Cancer is a significant public health problem worldwide. The global burden of cancer will continue to grow because of the growth of the world’s population, the aging of the population, and the increasing adoption of cancer-causing behaviors (smoking, physical inactivity, and “westernized” diets) in developing countries. Based on recent estimates, about 12.7 million cancers and 7.6 million cancer deaths occurred worldwide in 2008. While incidence rates for all cancers combined in economically developed countries are nearly twice as high as in developing countries in both males and females, death rates for all cancers combined in developed countries are only 21% higher in males and only 2% higher in females. In males, lung, prostate, and colorectal cancers account for the largest percentage of new cases, and lung, liver, and stomach cancers account for the largest percentage of deaths, worldwide. In females, breast, colorectal, and cervical/uterine cancers account for the largest percentage of new cases, and breast, lung, and colorectal cancers account for the largest percentage of cancer deaths, worldwide. Each of these cancers is associated with significant pain related to the disease or its treatment.

Prevalence and Undertreatment of Cancer Pain

Patients with cancer may experience acute and chronic pain as a result of their disease or its treatment, as well as pain unrelated to their cancer. In a recent systematic review of 52 studies, pooled prevalence rates for cancer pain were reported for four subgroups of patients: (1) studies that included patients after curative treatment, 33% (95% confidence interval [CI] 21% to 46%); (2) studies that included patients on cancer treatment, 59% (CI 44% to 73%); (3) studies that included patients with advanced or metastatic disease, 59% (CI 44% to 73%); and (4) studies that included patients at all stages of their disease, 53% (CI 43% to 63%). Across all of the studies evaluated, approximately 33% of the patients reported pain in the moderate to severe range. These findings suggest that cancer pain is a significant problem for a large percentage of patients and that it is often undertreated. Several forms of chronic pain can be distinguished. Somatic nociceptive pain results from tissue damage and activation of nociceptors that innervate the skin, the ligaments, small joints, muscles, and tendons and is usually characterized by a well-localized pain. Visceral nociceptive pain, often characterized by colic, occurs in the hollow organs, mesenterium, capsules, and some parenchyma (e.g., the pancreas).

In addition to these nociceptive types of pain, chronic pain can also occur if the nervous system itself is damaged, which in the case of cancer may occur by tumor...
Neuropathic pain is defined as “pain arising as a direct consequence of a lesion or disease affecting the somatosensory system.”

Cancer–Related Neuropathic Pain Syndromes

Common neuropathic pain syndromes are listed in Table I.

<table>
<thead>
<tr>
<th>Table I</th>
<th>Cancer-related neuropathic pain syndromes</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Cancer-Related Neuropathic Pain</strong></td>
<td>Paraneoplastic neurological syndromes</td>
</tr>
<tr>
<td></td>
<td>Tumor/metastasis infiltration or compression of the peripheral nervous system (e.g., nerves and plexuses)</td>
</tr>
<tr>
<td></td>
<td>Tumor/metastasis infiltration or compression of the central nervous system (e.g., spinal cord compression)</td>
</tr>
<tr>
<td><strong>Cancer-Therapy-Induced Neuropathic Pain</strong></td>
<td>Surgical interventions (e.g., postmastectomy pain)</td>
</tr>
<tr>
<td></td>
<td>Radiation treatment (e.g., plexopathies)</td>
</tr>
<tr>
<td></td>
<td>Chemotherapy-induced peripheral neuropathy (CIPN)</td>
</tr>
<tr>
<td><strong>Cancer-Associated Neuropathic Pain</strong></td>
<td>Postherpetic neuralgia</td>
</tr>
</tbody>
</table>

Cancer–Related Neuropathic Pain

Paraneoplastic neurological syndromes sometimes occur in association with a malignancy and are not due to the presence of metastases or direct infiltration of the cancer into the nervous system. The most frequent neurological manifestation is a peripheral neuropathy. Paraneoplastic neuropathy patients can be categorized into two groups. One group will have signs and symptoms of a predominant loss of large fibers, with dysesthesia, numbness, sensory ataxia, and sometimes pain. In the other group, a predominant loss of small fibers leads to marked neuropathic pain, often with mechanical hyperalgesia and allodynia. The diagnosis of these neurological syndromes is of particular importance because it potentially enables the early detection of the underlying malignancy. Other cancer-related neuropathic pain syndromes result from a direct tumor/metastasis infiltration or compression of nerves and plexus (peripheral neuropathic pain) or of the central nervous system (e.g., tumor involvement of the spinal cord). One example is spinal cord compression, which occurs in approximately 5–10% of oncology patients. It is the result of metastasis to the vertebral bone or direct extension of the tumor into the epidural space. Diffuse back pain is usually the presenting symptom in spinal cord compression.

Cancer Therapy–Induced Neuropathic Pain

Neuropathic pain can arise as a side effect or complication of therapeutic interventions. During surgical interventions, peripheral nerves often cannot be adequately protected. Such post-traumatic neuropathic pain syndromes develop frequently after mastectomy or thoracotomy. Chronic pain occurs in 25–50% of patients following thoracotomy and about 25–60% of patients following surgery for breast cancer. Another example is phantom limb pain or stump pain. Radiotherapy—which can lead to fibrotic changes in peripheral nerves or plexuses—can induce neuropathic pain, which in some cases can begin months and years after radiation treatment. Chemotherapy-induced peripheral neuropathy (CIPN) is the most prevalent neurological complication and a major dose-limiting side effect of chemotherapeutic agents (Tables II, III). The incidence of CIPN can be variable, with estimates ranging from 10% to 100%. These widely varying rates are dependent on a number of factors including the chemotherapy itself, the patient’s age, the cumulative dose, dose intensity, treatment duration, coadministration of other neurotoxic drugs, and preexisting neuropathy of other origin, such as diabetes mellitus.

Neuropathic pain can arise as a side effect or complication of therapeutic interventions

CIPN can affect small and large peripheral nerve fibers. Clinical symptoms of large-fiber damage include numbness, difficulties with fine motor skills due to less of afferent feedback, decreases in sense of vibration and proprioception, and progressive loss of deep tendon reflexes. Symptoms of small-fiber loss include burning pain and decreased nociceptive and thermal perception. The pain can be so excruciating that some patients are unable to complete the optimal treatment regimen (e.g., bortezomib).

Cancer–Associated Neuropathic Pain

Acute herpes zoster is more likely to occur in cancer patients than in the general population because of the higher incidence of immunosuppression in cancer patients. Approximately 25% to 50% of patients develop postherpetic neuralgia following an acute infection.

<table>
<thead>
<tr>
<th>Table II</th>
<th>Common cancer chemotherapy drugs associated with peripheral neuropathy</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Bortezomib</strong></td>
<td>Platinum compounds (cisplatin, carboplatin, oxaliplatin)</td>
</tr>
<tr>
<td><strong>Taxanes</strong> (paclitaxel, docetaxel)</td>
<td>Thalidomide, lenalidomide</td>
</tr>
<tr>
<td><strong>Vinca alkaloids</strong> (vincristine, vinblastine, vindesine, vinorelbine)</td>
<td></td>
</tr>
</tbody>
</table>

Diagnosis

As noted in a recent review, there is a critical need to develop a more reliable and systematic assessment of neuropathic pain in cancer patients in order to better characterize the various types of pain and to facilitate the development and evaluation of mechanistically based therapies.

The assessment of neuropathic pain requires a detailed pain history and physical examination. The detailed pain history should include questions about onset and temporal pattern, description, location (with the use of a body map), intensity, aggravating and relieving factors, previous and current pharmacological and
nonpharmacological treatments and their effectiveness, and the impact of pain on function. Particular attention should be given to having patients rate the quality of their pain using standardized measures such as the McGill Pain Questionnaire\textsuperscript{11} or the Pain Qualities Assessment Scale.\textsuperscript{12}

There is a critical need to develop a more reliable and systematic assessment of neuropathic pain in cancer patients

Several scales have been developed to evaluate various symptoms associated with neuropathic pain, including the Leeds Assessment of Neuropathic Pain,\textsuperscript{13} the Pain Neurotoxicity Questionnaire,\textsuperscript{14} and painDETECT.\textsuperscript{15} These scales include patient self-reported data, as well as various components of a physical examination. The common denominators across these questionnaires include a common set of descriptors (sensations of pins and needles, heat or burning, impaired temperature sensitivity, numbness, and electric shock-like sensations; whether or not the pain becomes worse with touch, and whether the joints are painful).\textsuperscript{10}

A careful clinical examination is needed to support the findings from the detailed pain history.\textsuperscript{16} Sensory testing with simple tools is an important part of the clinical examination and should include components such as touch, pinprick, pressure, cold, heat, and vibration. In addition to the sensory examination, clinicians should evaluate motor function (muscle strength and tone), deep tendon reflexes, and cranial nerve function (Table IV). Electrophysiological techniques, quantitative sensory testing, skin and nerve biopsies, and magnetic resonance imaging can be useful to help the attenuation of neuronal function and detect lesions of the central or peripheral nervous system.\textsuperscript{17}

Management of Neuropathic Pain in Patients with Cancer

The management of nociceptive cancer pain should usually follow the World Health Organization (WHO) analgesic ladder for cancer pain relief. These guidelines can relieve 80% of nociceptive cancer pain.\textsuperscript{18} Cancer-induced bone pain and neuropathic pain conditions are often much more difficult to treat and require

\begin{table}[h]
\centering
\begin{tabular}{|c|c|c|c|c|c|}
\hline
Chemotherapy & Sensory Findings & Pain Character & Motor Findings & Autonomic Findings & Reflexes & Recovery \\
\hline
Cisplatin & Paresthesia, vibration ↓, proprioception ↓, thermal sensation ? & Dysesthesia & Normal & Rare (orthostatic dysregulation) & Reduced & Some recovery, but sometimes there is progression after the end of treatment \\
\hline
Carboplatin & Similar to cisplatin & Similar to cisplatin & Similar to cisplatin & Similar to cisplatin & Similar to cisplatin & \\
\hline
Oxaliplatin (acute) & Similar to cisplatin & Dysesthesia, cold allodynia, mechanical hyperalgesia & Muscle cramps & Normal & Normal & Recovery after a few days \\
\hline
Oxaliplatin (chronic) & Similar to cisplatin & Similar to cisplatin & Similar to cisplatin & Similar to cisplatin & Similar to cisplatin & Similar to cisplatin \\
\hline
Paclitaxel, docetaxel & Paresthesia, proprioception ↓, vibration ↓, thermal and mechanical sensation ↓ & Dysesthesia, burning pain, paradoxical heat sensation & Rare (proximal > distal weakness) & Rare (orthostatic dysregulation) & Reduced & Generally no recovery, and progression is possible \\
\hline
Vinblastine, vincristine, vindesine, vinorelbine & Proprionceptive ↓, vibration ↓, thermal and mechanical sensation ↓ & Dysesthesia, burning, pricking pain & Distal accentuated weakness & Orthostatic dysregulation, constipation, impotence & Reduced & Generally after finishing treatment \\
\hline
Bortezomib & Proprionceptive ↓, vibration ↓, mechanical and thermal sensation ↓ & Dysesthesia, burning, electrical pain & Rare (distal weakness) & Rare & Reduced & Generally after finishing treatment \\
\hline
Thalidomide & Paresthesia, proprioception ↓, vibration ↓, mechanical and thermal sensation ↓ & Dysesthesia & Rare (weakness) & Rare & Reduced & ? \\
\hline
\end{tabular}
\caption{Clinical findings for chemotherapeutic substances}
\end{table}
Neuropathic Pain

Neuropathic pain is a significant clinical problem in patients with cancer. It can occur as a result of the disease itself or may be associated with cancer treatment. Management of neuropathic cancer pain is different from the management of nociceptive cancer pain and requires a different treatment approach from that recommended in the WHO analgesic ladder for cancer pain relief. Most of the pharmacological and nonpharmacological interventions that are used to manage neuropathic cancer-related pain have been evaluated in other neuropathic pain conditions. Their use in neuropathic cancer-related pain was extrapolated from these studies. However, the mechanisms that underlie the development of neuropathic pain in patients with cancer may be distinct, and they warrant investigation in animal and human studies. Additional research is necessary to characterize the distinct circumstances that occur in cancer patients and to determine the most efficacious treatments for each of these neuropathic pain problems. All these scientific and clinical efforts must take into account the

Prevention and Management of Chemotherapy-Induced Peripheral Neuropathy

A wide variety of agents have been evaluated for the prevention and management of symptoms associated with CIPN. The majority of these studies are limited by relatively small sample sizes, heterogeneous patient populations, and a lack of standardized subjective and objective outcome measures. Rigorously designed clinical trials, enrolling appropriate oncology patients in adequate numbers, using standardized measures, and including longitudinal follow-up, are needed to evaluate agents for efficacy and safety in the management of CIPN.

Rigorously designed clinical trials are needed to evaluate agents for efficacy and safety in the management of chemotherapy-induced peripheral neuropathy

Pharmacological Management of General Neuropathic Pain

The best therapeutic approach is a stepwise process to identify which drugs or drug combinations provide the greatest pain relief with the fewest side effects. Three main types of drugs (anticonvulsants, opioids, and antidepressants) and add-on medications such as topical lidocaine and capsaicin have shown consistent efficacy in clinical trials and meta-analyses on neuropathic noncancer pain.

Anticonvulsants

Anticonvulsants are used in the management of neuropathic pain in patients with cancer. Probably the most widely evaluated drug is gabapentin, which has demonstrated efficacy in other neuropathic pain conditions such as diabetic neuropathy and postherpetic neuralgia. Gabapentin has shown some efficacy in the management of neuropathic cancer pain. However, in a Phase 3 placebo-controlled trial of patients with CIPN from platinum compounds, taxanes, and vinca alkaloids, gabapentin was not effective in reducing mean pain scores or improving patients’ quality of life. Additional anticonvulsants that were evaluated in the management of CIPN and failed to demonstrate efficacy include pregabalin, lamotrigine, and valproic acid.

Opioid Analgesics

Opioid analgesics are used to manage neuropathic pain, and their efficacy has been reported in several randomized controlled trials in central and peripheral neuropathic pain.

Antidepressants

Tricyclic antidepressants and selective serotonin norepinephrine reuptake inhibitors (venlafaxine and duloxetine) have demonstrated efficacy in the management of painful diabetic neuropathy and postherpetic neuralgia.

Topical Treatment

Topical lidocaine (5% lidocaine patch) and a high-concentration capsaicin patch (8%) have shown efficacy and good tolerability in many studies with different types of peripheral neuropathic pain and postherpetic neuralgia.

Nonpharmacological Management of Cancer-Related Neuropathic Pain

In an excellent review, Cassileth and Keefe summarize the evidence for the use of massage, acupuncture, hypnosis, mirror therapy, and cognitive restructuring in the management of neuropathic pain associated with cancer. The advantages of these complementary approaches is that they are inexpensive, safe, and noninvasive, and (with the exclusion of acupuncture) they have no side effects. These techniques can be used in combination with pharmacological approaches to enhance pain management.

Summary

Neuropathic pain is a significant clinical problem in patients with cancer. It can occur as a result of the disease itself or may be associated with cancer treatment. Management of neuropathic cancer pain differs from the management of nociceptive cancer pain and requires a different treatment approach from that recommended in the WHO analgesic ladder for cancer pain relief. Most of the pharmacological and nonpharmacological interventions that are used to manage neuropathic cancer-related pain have been evaluated in other neuropathic pain conditions.
special situation of patients with cancer and their potentially limited lifespan. The benefits of treatment must be carefully weighed against the patient’s quality of life.

References


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