy for cancer pain (World Health Organization, 1990) (*Figure 3*).

Systemic oral analgesia should be given regularly and titrated against need. Morphine is recommended as the first choice step III opioid for moderate to severe cancer pain (Caraceni et al, 2012). However, other strong opioids such as oral oxycodone and hydromorphone may be used, if morphine is not well tolerated.

Opioid titration: Low dose opioids should be started using either immediate-release (e.g. Oramorph) or slow-release oral preparations. Oramorph has relatively fast onset (20 minutes) but its effects wane after 4 hours.

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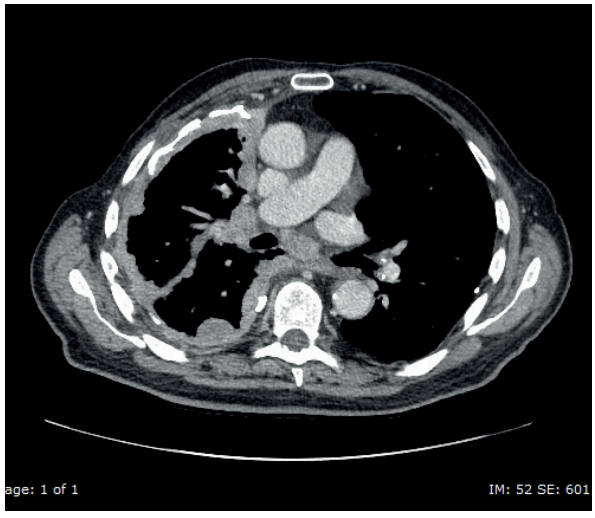


Figure 1. Axial contrast-enhanced computed tomography demonstrating right-sided circumferential enhancing pleural thickening, consistent with malignant mesothelioma. Anterior pleural plaque.

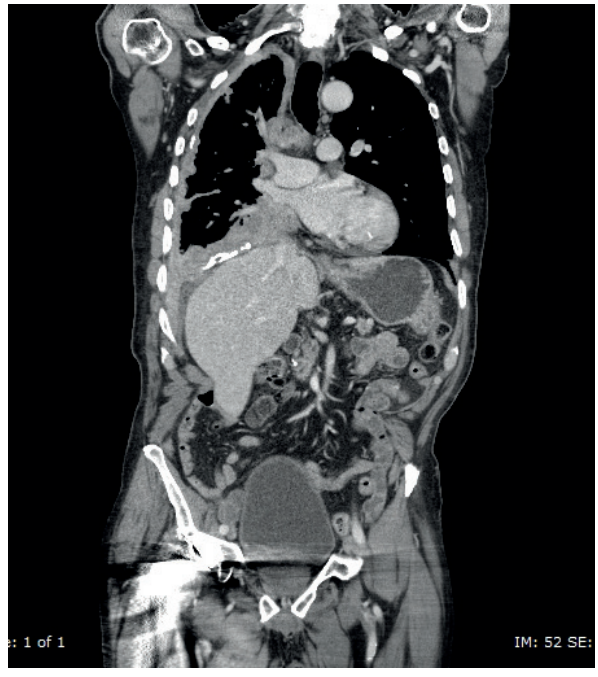


Figure 2. Coronal contrast-enhanced computed tomography demonstrating right-sided circumferential enhancing pleural thickening, consistent with malignant mesothelioma. Anterior pleural plaque.

For opioid-naïve patients a starting dose of 2.5–5 mg Oramorph maximum hourly as required can be commenced or given regularly every 4 hours (with additional as required).

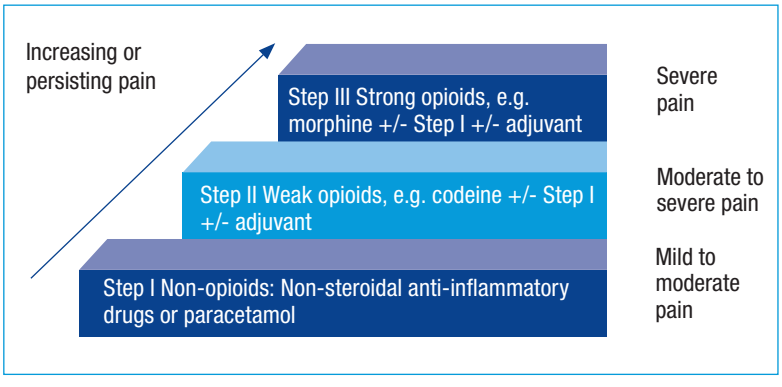
Patients taking weak opioids should have their dose converted to the equivalent dose of slow-release morphine. An additional immediate-release preparation should be prescribed for breakthrough pain (calculated as 1/6 of total dose given in 24 hours).

It is essential to regularly review, checking efficacy, breakthrough requirements and converting or adjusting the dose of slow-release morphine preparation accordingly. See *Table 1* for opioid conversion.

Rapidly escalating doses may be required for mesothelioma patients with opioid-responsive pain (Parker and Neville, 2003). Adjuvant agents should be considered early in patients with poorly opioid responsive pain.

Opioids in renal failure: Opioids should be used with caution in patients with severe renal impairment (i.e. estimated glomerular filtration rate <30 ml/min/1.73m^2) to avoid accumulation and development of opioid toxicity.

Figure 3. World Health Organization analgesic ladder. From World Health Organization (1990).



Best practice recommends a renal analgesic ladder using low dose tramadol (50 mg three times daily), escalating to hydromorphone and using either transdermal fentanyl or buprenorphine patches once pain is stable (Wilcock, 2011).

Specialist palliative care advice should be sought where there is uncertainty over drugs and doses.

Adjuvant analgesia: The pain from pleural mesothelioma can often be opioid resistant and adjuvant analgesia is frequently required in addition (Scherpereel et al, 2010; Caraceni et al, 2012). Tricyclic antidepressants (e.g. amitriptyline) or anti-epileptics (e.g. gabapentin) should be considered for partially opioid-responsive neuropathic pain (Caraceni et al, 2012). Careful titration, starting with low doses, is required to avoid side effects.

Radiotherapy: A systematic review of radiotherapy solely for pain relief demonstrated marked heterogeneity and no high quality evidence currently exists to support

Table 1. Opioid conversion

Analgesic	Oral morphine equivalent
Codeine 30 mg	3 mg oral morphine
Codeine 60 mg four times daily	24 mg oral morphine/24 hours
Tramadol 50 mg	7.5 mg oral morphine
Tramadol 100 mg four times daily	40–60 mg oral morphine/24 hours
Hydromorphone immediate release 1.3 mg	10 mg oral morphine

radiotherapy for pain (Macleod et al, 2014). There is a role in the management of chest pain secondary to bone erosion or secondary cutaneous tumour nodules (Davis et al, 1994).

The recently published SMART randomized controlled trial demonstrated no evidence of benefit for prophylactic radiotherapy following pleural intervention to prevent procedure tract metastasis. It also had no benefit on symptom control including pain, quality of life or survival (Clive et al, 2016).

Cordotomy: Percutaneous cervical cordotomy can be considered in refractory chest wall pain despite optimal analgesia (Parker and Neville, 2003). Radiofrequency current interrupts the spinothalamic tract at C1/2, resulting in contralateral loss of pain sensation. A systematic review noted that although evidence is limited in quality and quantity, the majority of patients obtained good pain relief, although the benefit reduced with time. Performance status and total sleeping hours also improved (France et al, 2014).

Following cordotomy, opioids should be halved to prevent respiratory depression, although most study patients continued to take some form of analgesia. Further reductions can be made slowly over the ensuing weeks to prevent withdrawal. Referral must be early enough so patients can tolerate both the procedure and also the travel to a specialist centre.

Breathlessness

Breathlessness is a common and disabling symptom in mesothelioma. Pleural effusions are a common cause, although pleural thickening causing restriction can cause breathlessness later in the disease. Consideration of pleural drainage is important (see Bibby et al, 2015).

While the sensation of breathlessness is a somatic phenomenon, it can be exacerbated by fear, distress and anxiety. As with pain, severity may not directly correlate to the extent of disease.

Non-pharmacological approaches: Non-pharmacological interventions are central to the management of breathlessness. Farquhar et al's (2014) randomized controlled trial of a breathlessness intervention service in patients with advanced cancer demonstrated reduced patient distress, fear and worry, and increased confidence in dealing with breathlessness. It was more cost effective than standard care in reducing distress. Breathlessness services incorporating breathing control, activity pacing and relaxation techniques are increasingly available, often through hospice services.

Pharmacological treatment: There is no clear evidence for the generic use of oxygen in advanced cancer in breathlessness (Booth et al, 2004). Despite this it may be helpful to some patients and thus individual assessment and trial should be considered. For some patients, it can restrict movement and communication, and can cause dry mouth, anxiety and dependency. Simple stimulation of the trigeminal nerve with air movement using a hand-held fan might provide as much relief.

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A Cochrane review supports the use of oral or subcutaneous opioids for breathlessness in malignancy, although the effect is small. Opioids do not improve exercise tolerance, and there is no evidence for the nebulized route (Jennings et al, 2001). In opioid-naïve patients, a starting dose of immediate-release oral morphine 2.5 mg four times daily with 2.5 mg hourly as required may be trialled. Requirements for as required medication should be reviewed and should be converted to slow-release preparations.

Physicians may have concerns regarding respiratory depression especially as patients may have co-existing chronic obstructive pulmonary disease. The Cochrane review did not demonstrate clinically significant carbon dioxide retention or any reduction in oxygen levels (Jennings et al, 2001). Clinicians' concerns should not be a barrier to opioid use as it can have a vital role in symptom control.

A Cochrane review identified no benefit for benzodiazepines in breathlessness in cancer (Simon et al, 2016). However, if there is significant anxiety as a result of breathlessness their anxiolytic effect may be beneficial, or trialled as second or third line. Although drowsiness is reported, the clinical effect seen was only mild or moderate with no respiratory depression.

Cough

Persistent cough can be troublesome in mesothelioma. A Cochrane review of cough in cancer has not demonstrated consistent efficacy for any intervention (Molassiotis et al, 2015), but there was some indication of positive benefit of morphine, codeine and cough syrup. Cough suppressants such as codeine linctus could be trialled.

Fatigue and weight loss

A Cochrane review demonstrated no evidence that any intervention improves fatigue or weight loss (Minton et al, 2010). However, high-energy, small volume frequent meals, avoidance of constipation and dehydration and treatment of oral candida if present may help. A trial short course of low-dose oral steroids for appetite stimulation could be considered.

Constipation

Constipation is likely to be multifactorial from inactivity, poor oral intake and opioids. Laxatives should be prescribed proactively and taken regularly. All patients receiving opioids must have laxatives prescribed to avoid opioid-induced constipation. There is no evidence that one laxative is superior.

> Failure to identify and treat psychological illness can impact on patients' ability to adjust to their illness, put their affairs in order and may also affect their relationships.

Sweating

Avoidance of restrictive clothing and use of a fan should be advised (Scherpereel et al, 2010). There is no evidence for pharmacological treatment. Unilateral sweating involving the face, neck and thorax may signal encroachment of an ipsilateral tumour on the sympathetic chain ganglia or postganglionic sympathetic fibres. Associated signs may include Horner syndrome, upper limb weakness and sensory loss (Pancoast syndrome) (Cheshire and Freeman, 2003).

Encasement

Pleural mesothelioma spreads locally and can encase other structures within the thorax occasionally causing tracheal constriction, great vessel encasement with superior vena cava obstruction and dysphagia. These problems should be managed on an individual basis and may require stenting and radiotherapy.

Peritoneal mesothelioma

Less commonly malignant mesothelioma can arise from the peritoneum rather than the pleura. Symptoms are often vague and may include abdominal pain, distension secondary to ascites and occasionally bowel obstruction.

As for other malignant causes of ascites, drainage can provide symptomatic benefit and, if recurrent, an indwelling peritoneal catheter could be considered.

Psychological needs

Managing uncertainty

A diagnosis of mesothelioma, with its poor prognosis and aggressive nature, can be very distressing. Many patients feel 'it's all bad news', with feelings of uncertainty and lack of control, frequently leading to emotional, physical and psychosocial distress (Arber and Spencer, 2013). Support during this hugely challenging time is essential and psychological pain must not be overlooked.

Patients may experience many fears and anxieties including loss of social functioning, changing role within the family, the future, and their impending death. It is essential to help the patient explore individual concerns. Health-care professionals must be skilled in allowing patients to talk freely about difficult subjects such as death and dying. The therapeutic role of active listening, encouraging the patient to voice concerns and helping him/her address them, is key. Simply allowing time for patients to voice feelings and concerns can reduce feelings of isolation, validate their feelings as normal and provide support. Spiritual distress should also be identified and individual spiritual support accessed. Patient groups such as Mesothelioma UK, hospices and other cancer support groups can also provide support.

Psychological illness such as anxiety and depression can develop. The incidence of anxiety and depression in mesothelioma is not clear but in a large study of cancer patients by Linden et al (2012) 19% reported clinical symptoms of anxiety and 12.9% reported clinical symptoms of depression. Any underlying organic causes should be excluded. Psychological distress can exacerbate physical symptoms.

Failure to identify and treat psychological illness can impact on patients' ability to adjust to their illness, put their affairs in order and may also affect their relationships.

Management

Anxiety and depression in patients with cancer are best managed using a combination of psychological and pharmacological approaches. Individual and group therapies combined with educational interventions and relaxation are effective (Sheard and Maguire, 1999).

Antidepressant selection is guided by urgency for treatment effect and prognosis. Patients need to have a life expectancy long enough to benefit from antidepressants, as selective serotonin-reuptake inhibitors take 4–6 weeks to have their full effect. In those with limited life expectancy psychological support is the mainstay of treatment. Benzodiazepines such as lorazepam can be used in anxiety. In complex cases, psychiatric referral is warranted.

Care planning

Information needs

Patients' information needs will vary, and it is essential to ascertain this before imparting information, especially with regard to discussions about prognosis. Patients worry about the short-term day-to-day impact of their cancer but often work to address and discuss these aspects. However, longer term prognosis and speed of deterioration, which can cause significant psychosocial distress, is sometimes not addressed by health-care providers to avoid distress (Arber and Spencer, 2013). It is important to be open and honest in communication. Innes and Payne (2009) identified that the majority of patients wish to hear a broad indication of prognosis although quantitative wishes vary. Patients want to know where they can access information when they want it. This has been shown to be associated with realistic awareness of prognosis and what to expect. This realistic awareness enhances feelings of control and end of life planning which can engender hope (Innes and Payne, 2009).

Sensitive facilitated patient-led communication is vital. However, we must respect some patients' choice for limited information as a need to maintain hope. Therefore health-care providers must be equipped with the communication skills and tool set to initiate and facilitate these difficult but vital conversations, which must be individualized. Early palliative care referral can help address support and management strategies (Arber and Spencer, 2013).

Advance care planning

Advance care planning is a voluntary process helping patients to express their hopes and wishes about their future care. While the majority of patients wish to die at home, a large number are admitted to hospital at the end of life. Patient-centred advance care planning can help patients receive care that is aligned with their wishes.

Although evidence demonstrating benefit of advance care planning is limited, Mullick et al (2013) identified that patients can find advance care planning discussions helpful, particularly when conversations focus on their goals, values and beliefs, rather than on particular treatments or interventions. Wright et al (2008) demonstrated that possible benefits of advance care planning include less aggressive medical treatment, improved quality of life, reduced hospital admissions and increased rates of hospice admission. Reduced stress, anxiety and depression in bereaved relatives was also seen.

Advance care planning conversations must be reviewed regularly (*Figure 4*). However, it is important to recognize that despite meticulous planning, unforeseen situations may arise meaning that it may not be possible to deliver care in the patient's chosen setting.

Triggers

- Patient initiates conversation
- When diagnosis of a progressive life-limiting illness is made
- A change or deterioration in condition
- Change in the patient's personal circumstances, e.g. moving into a care home
- Routine review of the patient

Elements of advance care planning may include:

- Clarifying a patient's understanding of his/her illness and treatment options
- Understanding the patient's values, beliefs and goals of care
- Identifying a patient's wishes including those regarding preferred place of care and preferred place of death
- Advance statements
- Advance decisions to refuse treatment
- Lasting powers of attorney
- After death wishes

Figure 4. Triggers for initiating or reviewing advance care planning discussions. From Mullick et al (2013).

Caregivers' needs

Informal caregivers provide the majority of support for patients with advanced cancer. Bee et al (2009) highlighted the lack of practical support for caregivers, often relating to inadequate information exchange. They demonstrated that increasing knowledge and understanding of strategies for symptom control, especially pain management, is important. Farquhar et al (2014) demonstrated that a breathlessness intervention service that included carers led to increased knowledge, legitimised symptoms and made patients and carers feel 'less alone'. Open communication and provision of practically based written information is vital.

Carers can also be at risk of depression and anxiety so adequate support for them is vital. As part of advance care planning, discussion with carers about what to expect during the terminal phase can help alleviate fears about death and dying and can empower them.

Legal aspects of mesothelioma

Compensation

As mesothelioma often arises from occupational asbestos exposure, a detailed occupational history is essential. Compensation should be discussed early in the diagnosis and expert advice through a lung cancer specialist nurse and specialist solicitor is important. Financial support can include Industrial Injuries Disablement Benefit, Disability Living Allowance, Attendance Allowance and War Disablement Pension for cases of armed forces exposure. Carers Allowance may also be available.

After death

Because mesothelioma can be an industrial disease there is a legal obligation to inform the coroner on death, even if it was not the primary cause. The majority of coroners will require post-mortem examination. The patient and family should be made aware of this before death to avoid distress. Release of the body should not be delayed for more than a few days. Some coroners may feel a post-mortem is not needed if there is substantial evidence of occupational asbestos exposure with positive histology and indicative radiological findings, and compensation organized for the patient and his/her family; however, post-mortem is usually required.

End of life care

Care needs

As a patient approaches the end of life, it is important to review the care needs with the patient and family to ensure the needs can be met in that setting. If not, either additional support or an alternative place of care must be sought. Patients and carers must know how to access additional advice and support when needed, especially out of hours.

Anticipatory prescribing

As a patient approaches the terminal phase of his/her illness, anticipatory prescribing for symptom control at end of life is vital. The goal is to try and minimize the risk of patients suffering uncontrolled symptoms and distress. When patients are being cared for in the community, this simple measure can prevent some avoidable hospital admissions. First-line anticipatory medication for end of life in the opioid-naïve patient is suggested in *Table 2*.

Anticipatory medication should be administered subcutaneously. This medication is sometimes provided in 'just in case boxes' for patients in the community, which must be accompanied with appropriate authorization for administration. This may need a GP community prescription chart if provided from hospital so GPs should be contacted.

KEY POINTS

- Malignant mesothelioma has a high symptom burden that significantly impacts quality of life.
- From diagnosis, care must be patient-centred, focussing on individual needs.
- Pain can often be opioid resistant and adjuvant analgesia is frequently required.
- In patients with refractory chest pain percutaneous cervical cordotomy should be considered early.
- Patients should be referred to breathlessness services and opioids considered.
- The diagnosis can cause significant psychological distress and it is vital to explore concerns and provide support.
- Advance care planning can help patients receive care that is aligned with their wishes.
- Anticipatory end-of-life medication must be prescribed for all patients at end of life.
- Early referral to specialist palliative care is recommended.

Table 2. Anticipatory medication for end of life symptom control

Anticipatory symptom control prescription (for opioid-naive patient)	
Pain	Morphine sulphate 2.5–5mg hourly subcutaneously as required *†
Agitation	Midazolam 2.5–5 mg hourly subcutaneously as required
Respiratory secretions	Hyoscine butylbromide (Buscopan) 20 mg 2-hourly subcutaneously as required
Nausea and vomiting	Haloperidol 1.5 mg subcutaneously twice daily‡

**should be 1/6th 24-hour opioid requirement converted to intravenous equivalent in patients already on opioids. †Subcutaneous morphine is twice as potent so dose of oral needs to be halved. ‡Cyclizine 50 mg three times daily may be used but is incompatible with hyoscine butylbromide in a syringe pump*

If a patient requires frequent breakthrough subcutaneous doses, continuous administration of medication via a syringe pump is less intrusive and usually provides better symptom control.

Oral analgesia and other symptom control medication must be converted to the subcutaneous route via a syringe pump when the patient is unable to swallow. All other non-essential medications should be stopped following communication with the patient and carers.

Bereavement support

Grief after death is a normal emotional response. Through advance care planning, carer support and high quality palliative care, clinicians can help prepare those close to the patient for his/her death and try to minimize the risk of complicated grief. A loved one's death may have a significant impact on the bereaved, both physically and emotionally, so it is important to ensure that they have appropriate support. For patients who die in a hospital or a hospice, it is important the GP is informed when the patient is reaching end of life and promptly notified of death to enable family support. Bereavement support groups can be helpful.

Conclusions

Mesothelioma is a rapidly progressive cancer with a very limited prognosis and high symptom burden. From diagnosis clinicians must endeavour to deliver patient-centred care, align themselves with the needs of the patient, and optimize symptom control. It is vital that the quality of the short time the patient has left is maximized. Honest and sensitive dialogue is essential during this uncertain time.

The vast majority of patients will have palliative needs during their illness, but where symptom control or psychological needs are complex, early specialist palliative care referral is warranted.

High quality end of life care should always be aimed for in all settings. It is imperative that any symptoms are well controlled and place of care is aligned with the patient's wishes if possible. **BJHM**

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