Cancer-Related Neuropathic Pain: Review and Selective Topics

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KEYWORDS

• Neuropathic • Pain • Neuroinflammation • Neuroplasticity • Analgesics
• Cannabinoids

KEY POINTS

- Neuropathic pain arises from neuroinflammation and neuroplasticity involving the somatosensory system.
- Guidelines for treating cancer-related neuropathic pain rely on trials involving patients with noncancer neuropathic pain. Few trials are limited to cancer-related neuropathic pain.
- Opioid effectiveness in treating neuropathic pain is poorly defined with few high-quality studies. Combinations of antidepressants, anticonvulsants, and opioids are better than monotherapy and should be considered for patients not responding to single analgesics.
- Cannabinoids are popular, but benefits in managing neuropathic pain are not well defined with few high-quality trials. Many cannabinoids other than THC may have analgesic properties that should be explored.
- Scrambler therapy is a noninvasive modality with low risks as demonstrated in small single-arm studies.

INTRODUCTION

Neuropathic pain is defined by the International Association for the Study of Pain as "pain arising as a direct consequence of a lesion or disease which affects the somatosensory system."[1] Central neuropathic pain arises largely from spinal cord injury, demyelinating diseases, or transverse myelitis. Peripheral neuropathic pain arises from damage to peripheral nerves and is more common than central neuropathic pain. Peripheral neuropathic pain will likely increase as the elderly population increases, and because of the increased incidence of diabetes mellitus, cancer, and cancer treatment-related neuropathy. Treatable causes of neuropathic pain include nutritional deficiencies (B_{12}, thiamine), cancer-induced nerve compression, spinal

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cord compression, and brain metastases. Radiation-induced nerve damage and plexopathy, diagnostic and therapeutic surgery-induced injury, and paraneoplastic syndromes are not preventable and require palliation.[2]

Physical findings, symptoms, and radiographs define cancer pain syndromes[3] (See Russell K. Portenoy and Ebtesam Ahmed's article, "Cancer Pain Syndromes," in this issue, for a full discussion). Patients should be assessed for depression, insomnia, quality of life, and reduced function, which occur with increasing frequency in patients with neuropathic pain, and complicate management.

Epigenetic changes from nerve injury, neuronal microRNA (miRNA) changes, activation of certain histone deacetylases, and DNA (deoxyribonucleic acid) methylation contribute to neuropathic pain and diminish analgesic responses. These epigenetic changes are biomarkers and potential targets for personalized pain management.

Treatment algorithms for cancer-related neuropathic pain are largely based on noncancer-related neuropathic pain guidelines; there are few studies restricted to patients with cancer-related pain. Recent studies suggest that in patients with noncancer neuropathic pain, therapy can be directed by phenotyping pain using specific questionnaires and quantitative sensory testing. Additional research studies examine the role of functional MRI (fMRI) and magnetic resonance spectroscopy.

EPIDEMIOLOGY OF NEUROPATHIC PAIN IN CANCER

Several studies explore the prevalence and associated morbidities of neuropathic pain in patients with cancer. Of 371 patients surveyed using the neuropathic pain questionnaire, the Douleur Neuropathique en 4, one-third had mixed nociceptive and neuropathic pain. Individuals with neuropathic pain more often had depression and insomnia compared with those who had nociceptive pain. Patients with neuropathic pain had a greater frequency of incident pain (odds ratio [OR], 2.63) and spontaneous breakthrough pain (OR, 3.67), were more likely to have received chemotherapy (OR, 2.93) and/or undergone surgery (OR, 3.6), and were on adjuvant analgesics (OR, 2.93). Pain lasted greater than 3 months (OR, 2.35) more often, and was of greater intensity (OR, 1.47).[4]

In a second survey of more than 1000 patients, one-third of whom had neuropathic pain,[5] the most common descriptor "pins and needles" (65%) was associated with greater pain severity than nociceptive pain and poorer quality of life.

MECHANISMS OF NEUROPATHIC PAIN

Cancer, its treatment, or related infections damage inhibitory interneurons within the superficial lamina of the dorsal horn, and cause alterations in anterior cingulate and amygdala connections to periaqueductal gray and loss of downward inhibition from the periaqueductal gray to the dorsal horn through the dorsal funiculus, in part from neuroplasticity involving receptors and neurotransmitters or microglia activation (neuroinflammation).[6–9]

Dorsal horn A-beta low-threshold afferents change from mechanical to sensory sensors, causing allodynia. Neuromas form and spontaneously discharge causing lightning-like pain. Upregulation of surviving neuron sodium and voltage-gated calcium channels cause continuous dysesthesia, spontaneous breakthrough pain, and allodynia. Loss of repolarizing potassium channels leads to spontaneous pain. Central sensitization causes more widespread pain outside of the injured dermatome.

The periaqueductal gray facilitates transmission of pain signals when the balance between inhibition and facilitation ("off" and "on" cells, respectively) is lost. With chronic pain, increased wide dynamic range neuron activity within the spinal cord