

Palliative care 2 - symptom control

The aim of symptom control in palliative care is to improve quality of life. Anticipating and addressing reversible causes of symptoms in cancer patients avoids unnecessary suffering. Accurate assessment of symptoms is crucial. A useful framework to follow is to consider whether symptoms are caused by:

- ◆ the cancer itself (e.g. an increasing tumour mass causing increasing pain),
- ◆ the treatment (e.g. constipation caused by opioids), or
- ◆ something unrelated (e.g. viral gastroenteritis).

The emphasis of this bulletin is on pharmacological management, considering first-line approaches to some common problems. If these measures fail, then advice should be sought from your local palliative care team. It is also important to note that in many instances it is appropriate to try non-medical measures before or alongside medical therapies.

Summary

- ◆ Symptoms arising from cancer and cancer therapies can and should be treated. It is also important to consider whether symptoms might be caused by something unrelated.
- ◆ Preventative routine mouth care and prophylactic laxative therapy should be implemented to avoid unnecessary problems.
- ◆ First-line symptomatic treatments are outlined in this bulletin. If these fail, then advice should be sought from the local palliative care team.

The accompanying WeMeReC Bulletin contains information on **pain control** in palliative care.

Gastrointestinal symptoms

Mouth care should be routine and gentle brushing of teeth or dentures is essential. All patients are potentially at risk of developing mouth problems, the most common being dryness and soreness.

Dry mouth may be caused by dehydration, hypercalcaemia, and medicines such as morphine, antimuscarinics, and diuretics. If possible, fluid intake should be increased or the medicine responsible stopped. If this is not feasible, the patient can be offered ice cubes, ice lollies, or fruit segments to suck. (Pineapple contains ananase, which is a cleansing enzyme.) Some care is needed, however, as acid and sugar may hasten tooth decay in a dry mouth. Several artificial saliva products are available. Glycerin mouthwashes and lemon juice should be **avoided** as they exacerbate dryness.

Potential causes of **sore mouth** include dryness, ulceration, oral infection, or ill-fitting dentures. For

generalised mouth pain, benzydamine hydrochloride oral rinse (*Difflam*[®]) may be helpful. (If stinging occurs, the rinse may be diluted with water.) Severe pain occasionally needs systemic analgesia. Aphthous ulcers may be treated with corticosteroid pellets (*Corlan*[®]) or paste (*Adcortyl in Orabase*[®]).

Candidiasis is the most common oral infection, often presenting with loss of taste or dysphagia. It should be treated, initially, with regular nystatin (oral suspension or pastilles) or miconazole (*Daktarin*[®] oral gel). If applicable, dentures should also be treated (e.g. soaked in chlorhexidine mouthwash).

For more severe cases, ketoconazole tablets (*Nizoral*[®]) or fluconazole capsules may be prescribed. There are interactions between these and other medicines, so caution is advised. Note that resistance to antifungals has been described; seek advice if resistance is suspected.

Nausea and vomiting are common symptoms in advanced cancer, affecting between 50-60% of patients. There is a wide range of potential causes and it is important to identify any that can be specifically managed, such as hypercalcaemia, infection, gastritis, constipation, raised intracranial pressure, intestinal obstruction, and uraemia. Although there may be more than one cause, it can be helpful to base the choice of anti-emetic on the most likely mechanism for the nausea and vomiting. These can be broadly categorised as:

- ◆ direct or central – effects on the gastrointestinal tract or the vomiting centre
- ◆ chemical – via the chemoreceptor trigger zone (predominantly nausea with occasional vomiting)
- ◆ mechanical - delayed gastric emptying (predominantly vomiting often with little nausea)

Bear in mind the framework for assessing symptoms – consider whether they are caused directly by the cancer, the treatment, or by something unrelated.

If the symptoms have been induced by treatment, consider stopping the responsible agents. Note that the nausea associated with starting strong opioids may be self-limiting. Using an anti-emetic, such as haloperidol (see below), will usually be effective although a small number of patients will remain nauseated and require continued treatment. A still smaller number of patients will suffer nausea that will affect their quality of life enough to require a change in their opioid therapy.

Anti-emetics should be given orally when possible. In practice, the initial choice of anti-emetic usually lies between the following three agents:

Cyclizine (50 mg three times a day) is an antihistamine that acts principally on the vomiting centre. It is useful with haloperidol in patients with raised intracranial pressure or intestinal obstruction.

Haloperidol (1.5 mg at night, increasing to 3 mg if necessary) acts principally on the chemoreceptor trigger zone and helps to treat most chemical causes of vomiting (e.g. morphine and uraemia).

Metoclopramide (10 mg three or four times a day) aids gut motility and helps in gastritis and gastric stasis. Although useful in early bowel obstruction to increase gastric emptying, it can cause colic and, in some cases, this will limit its use.

If first-line treatment fails, then **levomepromazine**, (*Nozinan*[®]) may be useful. This is a broad spectrum centrally-acting anti-emetic (suggested starting dose 6.25 - 12.5 mg daily; 6 mg tablets are available on a named-patient basis). Postural hypotension and sedation are more likely at higher doses.

In some cases, more than one anti-emetic may be needed to obtain adequate control; however, medicines with antagonistic actions should not be used concomitantly (e.g. **metoclopramide** and **cyclizine**). In order to achieve adequate plasma concentrations and gain control of symptoms, it may be necessary to administer anti-emetics, temporarily, by subcutaneous infusion.

Constipation should be anticipated in all patients on opioids, and regular laxatives should always be prescribed with any opioid. Other common causes include dehydration, antimuscarinic use, lack of privacy, hypercalcaemia, intestinal obstruction, and spinal cord compression. As many as 80% of patients admitted to specialist centres require laxatives. Suitable therapy consists of a stimulant laxative (e.g. danthron, docusate sodium, or liquid senna) with a softener or osmotic laxative (e.g. magnesium hydroxide or lactulose). Macrogols (e.g. *Movicol*[®]) used alone may be useful alternatives for some patients. Bulk-forming laxatives are rarely, if ever, suitable in palliative care. Once corrected, prophylactic treatment should be continued.

Anorexia can be associated with nausea, infection, constipation, and anxiety, or with problems such as sore mouth or ill-fitting dentures. Non-medical treatment should be tried in the first instance. The appetite stimulant effect of steroids or megestrol acetate may be beneficial but because of the potential for incapacitating adverse events, such medicines should be used with caution. Intensive nutritional supplementation has little value for patients with advanced and progressive disease.

Hiccups can be due to gastric distension, in which case metoclopramide may be helpful. Baclofen or sublingual nifedipine can also be tried. Chlorpromazine or haloperidol may be effective but only at doses that are sedating.

Intestinal obstruction can be associated with symptoms such as foul smelling, large volume vomits, abdominal discomfort, and colic. Single-site obstruction may be amenable to surgery or the insertion of a stent. Chemotherapy may also be useful in sensitive tumours (e.g. in ovarian disease). In advanced cancer, intestinal obstruction usually occurs at multiple sites and requires medical management. Metoclopramide may increase gastric emptying in the early stages, but colic can be a problem. Subcutaneous therapy with anti-emetics (e.g. haloperidol with cyclizine) in combination with hyoscine hydrobromide and diamorphine are often needed. Seek advice from the palliative care team.

Respiratory symptoms

Breathlessness affects between 50-70% of cancer patients in their last six weeks of life. Reversible causes must be considered and include infection, bronchospasm, pleural effusion, multiple pulmonary emboli (which may warrant anticoagulation), large airways obstruction (which may warrant radiotherapy), or heart failure. For symptomatic relief, oxygen therapy is only helpful if the patient is hypoxic. Benzodiazepines and oral opioids may be useful, especially if there is an element of anxiety. Diazepam 2 mg three times a day, sublingual lorazepam 0.5 - 1 mg as necessary, or subcutaneous midazolam at a starting dose of 5 - 10 mg over 24 hours can be helpful. Strong opioids may also be used (e.g. oral morphine 2.5 mg 4 hourly then titrated as for pain control). There is little evidence to support the use of nebulised opioids. Non-medical management should not be overlooked.

Cough can precipitate exhaustion, breathlessness, vomiting, rib fracture, chest, or abdominal pain.

A tumour near the carina may respond to radiotherapy. Symptomatic treatment may include steam inhalation, simple linctus, and opioids such as pholcodine, or codeine linctus. If the patient is taking morphine and is still troubled by cough, then methadone linctus (at a usual starting dose of 2 mg) may be helpful. Care is needed as methadone has a long half-life and may accumulate.

Haemoptysis is usually caused by tumour growth affecting local blood vessels. Radiotherapy may be useful in some cases. Using tranexamic acid and stopping oral anticoagulants may be considered on an individual basis.

It is useful to establish a patient's wishes for their end-of-life care. Small haemoptysis may herald a large fatal bleed. Communication within the primary healthcare team and with the family is vital. Provision of large doses of anxiolytics (intramuscular midazolam 10 mg) in the house may be considered.

Central nervous system symptoms

Depression may be undiagnosed in as many as half of all cancer patients. Lack of treatment may lead to social withdrawal and prevent the completion of "unfinished business". This suffering is unnecessary as the response to therapy is good. Psychological support should be considered.

Anxiety may aggravate other symptoms. Patients should be encouraged to discuss their fears. If necessary, a benzodiazepine may be helpful but, because anxiety is often a presenting symptom of depression, an antidepressant should be considered.

Confusion is potentially caused by hypercalcaemia, urinary retention, infection, dehydration, and medicines, such as sedatives, opioids, and corticosteroids. If a medicine is suspected then, if possible, it should be withdrawn or changed. If other causes are eliminated and the patient is "muddled without distress", then treatment may not be necessary. Other disease, such as cerebrovascular dementia or transient ischaemic attacks may be suspected. If specific treatment for these is indicated then advice should be sought from the local palliative care team.

Other problems

Hypercalcaemia occurs in approximately 10% of cancer patients, causing severe nausea and vomiting, dehydration, drowsiness, confusion, constipation, and worsening pain. Patients may appear to be seriously unwell clinically, but it is important to recognise that hypercalcaemia (especially the first episode) is a potentially reversible problem.

Hypercalcaemia is defined as a corrected calcium plasma concentration > 2.6 mmol/l. Mild cases are usually asymptomatic, although patients may feel better after treatment. For severe cases (≥ 3 mmol/l), immediate intravenous hydration and bisphosphonate therapy is required. For some recurrent cases, it may

be possible to administer regular bisphosphonate infusions on a day-case basis.

Raised intracranial pressure may be due to direct tumour pressure or to surrounding cerebral inflammation. Headache, vomiting, confusion, blurred vision, and focal neurological signs may be present. Corticosteroids reduce oedema around the tumour and dexamethasone (16 mg daily for four or five days, reduced to 4-6 mg daily if possible) is commonly used. If the response is dramatic, radiotherapy should be considered, even in advanced disease. It may be possible to remove isolated cerebral metastases surgically.

Spinal cord compression is a medical emergency that occurs in up to 5% of cancer patients. The main problem in clinical practice is with diagnosis. The earliest symptom is back pain, often described as a “band of pain” that tends to be worse on coughing or straining. Spinal pain, particularly on movement, may be a pointer to an unstable spine. Initially, stiffness rather than weakness may be present; most patients have pain for weeks or months before they start to detect weakness. Tingling and numbness usually starts in both feet and progresses up the legs.

Painless retention of urine can be a presenting feature. Patients should be warned to report sinister symptoms such as sensory change, weakness, pain, and bladder or bowel dysfunction.

If spinal cord compression is suspected, urgent treatment is required. Patients should be referred to an oncologist without delay for consideration of radiotherapy or neurosurgery, and dexamethasone (16 mg orally) should be given immediately.

End of life

When prescribing in the last days of life it is important to recognise that treatment intent changes (“changing gear”). As the patient becomes semi-conscious and unable to take medicines orally, the subcutaneous and rectal routes can be used. (The use of syringe drivers is discussed in the accompanying bulletin on pain control.) To simplify care, all of the patient’s medication should be reviewed and unnecessary items discontinued.

Another cause of terminal restlessness is terminal anguish, which is a tormented state of mind, often owing to long-standing unresolved and emotional problems and a fear of dying. When death is near, counselling becomes inappropriate and anxiolytics, such as subcutaneous midazolam (10 mg, or higher doses when sedation is need) may be appropriate.

Some of the symptoms that may be experienced at the end of life are discussed here. It is not an exhaustive list of possible conditions and only medical treatments are discussed. It is important to seek advice early if a patient does not settle easily – no patient should die in an agitated state. In some areas of Wales, the “care of the dying pathway”, a set of standardised suggestions for care, is used. Your local palliative care team or facilitator will have information for your area.

Agitated delirium is commonly associated with metabolic encephalopathy resulting from organ failure, overdose of antimuscarinics, electrolyte imbalance, or sepsis. It is a confused state associated with hallucinations and paranoid ideas. Treatment options include haloperidol or levomepromazine but occasionally it is necessary to sedate the patient with either midazolam or diazepam.

For patients with **terminal restlessness** any potentially reversible causes of distress should be addressed. These include pain, urinary retention, constipation, and gastric stasis. Failing this, midazolam, levomepromazine, or diazepam can be tried. Note that diazepam is irritant and unsuitable for subcutaneous administration.

Noisy respiratory secretions (death rattle) are heard in patients who are too weak to expectorate. This symptom may be especially distressing for relatives. An anti-secretory agent, such as hyoscine hydrobromide or glycopyrronium, should be initiated promptly (existing secretions will not be reduced). Subcutaneous doses should be administered regularly or by infusion (e.g. hyoscine hydrobromide 400 micrograms *stat* or 1.2 - 1.6 mg in 24 hours).

Information sources:

www.pallcare.info

- links to the *Palliative Medicine Handbook*, the Welsh Care Pathway, and to information on syringe drivers.

www.palliativedrugs.com

- provides medicines information and a discussion forum.

Arrangements for out-of-hours support varies across different regions in Wales. Contact your local palliative care team for information. Palliative care telephone advice is also available out of hours for healthcare professionals on **029 2042 6000**. (Holme Tower Marie Curie Centre, Penarth).

- ◆ Watson M, Lucas C, Hoy A, Back I. Oxford handbook of palliative care. Oxford: Oxford University Press, 2005.
- ◆ Twycross R, Wilcock A, Charlesworth S, Dickman A. Palliative care formulary, 2nd ed. Abingdon: Radcliffe Medical Press, 2002.
- ◆ Fallon M, Hanks G. ABC of palliative care, 2nd ed. Blackwell BMJ Books, 2006.

Some of the recommendations for medicines discussed here are for **non-licensed indications and routes**. It is important for prescribing doctors to recognise the responsibility that such prescribing entails. Summaries of Product Characteristics should be consulted for full prescribing information.