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Neuropathic pain in cancer

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Editor's key points

- There is an increasing need for good cancer pain management as survival improves.
- Factors specific to the cancer itself will alter the neurobiological pain response.
- Most studies are of non-malignant pain and extrapolation to the cancer setting may be misleading.
- Further research is urgently needed for complex cancer pain syndromes such as neuropathy.

Summary. Cancer-related neuropathic pain is common; it can be disease related or related to the acute or chronic effects of cancer treatment. For example, chemotherapy-induced peripheral neuropathy occurs in 90% of patients receiving neurotoxic chemotherapy. Cancer treatments have become more effective; patients are living longer with cancer and there are more cancer survivors. However, side-effects (particularly neuropathy) have become more problematic. The key to management of cancer-related neuropathy is a considered assessment, remembering not to miss the opportunity of reversing the cause of the pain with appropriate oncological management. An increasing range of oncological therapies are available, including radiotherapy, chemotherapy, hormonal therapy, or one of the evolving approaches (e.g. immune therapies).

Patients are often elderly and with comorbidities; therefore, all treatment decisions have to be made carefully and reviewed appropriately. Cancer pain is often of mixed aetiology or, if purely neuropathic, may be one of several pains experienced by a patient. For these reasons, opioids are used more frequently in patients with cancer-related neuropathic pain. Standard guidelines for the use of anticonvulsants (e.g. pregabalin and gabapentin), antidepressants (e.g. duloxetine and tricyclics), and topical treatments (e.g. capsaicin and lidocaine) may be applicable, but there is a lack of good-quality clinical trials in cancer-related neuropathic pain. Choice is dictated not just by age, drug interactions, and comorbidities, but also by the coexistence of many symptoms in patients with cancer. Treating more than one symptom with a particular neuropathic pain agent can avoid polypharmacy.

Keywords: cancer; neuropathic; pain

The challenge of managing cancer-related pain has broadened over the last decades. Cancer-related pain can be sub-divided into pain related to: advanced cancer; active cancer; and cancer treatments. There has been a significant evolution in the types of tumoricidal treatments available, resulting in more cures and longer prognoses for those not amenable to cure. However, treatment-related problems have become more common, especially peripheral neuropathies (http://www.mysanantonio.com/sponsoredarticles/lifestyle/health-wellness/article/Advances-in-Cancer-Treatment-4097631.php).

Fundamentals of cancer-related pain management

Pain assessment in patients with cancer should characterize the pain complaint, taking into account the status of the underlying disease, clarifying the pain in terms of its cause, syndrome, and pathophysiology and obtaining details about other factors that may contribute to the illness burden.[1] Pain can be addressed with primary disease-modifying treatment (most often radiotherapy) if available, feasible, and consistent with the goals of care. The symptomatic treatment of choice for cancer pain is opioid-based pharmacotherapy and the aim is to optimize the positive outcomes from these drugs and minimize the side-effects. Effective opioid treatment depends on the appropriate selection of a drug and route, individualization of the dose, consideration of 'rescue' dosing for breakthrough pain, and treatment of common opioid side-effects. The addition of a non-steroidal anti-inflammatory drug to opioid treatment can be helpful, but the gastrointestinal, cardiovascular, and renal risks of these drugs should be weighed against their benefits on an individual basis.

Adjuvant analgesic drugs (e.g. glucocorticoids, antidepressants, and anticonvulsants) have many uses when opioid treatment alone is not sufficient. Specific use of adjuvant analgesics as neuropathic agents will be discussed in detail later. Many non-pharmacological treatments can be used to improve pain control, coping adaptation, and self-efficacy; mind-body strategies have established benefit and can be used in a restricted but potentially useful manner by non-specialists. Interventions, including nerve blocks, external, and implanted spinal lines, play a small but important part in the management of refractory pain. Success usually depends on appropriate patient selection.

Approximately 80% of cancer pain can be controlled using the WHO analgesic ladder; however, there are no agreed data on the burden of side-effects to achieve this figure.[2] Cancer-related neuropathic pain (including malignant bone pain) remains problematic, both in terms of degree of analgesia and burden of side-effects.

Cancer-related neuropathic pain syndromes

Common cancer-related neuropathic pain syndromes are outlined in Table 1.

Neuropathic pain may be challenging therapeutically and have a substantial impact on the quality of life, sleep, and mood. Treatment is often difficult and may involve interventions distinct from those typically used for nociceptive pains. Given these challenges, awareness of the various neuropathic pain syndromes and an understanding of issues related to assessment and treatment may lead to better recognition and improved outcomes. Clearly, pain in the presence of active cancer has a layer of complexity which is related to the presence of the tumour. Unlike non-malignant pain, there are specific tumour-related factors (e.g. proinflammatory cytokine responses) which may impact on the neurobiology of the pain syndrome. In addition, tumour factors and responses to these factors may be responsible for many co-existing symptoms such as cachexia.

Clinical characteristics

Cancer-related neuropathic pain is chronic and often consists of a background pain with acute exacerbations, peaking several times a day. These exacerbations are often spontaneous but can also be triggered. Such spontaneous and evoked types of pain are perceived in areas of sensory abnormality (hyposensitivity, hypersensitivity, or both). Spontaneous pain may be ongoing, with a constant or fluctuating pain intensity, or dominated by pain paroxysms of short duration with pain-free intervals or a less intense background pain. Other sensations, such as paraesthesia (abnormal sensation that is not painful or unpleasant) and dysaesthesia (unpleasant abnormal sensation) may be present spontaneously or occur only when evoked by a stimulus.[3] Allodynia is a type of evoked pain that is elicited by a non-noxious stimulation. Dynamic mechanical allodynia (or touch-evoked allodynia) is the most common form, but allodynia to cold or heat may also be present. Also, hyperalgesia (increased response to a stimulus that is normally painful) is often present but usually not described as a symptom by the patient.

Painful peripheral polyneuropathy as a complication of treatment with specific types of chemotherapy is of increasing importance.[4] Chemotherapy-induced neuropathy is usually a dose-dependent, cumulative side-effect with a 'glove-and-stocking' distribution. Symptoms include sensory loss, paraesthesia, dysaesthesia, and pain sometimes accompanied with muscle weakness. Oxaliplatin-induced neuropathy is associated with an acute phase of allodynia and pricking dysaesthesia affecting the hands and feet and also pharyngolaryngeal dysaesthesia with sensations of shortness of breath or swallowing difficulties induced by cold drinks.[5–7]

Table 1 Neuropathic pain syndromes

Plexopathies
Cervical plexopathy
Malignant brachial plexopathy
Malignant lumbosacral plexopathy
Sacral plexopathy
Coccygeal plexopathy
Painful peripheral mononeuropathies
Paraneoplastic sensory neuropathy
Leptomeningeal metastases
Painful cranial neuralgias
Glossopharyngeal neuralgia
Trigeminal neuralgia
Malignant painful radiculopathy

Pharmacological treatment of neuropathic pain

Treating neuropathic pain remains a challenge. The drugs that are used commonly have limited response rates and responders often experience only partial reduction in pain at tolerable doses. The treatment of neuropathic pain is often symptomatic; however, in some cases, the underlying cause can be treated (e.g. corticosteroids for compression of the spinal cord or peripheral nerve). In spite of criticism, the most commonly used approach for comparing treatments involves calculation of the number-needed-to-treat (NNT) and the number-needed-to-harm from clinical trials data. Finnerup and colleagues[8] have described >170 randomized controlled trials to support decision making providing a basis for evidence-based treatment algorithms, although it is important to note that very few trials focus on cancer-related neuropathic pain. Very few comparative drug trials have been reported.

Gabapentin and pregabalin

Gabapentin and pregabalin are structurally related compounds. Their analgesic mechanism in neuropathic pain is hypothesized as through antagonism of the $\alpha_2\delta$ subunit of voltage-dependent calcium channels at presynaptic sites.[9] Both drugs seem equally effective with NNTs ranging from 4.2 to 6.4. The effects of gabapentin and pregabalin are well established in post-herpetic neuralgia, painful diabetic neuropathy, spinal cord injury pain,[8] and neuropathic cancer pain.[10] Pain relief can be rapid (within the first or second week) and often accompanied by improvements in sleep and quality of life measures. In cancer patients, the sleep improvement can be significant initially and then wane.

Gabapentin and pregabalin have no known drug–drug interactions and are well tolerated. Somnolence and dizziness are the most common side-effects; peripheral oedema, weight gain, nausea, vertigo, asthenia, dry mouth, and ataxia may occur. Side-effects may resolve over time or improve with

dose reduction. Both gabapentin and pregabalin undergo renal excretion and renal impairment requires dosage adjustment. Pregabalin has anxiolytic effects in patients with generalized anxiety disorders[11] and may therefore be the first drug choice in patients with anxiety. It is still unknown whether patients failing to respond to one of these drugs will benefit from the other; however, anecdotally, a switch from one to the other can result in an improved side-effect profile. This can be useful when excellent analgesia is associated with significant side-effects.

Other anticonvulsants

The main pharmacological action of carbamazepine, and its analogue oxcarbazepine, is blocking of sodium channels. Carbamazepine and oxcarbazepine are first-line drugs for trigeminal neuralgia.[12] Trials comparing oxcarbazepine with carbamazepine have reported comparable analgesic effects but fewer side-effects with oxcarbazepine.[8] In view of both the side-effect profile and drug–drug interactions, neither drug is considered as a first-line treatment in cancer-related neuropathic pain. Lamotrigine and valproate have limited roles in the treatment of neuropathic pain as results from randomized controlled trials are conflicting.[8]

Antidepressants

Antidepressants have a well-established beneficial effect on various neuropathic pain states. Antidepressants used in neuropathic pain treatment include tricyclic antidepressants (TCAs) (e.g. amitriptyline and imipramine) and the selective serotonin norepinephrine reuptake inhibitors (SNRIs) (e.g. duloxetine and venlafaxine). The analgesic effects of the selective serotonin reuptake inhibitors (SSRIs) are dubious.[13] It is clear that the analgesic effects of antidepressants are specific and independent of their antidepressant effects. However, because of this dual effect, antidepressants may be the first drug of choice in patients with a coexisting depression. Additionally, drugs such as venlafaxine have been used successfully in the management of hot flushes and can be very useful in patients with breast cancer with neuropathic pain, menopausal flushes, and depression.

TCAs have been shown to be effective for different neuropathic pain conditions in several randomized controlled trials with NNT values ranging from 2.1 to 2.8;[8] it is also suggested that they are effective in neuropathic cancer pain.[10] Anticholinergic side-effects are common during TCA therapy (dry mouth, constipation, urinary retention, sweating, and blurred vision). Somnolence and confusion can be an issue when initiating treatment and particular vigilance is required in the elderly and those on polypharmacy, especially opioids. Orthostatic hypotension and gait disturbances are concerns, especially in the elderly. Combination with Class IC antiarrhythmics or SSRIs that are metabolized by P4502D6 may cause toxic serum concentrations of TCAs. They are contraindicated in patients with epilepsy, heart failure, and cardiac conduction blocks. A recent large retrospective cohort study found that TCAs in doses of $\geq$100 mg daily were associated with increased relative risk of sudden cardiac death.[14] The secondary amines (e.g. desipramine and nortriptyline) may be better tolerated than tertiary amines (e.g. imipramine, amitriptyline, and clomipramine), with imipramine causing less sedation than amitriptyline.[15] Initiation of TCA treatment is best done slowly, starting with 25 mg daily (10 mg in the elderly) and slowly increasing up to 50–150 mg daily. There is a large pharmacokinetic variability in the metabolic pathways of TCAs because of genetic polymorphism of the enzymes that metabolize these drugs; therefore, plasma concentrations can be irrelevant to drug dose. Unfortunately, much of the cancer population is potentially at high risk of adverse effects to TCAs.

Selective SNRIs have been shown to have some efficacy in neuropathic pain. Recent randomized trials have documented the effect of venlafaxine and duloxetine in painful diabetic polyneuropathy.[8] More recently, duloxetine has shown efficacy in a randomized controlled trial (RCT) of chemotherapy-induced peripheral neuropathy (CIPN). This is discussed later. The combined NNT from the five diabetic trials of SNRIs in painful polyneuropathy was 5.0 (range 3.9–6.8). The effect of duloxetine was present from Week 1 and the most effective dose associated with fewest side-effects was 60 mg once daily. Only one randomized trial has studied amfebutamone in neuropathic pain.[16] Results were positive and, while this drug is less sedating, it is not easy to use in the elderly. The SNRIs are generally well tolerated and side-effects tend to decrease with continued treatment.[17] The most common side-effect is nausea; others include somnolence, dizziness, constipation, anorexia, dry mouth, hyperhidrosis, and sexual dysfunction.[17] There is a risk of elevated arterial pressure with venlafaxine and regular monitoring is recommended. Duloxetine should not be used in patients with hepatic dysfunction and venlafaxine dose should be decreased in patients with renal or hepatic insufficiency.

Topical lidocaine

Randomized trials have shown positive effects of a lidocaine patch 5% in post-herpetic neuralgia and mixed peripheral focal neuropathy with allodynia.[18 19] This has developed as a useful add-on treatment for patients with cancer-related neuropathic pain, especially where allodynia is present. It has also been used in chemotherapy-induced peripheral neuropathy affecting the feet and in post-breast surgery pain syndromes. Side-effects are mild, usually skin irritation. Although there is minimal absorption, it should not be used in patients taking oral class I antiarrhytmic drugs. A maximum of three patches should be applied for 12 h per day.

Opioids

There are some practical considerations in relation to opioids when managing patients with cancer: (i) neuropathic pain may not exist in isolation but with another pain which can be highly opioid responsive; (ii) neuropathic pain may be inextricably linked with a painful mass which requires opioid treatment; and (iii) some patients may achieve a better analgesia/

side-effect profile with an opioid rather than an adjuvant for neuropathic pain.

Neuropathic pain is reported to respond to opioids with an effect size similar to antidepressants and gabapentin/pregabalin with no proved difference between various opioids (e.g. oxycodone, morphine, methadone, levorhanol, and tramadol).[8 20 21] The combined NNT in peripheral neuropathic pain ranges from 2.6 to 5.1. These data are helpful but need to be tempered by the fact that the work was not in cancer patients. In the recent European Association for Palliative Care evidence-based guideline for the use of opioid analgesics in the treatment of cancer pain, there was a weak recommendation that patients receiving step II opioids who do not achieve adequate analgesia and have side-effects that are severe or unmanageable, might benefit from switching to an alternative opioid, although there are no RCTs to support this.[22 23] In North America, the use of adjuvant analgesics for cancer-related neuropathic pain usually only comes after a trial of opioid analgesia. In the UK and Europe, the tendency is to use both types of drug early in the management strategy. An increased side-effect profile if an adjuvant analgesic is added to an opioid is an issue[24] and should be anticipated with appropriate opioid reductions.

N-methyl D-aspartate antagonists

In practice, *N*-methyl D-aspartate (NMDA) antagonists in the form of oral or parenteral ketamine, remain an important part of the therapeutic armamentarium for difficult to control cancer-related neuropathic pain. More broadly, it could be said they are useful drugs for any cancer-related pain displaying phenomena of central wind-up and with a neuropathic, inflammatory, ischaemic aetiology, or all. The evidence base has been difficult to evolve. NMDA antagonists given as i.v. infusions have been shown to relieve various types of neuropathic pain, but the effects of oral NMDA antagonists (e.g. dextromethorphan, riluzole, and memantine) have been less convincing because of low response rates and unfavourable therapeutic indices.[8] In cancer patients on morphine therapy, i.v. ketamine improved analgesia, but the study also pointed out the need to take central adverse effects into account.[25] However, a recent RCT could not confirm the efficacy of parenteral ketamine for opioid refractory cancer pain, although it did suggest that some patients could be 'good responders'.[26] This study was not specific for either neuropathic pain or patients with central wind up. The challenge in cancer pain studies is ensuring that patient selection is optimized by identifying those patients with clinical phenomena suggestive of central wind-up. There is not sufficient evidence to recommend these drugs for any uncontrolled cancer-related pain and use should be reserved for treatment resistent pain.

Cannabinoids

Cannabinoids have recently been studied in several RCTs with positive outcomes.[27] There seems to be a bimodal response curve and an optimum dose has been established in cancer pain studies. Cannabinoids were generally well tolerated with gradually increasing doses. Side-effects include dizziness, drowsiness, impaired psychomotor function, dry mouth (especially during the run-in period), and other psychoactive effects, e.g. dysphoria.[28] Cannabinoid use is associated with concerns about abuse and addiction and also legal and regulatory issues. Cannabinoids have antiemetic effects and improve appetite and may therefore be considered for treating neuropathic pain associated with nausea and decreased appetite.[29–31] There is strong clinical suspicion that cannabinoids may be useful in resistant cancer-realted neuropathic pain and this is being investigated presently. The cannabinoid spary (Sativex) is licenced for cancer-related pain in Canada.

Capsaicin

Capsaicin is thought to act via the transient receptor potential vanilloid 1 (TRPV1) receptor and may deplete substance P from primary afferent nociceptors. Recently, studies have found at least a 12-week modest pain reduction after application of a single high-concentration capsaicin patch on painful polyneuropathy and post-herpetic neuralgia.[8 32] The effect size is rather small and the application of capsaicin is painful and may require prior application of a local anaesthetic. However, the treatment has a long-term effect and no (or limited) systemic exposure and systemic side-effects, suggesting that it may be a safe treatment option. Qutenza, a cutaneous patch of capsaicin 8%, has been given marketing authorization in Europe for 'treatment of peripheral neuropathic pain in non-diabetic adults' and Food and Drug Association has approved its use for post-herpetic neuralgia.[32] There are emerging data on use of this patch in chemotherapy-induced peripheral neuropathy.

Combination therapy

If treatment with a single drug is only partly effective, other drugs may be added. In patients with painful diabetic neuropathy or post-herpetic neuralgia, high-quality studies have documented greater pain relief and less pain interference with the combination of gabapentinoids and TCAs or opioids compared with single drugs alone.[24 33–35] Also in patients with cancer-related neuropathic pain, gabapentin (400 mg) in combination with imipramine (20 mg) as add-on therapy caused a greater pain reduction than in patients receiving one drug.[36] In a systematic review including also open-label studies, the addition of an antiepileptic or antidepressant to existing opioid analgesia was shown to result in modest improvement in pain but also significantly more adverse events.[37] While some combinations reduce side-effects, others may cause intolerable side-effects. Sedation, dizziness, nausea, and other side-effects need to be monitored carefully. It is important to be aware of specific side-effects such as the serotonergic syndrome that may occur when combining tramadol with SRIs.

It is generally preferable to minimize polypharmacy because of possible additive side-effects, risk of medication overuse, and non-compliance.[35] Therefore, when combination therapy is needed, sequential add-on therapy is recommended in patients who show a partial response to the first or both drugs given alone and a rational approach is to use drugs

with complementary modes of actions. During the course of pain treatment, the level and character of the pain, and side-effects should be monitored and dose adjustments should be made.

Non-pharmacological treatment

Physiotherapy may be indicated in some patients with neuropathic pain to alleviate complications related to immobility or to other effects of the disease. The evidence for the use of non-pharmacological management strategies (e.g. massage, acupuncture, fitness, and mind-body techniques) to enhance pain management of neuropathic pain associated with cancer has been summarized.[38]

General treatment principles

The assessment and treatment of chronic neuropathic pain requires careful consideration of frequently occurring co-morbidities. In particular, there is an increasing likelihood that patients will be elderly with physical co-morbidities in addition to the wider problems of all age groups such as depression, sleep disturbances, and psychosocial problems. Clearly, neuropathic pain associated with malignancy treatment will be further complicated by the potential co-administration of multiple drugs to manage a variety of symptoms. The diagnosis of neuropathic pain is not always easy and often co-exists with other types of pain, particularly in palliative care. Often, the site of disease gives the greatest clue to mechanisms in cancer pain of mixed aetiology. Whenever possible, the underlying disease should be treated. Symptomatic treatment of pain and related disability should be managed alongside any tumoricidal treatment.

At present, there is no good evidence for choosing a particular pharmacological management of neuropathic pain. Current research may eventually change this; however, for now, the approach should be based on likely tolerability combined with any likelihood of benefiting other symptoms.

Treatment algorithms

Ideally, there should be a reliable, predictable, easy to use treatment algorithm: however, presently, all decisions have to be individualized. The general principles of good medicine should be applied taking into account all co-morbidities and drug interactions. Most randomized controlled trials are performed in patients with diabetic polyneuropathy and postherpetic neuralgia; to what extent a treatment which is found effective in one condition can be expected to relieve another is unknown.[39] However, with the caveat of HIV-related pain, it seems likely.[40]

Treatment algorithms for neuropathic pain have recently been updated.[41–43] The most important considerations are: the expected side-effect profile, existing comorbidities, and coexisting symptoms which might also benefit from a particular drug. First-line treatments may fail because of the lack of analgesia or unacceptable side-effects. Alternatively, there may be a partial response and another agent may be added to manage the uncontrolled elements of pain. The goal is always maximum analgesia with fewest side-effects. In neuropathic pain conditions (apart from trigeminal neuralgia), TCA, SNRIs (duloxetine and venlafaxine) or calcium channel $\alpha_2\delta$ agonists (gabapentin or pregabalin) are the first drug choices. In patients with focal peripheral neuropathy with allodynia, a topical lidocaine patch is also a first-line drug. Antidepressants may be the first drug choice in patients with depression, and both TCAs and calcium channel $\alpha_2\delta$ agonists may be considered in patients with sleep disturbances. Pregabalin may be the first choice in patients with anxiety. Opioids are frequently co-prescribed in cancer neuropathic pain as the cause can be mixed; neuropathic pain rarely exists in isolation in active cancer. Switching from one opioid to another may improve pain relief. Combination therapy may be considered in patients with insufficient effect from one drug.

Pain impacts on all dimensions of quality of life[44–47] and is one of the most distressing symptoms for patients with cancer.[48 49] Pain may even in some situations predict survival.[50]

Pain in cancer survivors

Five-year survival rates for many types of cancer have improved over the last 40 years, exceeding 80% for some malignancies. The 5-year survival rate for all cancers is currently ~68%, compared with 50% in 1975. Several key advances in cancer treatment are responsible for this improvement. Combination chemotherapy has had a major impact, leading to increased survival time for many cancers; however, it is associated with painful peripheral neuropathies. New cancer-treatment supportive therapies are helping relieve problems caused by many chemotherapy drugs. Drugs that control nausea, vomiting, mouth sores, pain, and other issues are now widely available. Better chemotherapy tolerability can be associated with painful neuropathy sequelae, as it allows chemotherapy dose escalation and prolongation. Newer targeted therapies are a significant advance, acting on specific molecular changes that either cause cancer or allow it to progress. Because they are directed against very specific cellular mechanisms, targeted therapies tend to have fewer side-effects than chemotherapy, and are often very effective. Some of the most successful targeted therapies, such as the proteosome inhibitor, bortezomib, may also be very neurotoxic.

Up to 40% of 5-year cancer survivors report pain.[51 52] Experiencing pain was related to poorer general health ($P=0.001$) and physical ($P<0.001$), role ($P<0.01$), and social ($P<0.001$) functioning in a group of patients who had survived cancer.[53] CIPN is common (estimated 60 000 new cases per year in the UK) and challenging to manage (Table 2). Treatments explored[54] include: topical baclofen, amitriptyline and ketamine cream, vitamin E, topical menthol and a form of Transcutaneous Electrical Nerve Stimulation called 'Scrambler' therapy. However, no good evidence exists to support standard management with any of these treatments at present. A positive RCT for duloxetine in CIPN[55] has been reported recently. Topical capsaicin has been reported to be effective in post cancer surgery pain.[56]

Table 2 Cancer-treatment-related pain

Surgery
Post-mastectomy pain syndrome
Post-thoracotomy pain syndrome
Post-thoracotomy frozen shoulder
Post radical neck dissection pain
Post-surgery pelvic floor pain
Stump pain
Phantom pain
Chemotherapy
Painful peripheral neuropathy
Raynaud's syndrome
Bony complications of long-term steroids
Avascular (aseptic) necrosis of femoral or humeral head
Vertebral compression fractures
Radiation
Radiation-induced brachial plexopathy
Chronic radiation myelopathy
Chronic radiation enteritis and proctitis
Lymphoedema pain
Burning perineum syndrome
Osteoradionecrosis

Declaration of interest

None declared.

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