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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