Pharmacotherapy for cancer pain

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General principles of cancer pain management

Pain management must involve treating the cause of the pain where possible, for example appropriate use of antibiotics for infection, fixation for fractures, spinal stabilization. Where the cause of pain cannot be removed entirely, treatment should be directed at modifying the disease process if possible, for example palliative radiotherapy and/or chemotherapy, bisphosphonates for hypercalcaemia, surgery for bowel obstruction. Attention to a patient's physical environment is important and simple measures, for example use of appropriate mattresses, orthotics, and mobility or bathing aids, can enhance comfort. Mood disorders are common in patients with cancer. Depression and anxiety may worsen a patient's pain experience; this should be diagnosed and treated.

Analgesic pharmacotherapy

Optimal oral opioid regimens can manage >75% patients with cancer pain. A number of different routes of analgesic administration are used in those with cancer pain. The oral route predominates; however, many patients in the latter stages of their illness are unable to tolerate regular tablets. Even so, if a patient cannot tolerate tablets, various liquids, suspensions and sublingual preparations are commercially available, particularly for opioid analgesics. Transdermal opioid patches (e.g. fentanyl, buprenorphine) are often used in patients with poor oral intake or a significant tablet burden. Transmucosal oral and nasal administration may be helpful for breakthrough and incident pain. In a community setting, once the oral route is lost, subcutaneous methods of drug delivery are used.

Effective pain control can be achieved by use of continuous subcutaneous injection (CSCI) systems. These systems consist of a battery-powered motor that operates a refillable syringe. A continuous small volume of analgesic can be administered over a 24 h period. After this, the syringe needs to be refilled. Opioid analgesics such as diamorphine, oxycodone and alfentanil are commonly used. Figure 1 shows our local guidelines for conversion to these drugs from oral morphine (it should be noted that these are not national guidelines). Non-steroidal anti-inflammatory analgesics (e.g. ketorolac or tenoxicam) can also be administered subcutaneously. Intrathecal drug delivery may be useful in about 1% of patients with cancer pain.

WHO analgesic ladder

The WHO ladder for pain management has been established for a number of years. It describes a method of pain control through a series of steps. It commences with simple analgesic and anti-inflammatory medications, progressing to weak opioids, and then to strong opioids. Undoubtedly, the use of this ladder has helped to rationalize analgesic treatments and it has been validated in an oncology setting.[4] However, there is currently some debate in the field of cancer pain management about whether all patients should start at step one of the ladder, as some patients have intense pain at presentation. In our opinion, the WHO ladder should be used as a general guide to management in most, but not all, patients with cancer pain. Table 1 shows the numbers needed to treat (NNT) for common analgesics. NNT is the number of treated patients required in order for one of them to achieve at least a 50% reduction in pain intensity.

Simple analgesics

Acetaminophen is the first step of the WHO ladder; it is an often under-rated adjunct in cancer pain. It is rapidly absorbed from the small intestine after oral administration. Rectal and parenteral formulations are available. It is effective when given alone for mild pain, and it can be used in combination with weak (e.g. codeine) or strong (e.g. oxycodone) opioids for moderate pain. The rectal route should only be used if the patient cannot take or absorb oral medication, as it produces unreliable absorption; 1 g every 6 h may be subtherapeutic for some adults. Acetaminophen 1 g has a NNT of

Key points

Cancer pain management services must integrate with palliative and primary care.

Pain is common in cancer and usually occurs in more than one site.

Careful assessment and treatments aimed at the causes of the pain are essential.

Optimal oral pharmacotherapy manages more than 75% of patients with cancer pain.

If specific anti-cancer therapy, drugs, physical and psychological treatments fail, then more invasive therapies should be considered early.

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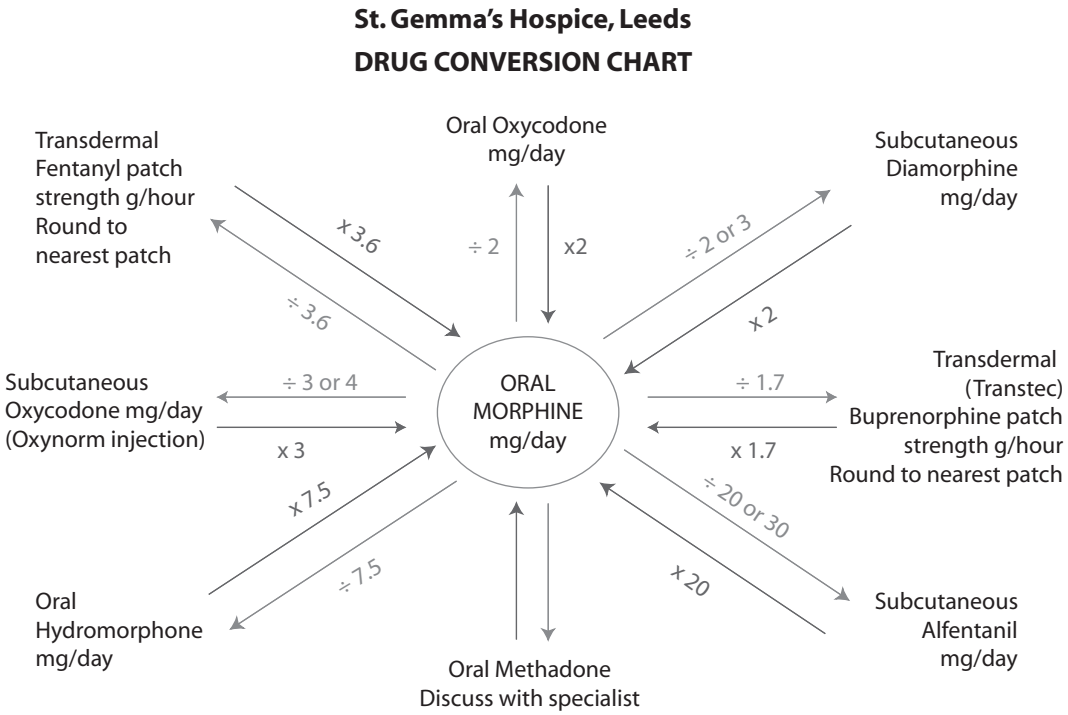

Fig. 1 Always go through the centre of the chart (via oral morphine) when converting between opioids.

Table 1 Numbers needed to treat (NNT) for common analgesics used as a single dose in an acute pain setting[9] and for adjuvant analgesics in particular neuropathic pain syndromes

Conventional Analgesic	Dose	NNT	95% CI
Ketorolac (i.m.)	20 mg	1.8	1.4–2.5
Acetaminophen plus codeine	1000/60 mg	2.2	1.7–2.9
Diclofenac	50 mg	2.3	2.0–2.7
Oxycodone I/R	15 mg	2.3	1.5–4.9
Ibuprofen	400 mg	2.4	2.3–2.6
Morphine (i.m.)	10 mg	2.9	2.6–3.6
Acetaminophen	1000 mg	3.8	3.4–4.4
Tramadol	100 mg	4.8	3.8–6.1
Aspirin	600/650 mg	4.4	4.0–4.9
Codeine	60 mg	16.7	11.0–48.0

Adjuvant Analgesic	NNT	Setting
Amitryptiline	2.3; 3.0	Post-herpetic neuralgia; diabetic neuropathy
Gabapentin	3.7; 3.2	Post-herpetic neuralgia; diabetic neuropathy
Carbamazepine	2.6	Trigeminal neuralgia
Lamotrigine	2.0	Trigeminal neuralgia
Paroxetine	6.7	Painful diabetic neuropathy

i.m. = intramuscular.

nearly 5; combination of acetaminophen with other analgesics improves the NNT. Acetaminophen does not affect peripheral cyclo-oxygenase receptors, so it has fewer side-effects than anti-inflammatory agents.

Anti-inflammatory drugs and COX-II inhibitors

Non-steroidal anti-inflammatory drugs (NSAIDs) and the more recent cyclo-oxygenase II (COX-II) inhibitors act via the cyclo-oxygenase pathway to reduce pain intensity. They are often used as a first step with acetaminophen in the WHO analgesic ladder or with opioids at greater levels of pain intensity. They are traditionally used for bony pain, but there is no hard evidence that they are specific for this problem. Side-effects are well known, such as gastroenterological (GI; heartburn, gastritis and gastric ulceration), renal impairment, exacerbation of asthma and cardiovascular problems, and bleeding. Different NSAIDs have different side-effects so switching drugs is sometimes useful. The NICE guidelines for NSAID use suggest that most patients with cancer pain fulfil the criteria for requiring routine GI protection. Although in general COX-II inhibitors have a lower incidence of some adverse effects, rofecoxib has been withdrawn owing to cardiovascular risks[5] and caution is needed when using other drugs of the same class.

Opioids

Opioid analgesia remains the mainstay in cancer pain management. In a community setting, patients are often commenced on weak opioids (e.g. codeine or tramadol). These are most effective if given on a regular basis, often used in combination with acetaminophen. Recently, there has been debate about their role in the analgesic ladder. Some authors suggest that if pain intensity is high enough, then the patient should be commenced on step 3 (opioids) from step 1, bypassing step 2 of the ladder. This may be correct in the management of individual cases. However, caution is needed when starting an opioid-naïve patient on strong opioids. A patient who is on maximum dose codeine

(240 mg day^{-1}) is receiving the equivalent of approximately 24 mg of morphine per day (assuming that they are amongst the 85–90% population who can metabolize codeine to morphine). Similar conversions can be made for the other weak opioids. A patient receiving this dose will probably be able to tolerate a strong opioid without experiencing adverse events. An opioid-naïve elderly patient may experience significant side-effects even on low doses of strong opioid. For this reason, many clinicians prefer to adhere to the three steps of the ladder or to commence these patients on low doses of short-acting strong opioid preparations initially to assess response.

Strong opioids are available as immediate and sustained release preparations and can be delivered by different routes (e.g. oral, parenteral, buccal, transdermal, transnasal and oral transmucosal). Optimum pain control is achieved by regular doses of analgesia and so most patients are maintained on sustained release preparations (e.g. oral MST and Oxycontin MR, and transdermal fentanyl and buprenorphine). Pain may not be fully controlled in every instance by simply using sustained release preparations. Immediate release preparations (e.g. Oramorph and Oxynorm) are co-prescribed in addition to sustained release morphine preparations for episodes of breakthrough pain. In general, the breakthrough dose required for a patient on a stable background strong opioid is about one sixth of the total morphine equivalent dose. The exception is transmucosal fentanyl when the dose has no relationship to the patient's fentanyl patch dose.[6] It is good practice to match the immediate release with the sustained release medication (e.g. MST with Oramorph); this makes calculation of the total daily dose easy. In the past, patients were started with immediate release opioids, and then titrated onto sustained release preparations once a stable dose was achieved. However, Klepstad and colleagues demonstrated that sustained release preparations were just as effective when commencing opioid treatment.[7] Escalating use of immediate release preparations in a patient on a sustained release preparation is a good guide to the required sustained release dose increase needed to achieve pain control. Maintenance therapy should be regularly reviewed; pain intensity tends to increase as the cancer progresses.

Side-effects common to all opioids include nausea and vomiting, constipation, dry mouth, and tiredness. Many of these improve after the first week of therapy, but patients must be prescribed anti-emetic and laxative therapy if this is a problem on initial titration. Metoclopramide, cyclizine and haloperidol are used commonly. They should be given regularly and may be stopped after initial titration. However, a significant number of patients receiving strong opioids need to remain on regular anti-emetics. The efficacy of pro-kinetics in this situation is questionable. Treatment of constipation starts with a good diet and regular fluid intake, but regular movicol is often required, particularly in the elderly. Second line laxatives include co-danthramer and co-danthrusate preparations. Drowsiness may be treated either by a change in strong opioid, dose reduction (where possible) or by use of psycho-stimulants such as methylphenidate. Less common side-effects include confusion, hallucinations, itch and ventilatory depression. Opioid dependency and addiction is rare if opioids are prescribed appropriately.[8] Different opioids have different side-effects, and prescribing a different opioid may reduce these. Opioids are sometimes switched because of suboptimal pain control. However, in practice it is better to titrate up the original opioid. If unacceptable side-effects occur at this higher dose, then an opioid switch can be considered.

Adjuvant analgesics

In 1987, Ventafridda and colleagues demonstrated, in a retrospective study, that the use of the WHO analgesic ladder for all cancer pain led to a reduction in pain intensity in 71% of patients.[4] Therefore, nearly a third of patients may need additional pharmacological and psychological management. This often requires the use of adjuvant analgesics.

Anti-depressants may be useful; older less specific drugs such as amitriptyline are more effective than the newer drugs that target fewer receptor sites (e.g. fluoxetine). The NNT for at least 50% pain relief for tricyclic antidepressants compared with placebo is 2–3 for most pain conditions. Many of the trials demonstrated analgesic benefit without significant changes in mood. The starting dose should be low (e.g. 10 mg amitriptyline at night) and titration should be supervised and slow. Side-effects include sedation, blurred vision, dry mouth, increased appetite and constipation. At higher doses cardiac arrhythmias, postural hypotension, urinary and sexual problems can occur. The number needed to harm (NNH) for minor adverse effects is 2–3 and for major effects about 17. Tricyclic antidepressants are more effective for pain than selective serotonin reuptake inhibitors that have an NNT of 6–7. Venlafaxine has been shown to be effective for post-surgical neuropathic pain (e.g. after breast surgery) and may be useful in neuropathic cancer pain.

There is good evidence that anticonvulsants are useful in managing neuropathic pains (e.g. trigeminal neuralgia has been treated with carbamazepine for many years). It has an NNT of 2–3, but about 10% patients cannot tolerate treatment due to side-effects such as dizziness, ataxia and sedation. Sodium valproate has been used for migraine and has an NNT of 3.5. It is also used for neuropathic pain, but there is little efficacy data. It has significant side-effects (e.g. nausea, dizziness, sedation and ataxia) with a NNH for stopping the drug because of side-effects of 9. Gabapentin is an anticonvulsant that has anti-hyperalgesic and anti-allodynic properties. Several large randomized controlled trials have demonstrated its efficacy in the treatment of a variety of neuropathic pains. Around 30% of patients achieve more than 50% pain relief. A similar number will also experience minor adverse events; the most common of which are somnolence and dizziness. Lamotrigine is an anticonvulsant that blocks sodium channels and inhibits glutamate release. It is effective

for trigeminal neuralgia (NNT 2) and post-stroke pain, but is use for other neuropathic pains remains unproven. It has some troublesome side effects and it is often poorly tolerated. Pregabalin is a newer anticonvulsant that is effective for some neuropathic pains; it has the advantage over gabapentin in that it can be given twice, instead of three times, daily.

I.V. lidocaine has been shown to be effective for neuropathic pain. Mexilitine has been given orally to try to produce a more sustained effect; there is no evidence to support its efficacy and side-effects are a problem. Cannabinoids have been used, however, there is poor evidence as yet that their efficacy is good and the side-effect burden is high. Ketamine is commonly used subcutaneously via a syringe driver for the management of difficult cancer pain. It is important to use low doses to reduce the incidence of psychomimetic side-effects. It has been used orally to manage a variety of difficult pain problems but their may be problems obtaining this drug in the community.

Steroids have a role in cancer pain via their anti-inflammatory effect. Specific indications include treatment of liver capsule pain, bony metastases and headache caused by cerebral metastases. Steroids have well-known long-term side-effects, and so they should be stopped after a short trial course of therapy if they are ineffective. If steroids provide good pain control, the dose should be reduced in a step-wise fashion to the lowest effective dose. Concomitant use of NSAIDs increases the risk of gastrointestinal bleeding significantly.

Further treatment of cancer pain

Pharmacotherapy is only one part of the overall management of cancer pain. Prolonged uncontrolled severe cancer pain may be become resistant to ever increasing doses of drugs. If pharmacotherapy becomes ineffective and if there is no physical, psychological or specific anti-cancer therapy available, then more invasive therapies should be considered early. These may include nerve blocks, neuromodulation and neurosurgical procedures.

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