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Palliative management of advanced cancer

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ABSTRACT The goal of this article is to review important developments in symptom management, drugs, complications and communication pertaining to the palliative management of advanced cancer. Pain and fatigue are the most common symptoms of advanced cancer. Pain is often well controlled with analgesics, although some cancer pain is more difficult to control. Risk factors for refractory pain include breakthrough and neuropathic pain, both of which will be discussed in this review. Methadone and gabapentin both have a role in the management of neuropathic pain and will be discussed in detail. Complications of advanced cancer amenable to medical treatment include delirium and bowel obstruction. Good communication is paramount in the management of advanced cancer. The issues of how to deliver prognostic information and hold a family conference will be covered by this review.

KEYWORDS Advanced cancer, communication, complications, pain, palliative medicine

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PAIN

Breakthrough and neuropathic pain are both risk factors for refractory or difficult to control cancer pain.

Breakthrough pain

Breakthrough pain is defined as a transient increase in pain on a background of stable pain. It is common, affecting 40–80% of cancer patients. Most episodes involve a rapid onset of moderate or severe pain (>5 on a 0–10 verbal rating scale) and are of short duration (15–30 minutes).

Breakthrough pain may be further characterised as incident or non-incident. Incident pain is precipitated by movement, weight bearing, coughing or straining, and is often a characteristic of bone metastases or radiculopathies.

Non-incident breakthrough pain includes:

- End-of-dose failure – pain near the time long-acting opioids are due to be administered.
- Somatic pain – transient bone or soft tissue pain unrelated to movement.
- Neuropathic pain – spontaneous lancinating or burning pain, due to spontaneous neuronal activity.
- Visceral pain – due to spontaneous visceral contraction, e.g. intestinal or bladder spasm.

Management

All people with moderate to severe cancer pain should have access to short-acting oral, sublingual or transmucosal opioid. The timing of oral morphine peak action (30–60 minutes) may be too long to be effective for many breakthrough pains. Some opioids (alfentanil, buprenorphine, fentanyl, sufentanil) are rapidly absorbed sublingually. Transmucosal fentanyl citrate lozenges have been produced specifically for breakthrough pain.

Recommended opioid doses for breakthrough pain are often prescribed as a proportion of the baseline dose (e.g. 5–10% of the 24-hour dose, 2–3 hourly). This should be a guide only as randomised trials of transmucosal fentanyl citrate have demonstrated no relationship between baseline and breakthrough doses. Breakthrough doses should be evaluated for amount and duration of pain relief and should be increased if ineffective. Frequent breakthrough (more than four non-incident episodes per day) or episodes close to the time of long-acting opioid administration indicate the need to adjust the baseline dose.

Predictable incident pain (e.g. with movement or dressing change) should initiate pre-emptive dosing. For bone pain, non-steroidal or steroid anti-inflammatories, radiotherapy, orthotic bracing, surgery or bisphosphonates may be effective and reduce the need for opioid analgesics. For dressing changes, sublingual, transmucosal or subcutaneous opioids, inhaled analgesia (nitrous oxide) or topical local anaesthetic may be used. Neuropathic breakthrough pain may respond to adjuvant analgesics (e.g. antidepressants or anticonvulsants) and visceral pain to antispasmodics.

Neuropathic pain

Clinical features

Cancer patients often have multiple pains and these are often of mixed type. Neuropathic features may co-occur with somatic or visceral pain. Neuropathic pain may be

TABLE 1 Mechanisms of sensitisation

Peripheral
• Recruitment of previously silent or sleeping nociceptors
• Increased excitability of neurons due to accumulation of sodium channels
Central
• Increased neuro-excitatory neurotransmitters (e.g. glutamate) activating *N*-methyl-D-aspartate (NMDA) receptors
• Reorganisation of dorsal horn so low threshold sensory neurons project to nociceptive areas causing pain response to normally non-painful stimuli

described as burning, shooting, lancinating or tingling. Distribution may be within a dermatome, nerve root or nerve territory. Associated features include hyperalgesia (heightened response to a normally painful stimulus, e.g. pinprick) or allodynia (pain produced by a normally non-painful stimulus, e.g. light touch).

Mechanisms

Cancer-related neuropathic pain is usually peripheral in origin. Nerve damage or compression may be caused by tumour invasion, inflammation or therapeutics (e.g. chemotherapy-related peripheral neuropathy). Nerve damage leads to sensitisation (wind-up), which promotes continued pain. Sensitisation is due to both peripheral and central neurological changes and may also be the mechanism of opioid tolerance and hyperalgesia (see Table1). Sensitisation leads to:

- Reduced threshold of response
- Increased intensity of response
- Spontaneous firing
- Pain outside the injured area

Management

Opioid responsiveness is controversial. Neuropathic pain does respond to opioids in the medium term (weeks), but the relative dose to response may be less than somatic pain. Higher opioid doses may be limited by adverse effects. Neuropathic pain does respond to adjuvant analgesics (antidepressants and antiepileptics) and *N*-methyl-D-aspartate (NMDA) receptor antagonists (methadone and ketamine).

DRUGS

Opioids in renal impairment

Many opioids have active metabolites that are excreted renally. In renal failure metabolites accumulate and can cause toxicity. Morphine is metabolised in the liver to glucuronides: morphine-3-glucuronide (M3G) and morphine-6-glucuronide (M6G). M3G is neuro-excitatory (myoclonus; seizures), and M6G is both a central nervous system (CNS) depressant and analgesic. Codeine, hydromorphone and oxycodone all have active metabolites. Fentanyl and methadone have inactive metabolites. Methadone metabolite excretion is 50% renal, 50% faecal. Both fentanyl and methadone are safe in renal failure and dialysis.

Methadone

Methadone is often used used in palliative medicine as a second-line opioid if intolerable side effects or insufficient analgesia are associated with morphine. It is also used in neuropathic pain due to actions at the NMDA receptor. Methadone may be administered orally, rectally or intravenously.

Pharmacology

Methadone is a synthetic opioid agonist and NMDA receptor antagonist. It is highly lipophilic, resulting in high tissue distribution and accumulation with chronic dosing. Hepatic metabolism by the cytochrome P450 system produces inactive metabolites, which are excreted in faeces and urine. There is significant inter-individual variation in pharmacokinetics, usually characterised by a rapid distribution phase and slow elimination phase (15–60 hours).

Drug interactions

Metabolism by the CYP3A4 isoenzyme of the cytochrome P450 system results in many potential drug interactions. Metabolism is inhibited by antibiotics (erythromycin, ketoconazole and ciprofloxacin), selective serotonin re-uptake inhibitors (SSRI) antidepressants (especially fluvoxamine), diazepam and antiviral drugs. Metabolism is induced by anticonvulsants, rifampicin and corticosteroids.

Dosing and conversion ratios

Methadone dosing is highly individualised and should be supervised by experienced practitioners. Conversion ratios in patients on morphine and other opioids vary depending on previous opioid dose. In opioid-naive patients the methadone–morphine ratio is close to 1:1, but in patients on high-dose morphine it may be greater than 10:1. Many regimes exist for methadone dosing for cancer pain. Owing to the risk of accumulation, dosing intervals are lengthened after the first 2–3 days.

Adverse effects

Side effects are similar to other opioids and include dry mouth, nausea, constipation and drowsiness. There is a risk of somnolence with accumulation in chronic dosing. Methadone prolongs the QTc interval. Ventricular arrhythmias have been reported, possibly associated with drug interactions.

Anticonvulsants for neuropathic pain

Gabapentin

Pharmacology

Gabapentin is a gamma aminobutyric acid (GABA) analogue. It does not bind GABA receptors but blocks voltage-dependent calcium channels in the CNS.

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Efficacy

Analgesic efficacy has been demonstrated in HIV neuropathy, post-herpetic neuralgia and diabetic neuropathy. One randomised controlled trial in cancer neuropathic pain demonstrated reduction in pain and dysesthesias, but differences compared with placebo were small. One trial in diabetic and post-herpetic neuralgias compared morphine or gabapentin alone and in combination with an active placebo (lorazepam). The combination was significantly more effective than either agent alone or placebo. The maximum tolerated doses of morphine and gabapentin were lower in combination than alone. Adverse effects of the combination were constipation, dry mouth and sedation.

Adverse effects

Drowsiness and dizziness are common.

Dosing

Initially 300 mg daily, titrate up to 600 mg three times daily. Doses up to 3,600 mg have been used. Slow titration is needed in the elderly, debilitated, those with impaired renal function and with CNS-depressant medication.

Antipsychotics for nausea and vomiting

The use of antipsychotics for nausea and vomiting is based upon the physiological mechanisms of these symptoms. Dopamine receptors are found in the chemoreceptor trigger zone (CTZ) in the fourth ventricle, the vomiting centre in the third ventricle, and in the stomach wall.

Haloperidol

Haloperidol is a strong dopamine (D2) receptor antagonist with activity at the CTZ. It is useful for CTZ-mediated nausea, e.g. opiates, chemotherapy / radiotherapy, renal failure and hypercalcaemia or when nausea occurs with delirium.

Case series suggest benefit in nausea and vomiting due to bowel obstruction. However, there are no randomised trials of haloperidol for nausea in palliative populations. Adverse effects include extrapyramidal symptoms and sedation at doses >5 mg. The long half-life allows once or twice daily dosing. Initial dosing for nausea is 0.5–2 mg up to four hourly.

Olanzapine

Olanzapine is an atypical antipsychotic with potent dopamine and serotonin receptor antagonist effects. Anti-emetic activity was demonstrated in phase I and II trials in patients receiving highly emetogenic chemotherapy. Case series and pilot studies have reported good response in advanced cancer patients with opioid-related or treatment-resistant nausea. Olanzapine has fewer extrapyramidal effects than haloperidol. Other adverse effects include drowsiness, orthostatic hypotension, constipation, increased blood glucose, prolonged QTc interval and lower seizure threshold. Initial doses for nausea are 1.25–2.5 mg up to twice daily as required and at night.

Bisphosphonates

The use of bisphosphonates is increasing for people with metastatic cancer. Indications are:

- Hypercalcaemia
- Prevention of bony complications in metastatic cancer
- Analgesia in bone metastases

Adverse effects

- Flu-like symptoms, fatigue, bone pain
- Hypocalcaemia
- Renal impairment
- *Osteonecrosis of the jaw.* Osteonecrosis of the jaw is a recently recognised complication of long-term use. Incidence is 0–1% in the first year, and 4–20% after three years. Rates are higher for zoledronic acid than for disodium pamidronate. Risk factors are duration of use, poor dental hygiene and dental procedures (60% of episodes occur following a procedure). The mechanism is thought to be due to the excessive suppression of bone turnover, causing microfractures combined with mucosal microtrauma which in turn causes exposure to oral microbes. Clinical features include chronic ulcers, visible necrotic bone, jaw and facial pain and sinus formation. Management involves discontinuing the bisphophonate, careful debridement, antibiotics, antiseptic mouth washes and analgesia. Since this condition is chronic, preventative measures (a dental review and any necessary procedures) are recommended prior to commencing long-term bisphosphonates. Good oral hygiene should be promoted during the treatment course.
- *Ocular inflammation.* Ocular inflammation is a rare side effect. Clinical features include blurred vision, non-specific conjunctivitis and uveitis. Conjunctivitis usually resolves without specific treatment, but some cases require referral to an ophthamologist and may require cessation of bisphosphonate.

COMPLICATIONS

Delirium

Incidence

Delirium is common, affecting 28–48% of advanced cancer patients admitted to hospital or hospice, with higher incidence in terminal phases. Delirium is under-recognised without screening and is distressing to patients, their families and caregivers.

Clinical features

Cardinal features are acute onset, fluctuating course, inattention, disorganised thinking and altered conscious-

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TABLE 2 Behavioural management of delirium

Family presence
Visible clock or calendar
Gentle reorientation to time and place
Provide glasses and/or hearing aid if needed
Avoid bright lights; use a nightlight
Limit noise
Limit staff changes
Avoid physical restraint if possible

ness. The acute onset and disturbance of consciousness distinguish delirium from dementia. Delirium is subtyped based upon arousal: hyperactive, hypoactive and mixed. Hyperactive delirium is most often detected due to the agitated, disinhibited behaviour of the patient. Hypoactive delirium is more easily missed as patients are withdrawn and monosyllabic. It should be included in the differential diagnosis of depression in hospitalised patients.

Screening

The Bedside Confusion Scale scores alertness (normal, hypoactive, hyperactive) and attention (patients are asked to recite months backwards). It is a brief, sensitive screen in palliative medicine.

Management

Initial management is to eliminate treatable causes: drugs (especially opioid toxicity in renal impairment), metabolic, infection or CNS pathology. Low-volume hydration may be considered if dehydration is present. Haloperidol is the first-line treatment in palliative medicine. Lorazepam was ineffective in the only palliative medicine randomised trial (for HIV). Atypical antipsychotics may be used as the second-line if haloperidol is ineffective after dose titration. Education and support for family and behavioural and environmental measures are also important (see Table 2). Opioid dose reduction or rotation may be needed.

Medical management of malignant bowel obstruction

Bowel obstruction is common in advanced ovarian and colorectal cancers. The mechanism of obstruction may be benign (adhesions) or malignant (intraluminal or extramural obstruction or motility disorder). Management considerations are as follows:

Surgery

Factors to consider include prognosis from malignancy, ability to correct the cause of obstruction, surgical complications and recovery time. Contraindications include disseminated intra-abdominal tumour, recurrent large volume ascites and no available anticancer therapy.

Stents

Stents may be useful in gastric outlet, proximal small intestinal and colonic obstruction.

TABLE 3 Communicating prognostic information

Prepare for the conversation
Know the pathology, treatment options, possible outcomes
Privacy
Who should be present?
Relate to the person
Show empathy and concern
Avoid exact timeframes
Elicit patient and caregiver preferences
Clarify preferences for how much and what type of information; cultural preferences; and preferences regarding medical decision making (individual or family)
Provide information
Use clear language, avoiding euphemisms
Acknowledge emotions and concerns
Foster realistic hope
Provide reassurance about continuing symptom management and support
Avoid false or misleading information
Encourage questions
Document

Adapted from: Clayton JM, Hancock KM, Butow PN et al. Clinical practice guidelines for communicating prognosis and end-of-life issues with adults in the advanced stages of life limiting illness, and their caregivers. *Med J Aust* 2007; 12:S77–108.

Nasogastric tube

This may be useful temporarily while initiating pharmacological management but should be avoided if possible, especially long term. For long-term decompression, percutaneous endoscopic gastrostomy may be placed.

Hydration/nutrition

Large-volume hydration may increase intestinal secretions. Low-volume hydration (1L per 24 hours of intravenous or subcutaneous normal saline) may reduce nausea. Oral ice chips and mouth care provide symptom relief. Total parenteral nutrition is only indicated if tumour prognosis is longer than that from potential starvation.

Analgesia

Opioid analgesic: the first-line is usually morphine. Fentanyl or methadone may have less action on intestinal motility.

Antispasmodic/anti-emetic

Metoclopramide is not recommended in complete obstruction as it may worsen colic. Antipsychotics or antihistamines may be useful. Stimulant laxatives (e.g. senna or bisacodyl) should be avoided.

Reduce secretions

Anticholinergic (hyoscine butylbromide) or octroetide (in refractory cases) are used to reduce intestinal secretions.

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TABLE 4 Family conference agenda

Diagnosis, extent of disease, illness course
Understanding of illness (patient and family)
Treatment of symptoms
Complications
Nutrition
Medications, side effects
Prognosis
Goals of care
Death education
Future plans
Discharge options
Future care needs
Emergency or crisis plans
Resources (including spiritual and social support)
Caregiver
Coping, stress, grief
Understanding and needs for information
Respite and other support

Adapted from: Powazki R, Walsh D, Davis MP et al. *The family conference: how we do it.* Montreal: 16th International Congress on Care of the Terminally Ill; 2006.

Corticosteroids

These may reduce tumour-related oedema and decrease intramural swelling or extramural compression.

COMMUNICATION

Communicating prognostic information (See Table 3)

In general, advanced cancer patients and their families have high information needs. The timing of prognostic information needs to be negotiated, but many express a need for this information at the time of advanced disease diagnosis. Patient and caregiver information needs may be different, especially as illness progresses: patients may want less information, while caregivers want more, especially about the process of dying. Caregivers may need a separate meeting (with the patient's permission) to discuss their information needs. The method of delivery may be more important than the actual information. Patients desire physicians to express empathy and optimism, to check understanding, promote questions, avoid euphemisms and promote realistic hope (e.g. for symptom control, support and comfort).

Family conference

A family conference is a multidisciplinary (physician, nurse, social worker, pastoral care) meeting, engaging the patient and family. The agenda varies according to the situation and may include information, medical, educational and psychosocial needs. Topics covered may include current illness, prognosis, complications, treatment options, goals of care, discharge planning and carer needs (see Table 4).

KEY POINTS

- Breakthrough pain is common in cancer and should be anticipated. Patients with moderate to severe pain should have access to short-acting opioids.
- Many cancer pains have a neuropathic component. Neuropathic pain responds both to opioids and adjuvant analgesics.
- Many opioids have active metabolites that accumulate and cause toxicity in renal impairment. Methadone and fentanyl are safe in renal impairment.
- Methadone is often used as a second-line opioid and may be beneficial in neuropathic pain. It can accumulate with chronic dosing and is susceptible to drug interactions.
- Bisphosphonates provide analgesia and reduce complications from bone metastases. Long-term use is associated with osteonecrosis of the jaw.
- Delirium is common in advanced cancer. Management includes modification of treatable factors, haloperidol and behavioural measures.
- Malignant bowel obstruction can be effectively palliated medically, often without a nasogastric tube.
- Cancer patients and their caregivers have high needs for prognostic information. This should be communicated in a clear, honest, empathetic manner. Family meetings may facilitate this communication.

FURTHER READING

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