Managing cancer pain: the palliative care perspective

Cancer is not synonymous with pain; however, pain is a very common and debilitating symptom. Cancer is primarily a disease of older people, who will frequently rely heavily on general practitioners and care of the elderly physicians. Inadequate knowledge of pain management by professionals has been identified as a barrier to cancer pain management. This article aims to provide an overview of the principles of cancer pain management, particularly in the elderly population.

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Pain is a very common and debilitating symptom in patients with cancer. It affects a third of patients overall, and this rises to three quarters as the disease advances.[1] Cancer is primarily a disease of older people. It is estimated that one in three people will develop some form of cancer during their lifetime.[2] This compares with one in 27 among people aged up to 50 years.

Inadequate knowledge of the principles of pain control by professionals has been identified as a barrier to appropriate cancer pain management.[3] Healthcare professionals caring for the elderly have to be confident in these principles and have to be able to tailor them to patients in the community (either at home or in residential care).

Assessment of pain

Pain is defined as an unpleasant sensory or emotional experience associated with actual or potential tissue damage, or described in terms of such damage.[4]

The concept of "total pain" encapsulates the physical, psychological, social and spiritual aspects that shape a person's experience of pain. In practice, good pain relief is hard to achieve without addressing all of these areas and is best obtained through the combined efforts of the multidisciplinary team.

The physical causes of pain in patients with cancer are numerous, and the picture is often evolving. Pain can be directly due to the effects of the cancer, for example tumour invasion of soft tissue or nerve compression, or can be due to the general effects of debility such as pressure sores and constipation.

In patients undergoing active treatment, pain may also be a consequence of this treatment, such as chemotherapy-induced neuropathy. It is also important to consider unrelated comorbidity as a source of discomfort in this population (eg, osteoarthritis or postherpetic neuralgia). Collation of a detailed history is vital to comprehensive pain assessment.

Pain appears to be under-recognised and undertreated in older people, particularly in those with cognitive or communication difficulties.[5] A number of patient barriers to appropriate pain management in the elderly appear to exist, including reluctance to report pain, misconceptions surrounding opioids and addiction, and concerns that they may be troubling family and staff.[5]

Some older people appear more willing to score pain on an intensity rating scale than discuss pain.[6] The use of standardised pain assessment tools such as the Visual Analogue Scale or the Numerical Rating Scale can also provide a quantifiable measure to chart response to treatment.

Regular assessment is key, particularly when pain is not adequately controlled. The perceived impact of pain on a patient's life should be the fundamental consideration in the planning of pain control interventions.

Assessment of pain in patients with cognitive impairment is fraught with difficulties, and potentially leads to underestimation and undertreatment of pain in this group.

The available evidence supports the use of self-assessment pain scales where feasible. In patients with severe cognitive impairment, unable to comply with self-assessment, observational rating scales should be used.

PACSLAC (Pain Assessment Checklist for Seniors with Limited Ability to Communicate) and the pain-assessment tool DOLOPLUS 2 appear to be of most value, although their usefulness relies on the patient being well known to the observer.[7]

Pharmacological management

In the elderly population, who often have high levels of comorbidity and greater drug sensitivity, the issues of polypharmacy are key. This should not, however, act as a barrier to provision of adequate analgesia. The World Health Organization (WHO) pain ladder recommends a three-step process for the management of pain: non-opioids (with or without adjuvant analgesics) at step one; weak opioids at step two (with or without non-opioids and with or without adjuvant analgesics); and strong opioids (with or without non-opioids and with or without adjuvant analgesics) at step three.[8]

Non-opioid treatment

Paracetamol and non-steroidal anti-inflammatory drugs (NSAIDs) are universally accepted as part of the treatment of cancer pain and should be prescribed unless contraindicated. Their use can improve the pain relief from opioids and permit the use of lower opioid doses. A number of factors have been demonstrated to increase the risk of NSAID-related, upper GI toxicity (Box 1). Combination of a proton pump inhibitor with an NSAID significantly reduces the risk of upper GI complications, compared with NSAID treatment alone.[9]

Opioids

Weak opioids suitable for mild–to-moderate cancer pain are codeine and dihydrocodeine. Combining an opioid with paracetamol (eg. co-codamol 30/500) provides synergistic analgesia and is a logical approach. It is worth noting that over-the-counter combination preparations containing 8 mg of codeine with paracetamol show no additional analgesic benefit compared with paracetamol alone, and these preparations are therefore not recommended.

In frail patients, there may be occasion to commence a small dose of morphine immediate release rather than commencing regular codeine, as it would offer greater dosing flexibility.

For severe pain (step 3 of the WHO ladder), oral morphine should be prescribed first line unless specifically contraindicated, and the dose titrated according to individual response. Morphine is available in a number of immediate- and modified-release preparations. In opioid naïve, elderly or frail patients, the convention is to start with a regular immediate release preparation, normally in the region of 2·5–5 mg at four hourly intervals. The same dose should be available additionally as required.

Pain should be assessed at least once per day, and the opioid dose escalated by 30–50% in those patients who still require two or more additional breakthrough doses in the preceding 24 hours. In frail patients, particularly in the community, it is logical to make smaller dose increments over a more prolonged timeframe. Once a stable dose appears to have been established, switching to a modified-release, 12-hourly preparation aids compliance and reduces tablet burden.

The WHO analgesic ladder has been demonstrated to improve pain in approximately 85% of patients with cancer. For the minority of patients in whom pain is not controlled and unacceptable side effects preclude dose escalation, an opioid switch is generally considered. The rationale is that although opioid analgesics share many side effects, qualitative and quantitative differences do exist.

In the UK, the most commonly prescribed second-line opioid is oxycodone. It is a useful, more expensive, alternative in patients who are intolerant to morphine. Oxycodone is available as immediate-release capsules, modified-release tablets and oral liquid preparations. The modified-release tablets have a biphasic, pharmacokinetic release profile;

this allows onset of analgesia within an hour of ingestion with a sustained analgesic duration of 12 hours.

Hydromorphone is prescribed at some centres as a third-line alternative opioid. According to the manufacturer, hydromorphone through oral and subcutaneous/intramuscular routes is approximately 7·5 times more potent than morphine (ie, morphine 10 mg = hydromorphone 1·3 mg). This awkward ratio for dose conversion somewhat limits the popularity of the drug. There is no oral liquid preparation of hydromorphone in the UK, but the capsules can be opened and sprinkled onto cold soft food in patients with swallowing difficulties.

The potency ratios for strong opioids vary widely in manufacturers' literature, and this is compounded by probable differences in drug metabolism between individuals (Table 1). When converting from one opioid to another, caution needs to be applied and regular patient assessment is warranted.

Transdermal opioids

Transdermal (TD) administration of opioids can aid compliance, particularly in patients with cognitive decline and offer an alternative route for patients with swallowing difficulties. These obvious advantages need to be weighed against an awareness of the limitations of this mode of administration, namely loss of dosing flexibility and delays in achieving steady state.

Fentanyl, like morphine, is a strong mu-opioid receptor agonist. However, unlike morphine, it is lipophilic and this makes it suitable for transdermal (TD) administration.

Its lipophilic nature may partly explain the differences in side effect profile compared with morphine, as it is sequestered predominantly within the central nervous system (CNS). In clinical practice, fentanyl is less constipating and possibly causes less nausea and vomiting than morphine.

TD fentanyl is useful in the management of stable, chronic pain. As it takes approximately 36–48 hours to achieve steady state, it should not be considered in cases where rapid dose titration for uncontrolled pain is required. TD fentanyl patches are available in five strengths, each requiring to be changed every 72 hours.

Buprenorphine is a partial opioid receptor agonist/antagonist, and its pharmacokinetics are not altered by advancing age or renal impairment. Additionally, the relatively low incidence of CNS side effects and constipation make it a favourable choice for elderly patients. Contrary to earlier concerns, no analgesic ceiling effect and no antagonism of combined pure mu-opioid receptor agonist (eg. morphine for breakthrough pain) have been observed within the therapeutic dose range. Buprenorphine is highly lipid soluble, making it suitable for TD delivery. It is available as two formulations delivering 5, 10 or 20 mcg/hr over seven days (BuTrans) or 35, 52·5 or 70 mcg/hr over four days (Transtec).[10]

Box 1: Factors increasing risk of upper GI toxicity associated with NSAIDs

- Increasing age (>65 years)
- Previous peptic ulcer disease
- Comorbid medical illness
- Smoking
- Type of NSAID (eg, ketoprofen, ketorolac [Toradol] are associated with high risk relative to other NSAIDs)
- Increasing NSAID dose
- Combined use with corticosteroids, anticoagulants, SSRIs, aspirin
- Existing renal, cardiac, hepatic impairment.

Managing opioid side effects and toxicity

The most common opioid side effects include nausea and vomiting, constipation and drowsiness. Both nausea and lethargy tend to resolve

Box 2 Opioids and renal impairment

In the presence of renal impairment, all opioids should be used with caution. The active metabolites of morphine accumulate in renal failure. Alfentanil (Rapifen), buprenorphine and fentanyl are the safest choices in such patients. Those unfamiliar with these drugs should seek specialist palliative care advice.

Table 1: Approximate dose equivalence chart

Oral to oral route conversions		
Codeine	Morphine	Divide by 10
Tramadol	Morphine	Divide by 5
Morphine	Oxycodone	Divide by 2
Morphine	Hydromorphone	Divide by 7·5
Oral to transdermal route conversions		
Morphine	Fentanyl	100:1 150:1*
Morphine	Buprenorphine	100:1 75–115:1*
Oral to subcutaneous route conversions		
Morphine	Morphine	Divide by 2
Morphine	Diamorphine	Divide by 3
Oxycodone	Oxycodone	Divide by 2
Hydromorphone	Hydromorphone	Seek specialist advice
Morphine	Alfentanil	30–40:1

* manufacturer's guidelines

within a few days of commencing an opioid. Light-headedness and motor imbalance, which might be well tolerated in younger patients, can have serious consequences in patients who already are at risk of falls. Constipation can also present a real problem and a laxative should be prescribed concurrently, in line with local guidelines, on commencing an opioid.

Opioid toxicity ranges from increasing drowsiness and poor concentration to hallucinations, myoclonus and delirium. Toxicity may be exacerbated by dehydration, change in disease status or co-administration of other drugs. The management strategy of dose reduction, hydration (often parenterally) and treatment of delirium with antipsychotics may be adequate, but if toxicity persists or pain is inadequately controlled, an opioid switch is indicated.

Tolerance to the respiratory depressant effects of opioids occurs rapidly; therefore, respiratory depression is extremely rare in the palliative care setting. Naloxone is only indicated in patients with significant respiratory depression; acute opioid withdrawal symptoms and rebound pain can be severe after its use.

Opioids in the last days of life

In the final days of life, comfort is paramount. Often patients will no longer be able to manage oral medication and non-essential medications should be discontinued. The daily oral opioid dose can be converted to a continuous subcutaneous infusion (CSCI), with parenteral analgesia available as required for breakthrough pain. Fentanyl or buprenorphine tablets, if previously prescribed, should be continued; if the opioid requirement increases, additional opioid can be given via a CSCI in addition to a patch.

New rapid-onset opioids

Breakthrough pain (BTP) is defined as a transient flare of pain arising on a background of controlled pain. It is usually severe, reaching peak intensity within a few minutes and has a variable duration with an average of about 30 minutes. BTP episodes encompass both predictable incident pain triggered by activity, for example coughing or movement, and spontaneous, unpredictable pains. These episodes have conventionally been treated with immediate-release opioid analgesics, at a sixth of the around-the-clock dose. The pharmacokinetics of immediate-release oral opioids are such that onset of analgesia occurs 20–30 minutes after ingestion, by which time the episode of BTP may be resolving spontaneously.

Ideally, the opioid analgesia prescribed would demonstrate pharmacokinetics more synchronous with the characteristics of BTP. In light of this, four new products have recently been licensed for treatment of BTP in adults with cancer already receiving maintenance opioid therapy. These products are collectively known as rapid onset opioids (ROO). Sublingual fentanyl (Abstral), buccal fentanyl (Effentora), and fentanyl nasal spray (Instanyl or PecFent) have the advantageous characteristics of faster onset and offset of action than conventional oral opioids. All of the above preparations appear to offer pain relief within 10–15 minutes of administration, so does

oral transmucosal fentanyl citrate (Actiq), which has been available for a number of years.

In patients with incident pain, the administration of an ROO, in advance of an activity known to precipitate pain, can offer sufficient short-lived analgesia to allow the activity (eg, showering) to be completed.

There is no relationship between effective doses for sublingual, buccal or nasal fentanyl, and the around-the-clock opioid dose. Therefore a titration period is needed that can be guided by a member of the specialist palliative care team. Prescribers should be aware, because of the differing absorption and elimination characteristics of oral fentanyl preparations, brands should not be considered interchangeable.

Adjuvants

Adjuvants comprise a group of pharmacologically unrelated drugs, with other primary uses, that can be effective analgesics in specific circumstances. They have a particular role to play in the management of neuropathic pain, which is usually only partly sensitive to opioid. This subject has previously been covered in detail in this journal and will only be mentioned in principal here.[11]

The most commonly prescribed anti-neuropathic agents consist of anticonvulsants and tricyclic antidepressants. Drug interactions and profound side effects may mean they are poorly tolerated in the older patient. It is best to initiate these drugs at lower doses than for the younger adult population and titrate in cautious increments.

Amitriptyline is the most frequently prescribed antidepressant in neuropathic pain; however, the secondary amine tricyclics (nortriptyline and desipramine) and serotonin and norepinephrine reuptake inhibitors (SNRIs), such as duloxetine (Cymbalta), appear to have a better side effect profile, and should be considered in the elderly.[12] Benefits are seen below conventional antidepressant doses.

Gabapentin is usually considered to be the first-line anticonvulsant for neuropathic cancer pain; however, the evidence to support its use in this context is limited. Most of the data pertains to its benefits in non-malignant neuropathic pain. Pregabalin (Lyrica) is generally reserved as second-line treatment for those who fail to tolerate gabapentin.

Interestingly, NICE suggests that pregabalin be prescribed as first-line treatment for neuropathic pain by non-specialists.[13] It is conceivable that the guidance on malignant neuropathic pain may change in line with this.

Bisphosphonates are osteoclast inhibitors, noted to reduce skeletal events and lessen cancer pain in patients with bone metastases. The data relate primarily to breast cancer and myeloma, but appears to also apply to other tumour types.[14] Bisphosphonates should be considered as part of the therapeutic regimen for the treatment of pain in patients with malignant infiltration of bone.

The application of topical, locally acting opioids to inflamed tissue, such as pressure sores, is frequently recommended in clinical practice, and can be particularly useful in older people However, the evidence to support its use is insufficient.

Additionally, the use of topical lidocaine 5% plasters (Versatis) is validated for the treatment of postherpetic neuralgia, but there is scant evidence regarding its use to treat neuropathic cancer pain.[15] This may well reflect a paucity of trials on lidocaine plasters as opposed to a lack of benefit and, given the lack of systemic side effects, they can be a useful option particularly in older people.

Although an exhaustive list of potential drug interactions is beyond the scope of this article, some basic principles hold true. Changes in a patient's performance status over time may allude to a change in renal or hepatic function, which may alter drug handling. Another important aspect to consider in patients undergoing either chemotherapy or radiotherapy is the effect this may have on a patient's pain. For example, a patient receiving palliative radiotherapy to a painful long bone metastasis may experience clinical improvement that lessens the requirement for analgesia. Failure to screen for this can lead to over sedation and drug toxicity. Above all, this highlights the need for good inter-disciplinary communication.

Non-pharmacological treatment

A large systematic review of the use of radiotherapy for bone pain demonstrated complete pain relief at four weeks in 27% of patients, and at least 50% improvement in an additional 42% of patients during the period of the trials. There appears to be no significant

difference in response rates between single and multiple fraction radiotherapy.[16]

The evidence to support the use of complementary therapies in the treatment of cancer pain remains limited. Despite this, most hospices are accepting of the role of complementary therapists and anecdotally patients appear to respond positively to the various therapies offered, although the benefits are often short term.

Specialist interventions

Despite multidisciplinary management of pain, in accordance with the WHO ladder, as many as 20% of cancer patients continue to have significant pain. The input of the specialist palliative care team should be sought, as a number of other options are available.

NMDA (N-methyl-D-aspartic acid) receptor channel blockers (namely ketamine [Ketalar] and methadone) are most commonly used in neuropathic pain failing to respond adequately to conventional therapies. These drugs should only be started under the direct supervision of the specialist palliative care team.

Patients who continue to have poorly controlled pain despite attempts to optimise drug therapy, particularly if known to have locally advanced disease, or are likely to have neuropathic pain or marked incident pain, should be referred for anaesthetic assessment and consideration of targeted nerve blockade or spinal opioids.

As the trend for palliative medicine specialists to become involved with patient care at an earlier stage of the illness strengthens, the proportion of patients who are still undergoing active oncology treatment has inevitably increased. The decision to embark upon or continue treatment of this nature must be carefully considered. This is particularly relevant in the elderly population for whom the cumulative effects of treatment and surveillance, both physically and psychologically, are great.

Conclusion

Cancer is primarily a disease affecting older people. The majority of these patients will experience pain either directly related to their cancer, their treatment or due to unrelated comorbidity.

Unfortunately, a number of barriers to good pain management in the elderly appear to exist, including difficulties assessing pain and a higher incidence of drug-related side effects in this population.

While this article focuses primarily on the pharmacological management of cancer pain in older people, the principles can be applied to the care of most life-limiting conditions.

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