REVIEW

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Neuropathic cancer pain: prevalence, pathophysiology, and management

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Neuropathic cancer pain (NCP) is caused by nerve damage attributable to the cancer *per se*, and/or treatments including chemotherapy, radiotherapy, and surgery; the prevalence is reported to be as high as 40%. The etiologies of NCP include direct nerve invasion or nerve compression by the cancer, neural toxicity, chemotherapy, and radiotherapy. NCP is subdivided into plexopathy, radiculopathy, and peripheral neuropathies, among several other categories. The clinical characteristics of NCP differ from those of nociceptive pain in terms of both the hypersensitivity symptoms (burning, tingling, and an electrical sensation) and the hyposensitivity symptoms (numbness and muscle weakness). Recovery requires several months to years, even after recovery from injury. Management is complex; NCP does not usually respond to opioids, although treatments may feature both opioids and adjuvant drugs including antidepressants, anticonvulsants, and anti-arrhythmic agents, all of which improve the quality-of-life. This review addresses the pathophysiology, clinical characteristics and management of NCP, and factors rendering pain control difficult.

Keywords: Neuralgia; Neoplasms; Chemotherapy drugs

INTRODUCTION

Cancer pain affects approximately 70% of those with advanced disease; over half experience moderate-to-severe pain and under-treatment is common [1]. Pain intensity is often underestimated and the etiology poorly understood. A failure to identify the pain mechanism in play and subsequent inappropriate management is of particular concern when treating those with neuropathic cancer pain (NCP); opioids alone are often ineffective, and the addition of adjuvant analgesics is essential [2]. NCP is a debilitating sequela of cancer *per se* and cancer treatment. NCP is common because advances in chemotherapy, surgery, and radiotherapy have significantly prolonged survival [3]. NCP management is ineffective in many cancer patients. Here, we briefly review the etiologies, prevalence, clinical characteristics and pathophysiology of NCP, and appropriate management strategies.

Definition and clinical characteristics of NCP

NCP is pain caused by direct damage to the nervous system. A nerve can be infiltrated or compressed by a tumor, or strangulated by fibrosis [4]. Once a peripheral nerve is damaged, the pain fibers become abnormally sensitive, triggering spontaneous pain that is amplified in the spinal cord; even a minor stimulus such as a touch can trigger pain (allodynia). The pain may persist for months or years after damaged tissue has healed. In such a setting, pain no longer reflects ongoing injury but, rather, a malfunctioning nervous system. NCP is part of a larger spectrum of neuropathy caused by the cancer *per se*, treatment, paraneoplastic syndrome, and comorbidities such as diabetic polyneuropathy and

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postherpetic neuralgia. Here, we focus on NCP caused by cancer *per se* and chemotherapy-induced peripheral neuropathy (CIPN) [5]. NCP is one of the three main types of cancer pain (the others are somatic and visceral pain). There are two principal forms of pain pathophysiology: nociceptive and neuropathic. NCP is nerve-related (typically neuron-related) pain characterized as a burning or electrical sensation; however, NCP sometimes manifests as decreased sensation or actual muscle weakness [6]. In clinical settings, both hypersensitivity and hyposensitivity symptoms often coexist. NCP is often a part of a mixed syndrome with other types of pain including somatic or visceral pain. NCP is chronic and often manifests as persistent background pain with acute exacerbations of breakthrough pain several times daily. The breakthrough pain is often spontaneous, but can also be triggered by movement, touch, cold, and heat. Such spontaneous or triggered pain is perceived as a sensory abnormality (i.e., hyposensitivity, hypersensitivity, or both), although paresthesia (an abnormal sensation, such as tingling, an electric shock, or burning) may also be considered a typical hypersensitivity symptom. Allodynia is a type of pain evoked by non-painful stimulation, such as a touch; hyperalgesia (increased response to a stimulus that is not normally painful) is often evident. Hyposensitivity symptoms such as diminished or absent cutaneous sensations often present with balance/gait disturbances. Reduced sensation compromises fine motor skills such as the use of chopsticks or buttoning of shirts.

In contrast, nociceptive pain is the result of injury to somatic and visceral structures, followed by activation of nociceptors in skin, the viscera, muscles, and connective tissue. Nociceptive pain can be divided into somatic and visceral pain. Somatic nociceptive pain is sharp, well-localized, throbbing, and pressure-like. However, visceral nociceptive pain developing secondary to compression, infiltration, or distention of the abdominal or thoracic viscera is often described as more diffuse, less localized, ache-like, and cramping in nature [4]. Table 1 summarizes the differences between neuropathic and nociceptive pain in terms of pathophysiology, symptoms and signs, duration, and impact on the quality-of-life.

Prevalence

Some types of NCP, such as spinal cord compression accompanied by motor and sensory changes, and tumor infiltration of the cord confirmed by imaging, are definitive. However, other NCPs are mixed with somatic or visceral nociceptive cancer-related pain; appropriate diagnostic standards remain to be established. Thus, few prospective data on the prevalence of NCP and the underlying mechanism(s) are available. An extensive meta-analysis of over 10,000 patients was published in 2012; the prevalence of NCP, both pure and mixed, was approximately 39% [3]. The prevalence rates of pure neuropathic pain, mixed pain, and pure nociceptive pain are approximately 19%, 20%, and 59%, respectively. The prevalence of NCP has been reported to be as high as 40% among cancer patients. The cited meta-analysis explored NCP etiologies. Sixty-four percent of NCP was caused by cancer *per se*, and 20% by treatments such as chemotherapy, radiotherapy, and cancer surgery. Notably, these proportions differed from those of all cancer pain caused by treatment (only 10%), suggesting that a higher proportion of NCP was caused by treatment(s).

A cross-sectional Dutch study reported that 23% of oncology outpatients (204/892) experienced moderate-to-severe pain [7] and 19% exhibited neuropathic symptoms (170/892). However, the NCP prevalence increased to over 40% in patients with moderate-to-severe pain, affecting the activities of daily life more severely than was the case for patients without neuropathic pain (mean interference score 4.7 vs. 4.17, $p = 0.054$). Even patients with mild neuropathic pain experienced significant interference with the activities of daily life. Despite the high prevalence and severity of such pain, only 8% were taking adjuvant analgesics.

Recently, a Korean, multicenter, cross-sectional observational study explored the prevalence and impact of NCP on the quality-of-life of cancer patients [8]. The prevalence of NCP of score ≥ 1 on a visual analog scale (VAS) was 36.0% (722/2,003). Approximately 20% of all patients reported moderate-to-severe pain. Importantly, those with VAS scores ≥ 4 exhibited a higher prevalence of NCP than did those with mild pain (42.4% vs. 27.4%). Cancer patients with NCP reported more high-level pain, more severe interference with the activities of daily life, and a poorer quality-of-life, than did those without NCP. However, only 49.6% of patients

Table 1. Differential diagnosis of neuropathic and nociceptive pain

	Neuropathic pain	Nociceptive pain	
		Somatic pain	Visceral pain
Pathophysiology	Injured nervous system Peripheral nerve, spinal cord Central nervous system	Injured muscle, bone, connective tissue	Compression, infiltration, distention of viscera
Symptoms	Dysesthesia/paresthesia: tingling, burning, electric shock like, lancinating Hypoesthesia: numbness resulting in balance disturbance, difficulty in fine motor skills, muscle weakness	Sharp and aching Well localized, throbbing, pressure like	More diffuse, less localized, dull and aching cramping colicky
Signs	Hypersensitivity: allodynia, hyperalgesia Hyposensitivity: diminished cutaneous sensation to vibration, temperature, pain, light touch	Referred pain to adjacent or distal part of the body	
Duration	Month to years Pain lasts beyond expected period of healing	Weeks to months Pain resolves upon healing of tissue injury	
Interference of daily life	Often more severe than nociceptive pain	Less severe than neuropathic pain	
Response to opioids	Unsatisfactory	Often responds well to opioids and pain medications	
Managements	Almost always needs combination therapy Adjuvant drugs (anticonvulsants, antidepressants) with opioids	Opioids with or without adjuvant analgesics	

with moderate-to-severe NCP received adjuvant analgesics including antidepressants and anticonvulsants. Similarly, the NCP prevalence in a Western study was approximately 40%; both the quality-of-life and the extent of interference with daily activities were more severely affected in patients with than without NCP [9]. In both Korea and Western countries, adjuvant drugs are under-prescribed.

In summary, the prevalence of NCP remains high, interfering significantly with the activities of daily life, and current management strategies are inadequate [3,7-10].

Etiology of NCP

NCP can be caused by direct cancer invasion or nerve compression, and/or cancer treatments including surgery, chemotherapy, and radiotherapy. NCP is divided into several categories: plexopathy, radiculopathy, peripheral neuropathy, paraneoplastic sensory neuropathy, leptomeningeal metastasis, cranial neuralgia, and malignant painful radiculopathy (Table 2) [5,11,12]. Awareness of the various types of NCP improves diagnosis, treatment, and outcomes. Cancer pain is often of a mixed nature or, if it is purely neuropathic, may be one of several pains experienced. NCP caused by the tumor *per se* usually involves both nociceptive and neuropathic components, and mixed pain is more common than NCP caused by cancer treatments [13]. Most NCP caused by chemotherapy is purely neuropathic in nature [14]. Various surgeries, such as mastectomy, neck lymph node dissection, laparotomy and thoracotomy, cause neuropathic pain. Occasionally, surgery-related NCP can become chronic, although improving over time.

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Table 2. Common etiologies of neuropathic cancer pain

Cancer related neuropathic pain
Radiculopathies (lumbosacral, cervical, thoracic radiculopathy)
Plexopathies (cervical, brachial, lumbosacral, coccygeal plexopathy)
Peripheral neuropathies
Cranial neuralgia (glossopharyngeal, trigeminal neuralgia)
Leptomeningeal seeding
Tumor related bone pain[a]
Spinal cord compressions
Treatment related neuropathic pain
Chemotherapy induced peripheral neuropathies
Chronic post-surgical pain syndromes: post-mastectomy, post-neck dissection, post-thoracotomy
Post radiation pain syndrome: radiation-induced brachial plexopathies, radiation myelopathy, lymphedema pain

[a]Tumor related bone pain is mixed type of neuropathic pain (somatic plus neuropathic).

CIPN: types, symptoms, mechanisms, and duration

CIPN is a common problem in cancer patients because survival has been significantly prolonged by advances in chemotherapy; however, neither the level of awareness of CIPN nor the management thereof is adequate. CIPN affects both the quality-of-life and eventual outcomes because of treatment delays, dose reductions, and drug discontinuation [15]. Many chemotherapeutic agents can cause CIPN, of which the most common are platinum agents (cisplatin, oxaliplatin, and carboplatin); the taxanes (taxol and docetaxel); and the *vinca* alkaloids (vincristine and vinorelbine) [16,17]. The symptoms range from early post-treatment pain, such as paclitaxel induced acute pain syndrome (P-APS) [18-20] and cold allodynia after oxaliplatin infusion, to chronic peripheral sensory neuropathy featuring tingling, pain, and decreased sensation [21-23]. CIPN is usually a dose-dependent, cumulative side-effect exhibiting a glove-stocking distribution. CIPN symptoms include sensory loss, paresthesia, dysesthesia and pain, sometimes accompanied by muscle weakness [16,24-26].

Paclitaxel is a chemotherapeutic agent used to treat breast, ovarian, lung, and head-and-neck cancer, and is associated with two types of neuropathic pain: P-APS (acute type) and a classical peripheral neuropathy (chronic type). P-APS occurs within days after each dose and usually also abates within days; it was earlier termed paclitaxel-induced arthralgia/myalgia, and has recently been named P-APS. This syndrome, described in up to 70% of patients, usually develops within 1 to 3 days of paclitaxel administration; however, the symptoms largely resolve within 7 days [19,24,26].

Oxaliplatin is a new-generation platinum compound widely used to treat various cancers including colorectal, stomach, and pancreatic cancers. Oxaliplatin-induced peripheral neuropathy is an acute prickly dysesthesia affecting the hands and feet, combined with spontaneous pharyngolaryngeal dysesthesia often triggered by cold. The conditions develop during oxaliplatin infusion and subside within few days. Oxaliplatin-induced early acute dysesthesia occurs in up to 90% of patients. Simply opening the door of a refrigerator or drinking cold water can induce a painful prickly sensation. Such oxaliplatin-induced, acute cold allodynia resembles P-APS. On repeated infusion, oxaliplatin-induced CIPN can include decreased feeling in the hands and feet, impairing balance and the sensing of vibration and touch [21,22].

CIPN mechanisms include disruption of axonal transport, changes in ion channel and receptor activities, neuronal injury and inflammation, oxidative stress, and mitochondrial damage [16]. Taxane, platinum, and vincristine affect the peripheral sensory neurons of the dorsal root ganglia (DRG) and the spinal cord; they are toxic to DRG neurons, and increase the activities of both voltage- and ligand-gated ion channels (the sodium, calcium, and transient receptor potential channels). Despite the common pathogenic pathways, taxane and vincristine trigger inflammation of the dorsal horn of the spinal cord more strongly than do platinum compounds. Taxane and vincristine activate cord microglia, astrocytes, and satellite glial cells, triggering release of tumor necrosis factor and interleukin-1β.

Unfortunately, CIPN can persist for several months to years, even after discontinuation of chemotherapy, and may never be completely eliminated. The symptoms and durations of CIPN are summarized in Table 3.

NCP assessment

Pain is very subjective and it is not always easy to ap-

Table 3. Characteristics of chemotherapy-induced neuropathic pain

Drugs	Type	Symptoms	Onset	Duration, recovery
Common	Chronic	Pain, cramps, numbness, tingling, paresthesia	Days to weeks	Over months to years
Taxane	Acute (P-APS)		Hours	3 to 5 days
	Chronic		Within days	6 to 24 months 25% no recovery
Platinum	Acute[a]	Cold induced	Hours	3 to 5 days
	Chronic		1 month	Over months to years Some resolution
Vincristine	Chronic		2 to 3 weeks	1 to 3 months Up to 2 years

P-APS, paclitaxel induced acute pain syndrome.
[a]Oxaliplatin induced acute cold allodynia.

proach patients complaining of pain. If NCP is diagnosed, the pain should have the characteristics of neuropathic pain, must be caused by a distinct lesion or disease of the somatosensory system, and should be assessed using electrophysiological tests to determine objectively the extent of nerve damage.

Grading system

In 2008, neuropathic pain was defined as, "Pain arising as a direct consequence of a lesion or disease affecting the somatosensory system," by the International Association for the Study of Pain (IASP) Special Interest Group on Neuropathic Pain (NeuPSIG) [6], which developed a three-level grading system. "Possible" neuropathic pain is pain associated with a history of relevant neurological lesion(s) or disease if the pain distribution is neuroanatomically plausible. If neurological examination reveals sensory signs associated with the pain distribution, neuropathic pain is "probable." "Definite" neuropathic pain requires diagnosis of a lesion or disease of the somatosensory nervous system that explains the pain [27].

In patients with a history of chemotherapy and subsequent complaints of tingling sensations, the pain is suspected to be CIPN if the chemotherapeutic agent used is known to be neuropathic, and the sensory symptoms are symmetrically distributed in the distal fingers or toes (the common phenotype of toxic neuropathy). If bedside neurological examination reveals negative sensory symptoms (e.g., numbness) or positive sensory symptoms (e.g., burning pain, allodynia, and hyperalgesia) in the distal fingers or toes, CIPN is "probable." "Definite" CIPN requires objective diagnosis of a lesion in the somatosensory system. Electrophysiological studies, skin biopsies, and quantitative sensory testing (QST) are used to this end. The same rules apply when evaluating a patient with trigeminal neuralgia caused by tumor infiltration of the trigeminal nerve or radicular pain with a pathological spinal fracture.

Screening and assessment questionnaires

Several specific questionnaires seek to differentiate neuropathic from nociceptive pain. As cancer pain is often mixed in nature, questionnaires can be useful to determine whether the pain is neuropathic. For clinical screening, all of the Leeds Assessment of Neuropathic Symptoms and Signs (LANSS), the Douleur Neuropathique en 4 Questions (DN4), and painDETECT, are helpful. The LANSS features five symptom items and two bedside examination items [28]. At a cut-off score > 12, the Korean version of the LANSS had a sensitivity of 72.6% and a specificity of 98.0% [29]. S-LANSS, a self-reporting form of LANSS, has been used in epidemiological studies on general populations. The DN4 is composed of seven symptom items and three clinical examination items. A total score > 4 suggests neuropathic pain [30]. The Korean version of the DN4 effectively distinguished neuropathic and nociceptive chronic back pain [31]. The DN4 exhibited high sensi-

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Table 4. Neuropathic Pain Symptom Inventory

Severity of the spontaneous pain		
Q1. Does your pain feel like burning?		
Q2. Does your pain feel like squeezing?		
Q3. Does your pain feel like pressure?		
Q4. During the past 24 hours, your spontaneous pain has been present: Permanently/8 to 12 hours /4 to 7 hours/1 to 3 hours/< 1 hour		
Severity of the painful attacks		
Q5. Does your pain feel like electric shocks?		
Q6. Does your pain feel like stabbing?		
Q7. In the past 24 hours how many of these pain attacks have you had? > 20 hours/11 to 20 hours/6 to 20 hours/1 to 5 hours/none		
Severity of your provoked pain		
Q8. Is your pain provoked or increased by brushing on the painful area?		
Q9. Is your pain provoked or increased by pressure on the painful area?		
Q10. Is your pain provoked or increased by contact with something cold on the painful area?		
Severity of abnormal sensations		
Q11. Do you feel pins and needles?		
Q12. Do you feel tingling?		
Total intensity score	Subscores	
1. Q1 =	1. Burning (superficial) spontaneous pain:	Q1 =
2. (Q2 + Q3) =	2. Pressing (deep) spontaneous pain:	(Q2 + Q3) / 2 =
3. (Q5 + Q6) =	3. Paroxysmal pain:	(Q5 + Q6) / 2 =
4. (Q7 + Q8 + Q9) =	4. Evoked pain:	(Q8 + Q9 + Q10) / 3 =
5. (Q11 + Q12) =	5. Paresthesia/dysesthesia	(Q11 + Q12) / 2 =
(1 + 2 + 3 + 4 + 5) = /100		

Select "0" if you have not felt such pain, or "10" if you have feel it the worst.

tivity when used to identify NCP 6 months after breast cancer resection, predicting that the paravertebral block effect was a risk factor for such pain [32]. PainDETECT is a self-reporting questionnaire with nine items, originally developed to detect the neuropathic component of chronic lower back pain [33]. This tool reliably distinguished neuropathic components among various causes of chronic pain. However, the questionnaires should not replace neurological examination and assessment, despite the fact they are easy to use.

When characterizing multiple neuropathic phenotypes, assessment questionnaires are useful. The European Federation of Neurological Societies recommended use of the Neuropathic Pain Scale (NPS) and the Neuropathic Pain Symptom Inventory (NPSI) to evaluate the effects of treatment on neuropathic symptoms [34]. The NPS does not explore a number of pain features commonly observed in those with neuropathic pain, and is fully validated only for multiple sclerosis patients [35]. The NPSI is a self-reporting 12-item questionnaire specifically designed to evaluate the symptoms of neuropathic pain [36], exploring 10 descriptors of spontaneous ongoing pain (burning, squeezing, and pressure), paroxysmal pain (electric shock and stabbing sensations), evoked pain (by brushing, pressure, or contact) and dysesthesia/paresthesia (pins and needles, tingling), each of which is quantified on a scale of 0 to 10. In addition, the duration of spontaneous ongoing and paroxysmal pain are assessed (Table 4). The NPSI is useful for defining subgroups of patients with neuropathic pain, and in the follow-up of responses to pharmacological treatment or other therapeutic interventions.

Clinical examination

During sensory examination, the functions of the large and small sensory nerve fibers are separately assessed. Patients with large-fiber involvement complain of numbness, a feeling that mud is stuck to the foot, or a sensation that they walk on a gravel road. Those with small-fiber involvement complain of painful burning sensations with shooting pain, and exhibit symptoms of autonomic dysfunction. As neuropathic pain is usually caused by a lesion or damage to small-diameter nerve fibers, a thorough sensory examination focusing on both pain and thermal sensation is important. Touch and vibration detected by large sensory (Aβ) fibers can be evaluated using a cotton bud or a brush, and a tuning fork, respectively. A pin or toothpick are used to evaluate pinprick sensing. Thermal sensitivity can be tested using tubes filled with warm or cold water, but is not commonly performed at the bedside, having been replaced by the pinprick test, which shares a common anatomical pathway. Skin color changes and/or the Raynaud phenomenon caused by vasomotor dysfunction may be observed in patients with neuropathic pain.

Confirmatory tests

Conventional nerve conduction and evoked potential studies assess only large myelinated nerve fibers; they do not detect damage to small fibers. Laser-evoked potentials stimulate skin Aδ fibers and can be used to assess the integrity of the peripheral free nerve endings of the sensory cortex [37]. However, the technique is available only in dedicated pain clinics or research laboratories. QST can be employed to assess the functionality of both large and small fibers. QST evaluates both negative symptoms and positive sensory phenomena by measuring the thresholds of pressure, the pinprick test, and vibration, as well as cold and warm perception [38]. However, the QST is a psychophysical test that often generates false-positive results, is time-consuming, and cannot localize lesions causing neuropathic pain.

Evaluation of intraepidermal nerve fibers (IENFs) via skin biopsy is the most objective and sensitive test for neuropathic pain. The diagnostic accuracy of the QST used to assess small fiber neuropathy is low (approximately 50%), but IENF quantification is highly sensitive and specific (up to 90%) [39]. Skin samples obtained via 3-mm punch biopsy are stained for protein 9.5, a pan-axonal marker. The number of stained Aδ fibers/mm that cross the dermal-epidermal junction is the IENF density, a decrease in which correlates with neuropathic symptoms and the results of other neurophysiological tests [40]. However, the test is available only in specialized centers.

PHARMACOLOGICAL TREATMENT

Unfortunately, no agent prevents NCP; current treatment focuses on reducing or alleviating symptoms. Although various drugs have been used for many years, the only drug proven to be effective (in a randomized controlled trial) is duloxetine. The American Society of Clinical Oncology guideline suggests that serotonin-norepinephrine reuptake inhibitors (SNRIs; e.g., venlafaxine and duloxetine) and gabapentinoids (e.g., gabapentin and pregabalin) should be the first drugs of choice for NCP [41]. However, this does not mean that other drugs are ineffective. Generally, there is no evidence that different drugs are variably effective when treating different types of neuropathic pain. We here briefly discuss the adjuvant analgesics commonly used to manage NCP. The primary indication for use of these drugs is not pain, but the drugs sometimes exhibit significant analgesic effects when used either alone or in combination with pure analgesics. Dosing, major adverse effects, and precautions required during use are summarized in Table 5.

Antidepressants

The tricyclic antidepressants (TCAs) have been used for decades. TCAs (amitriptyline, nortriptyline, and desipramine) demonstrated efficacy for moderate non-cancer neuropathic pain such as diabetic polyneuropathy, postherpetic neuralgia, migraine, and fibromyalgia [42]. Amitriptyline or nortriptyline are old but potent drugs. Although a recent Cochrane review found that TCAs afforded at least moderate pain relief (number needed to treat = 3.6) in patients with nonmalignant neuropathic pain [43], studies on cancer patients revealed only minimal analgesic effects. The cardiac side-effects (QT prolongation, orthostatic hypotension) and anticholinergic effects (confusion, sedation, dry mouth, somnolence, and bladder distension) limit the use of these drugs in

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Table 5. Drugs commonly used to treat neuropathic cancer pain

Medication	Starting dosage	Maximum dosage	Major side effect	Precaution	Avoid	Other benefits
TCAs	25 mg at bedtime	150 mg daily	Sedation, dry mouth, blurred vision, weight gain, urinary retention	Cardiac disease, glaucoma	Tramadol, SNRI	Improvement of depression and insomnia
Carbamazepine	100 mg twice a day	600 mg daily	Dizziness, sedation, skin rash, leukopenia	Drug interaction		Effective in neuralgic pain
Gabapentin	100–300 mg at bedtime or three times a day	3,600 mg daily	Sedation, dizziness, peripheral edema	Renal insufficiency		Improvement of sleep disturbance, no significant drug interaction
Pregabalin	75 mg twice a day	600 mg daily	Sedation, dizziness, peripheral edema	Renal insufficiency		Improvement of sleep disturbance, no significant drug interaction
Tramadol	50 mg once a day or twice a day	400 mg daily	Nausea, vomiting, constipation, drowsiness, dizziness	History of substance abuse, suicide risk, seizure	SNRI, TCA	Rapid onset
Oxycodone	30 mg daily	None	Nausea, vomiting, constipation, drowsiness, dizziness	History of substance abuse, suicide risk		Rapid onset
Topical lidocaine			Local erythema, rash			No systemic side effect
Venlafaxine	37.5 mg once a day or twice a day	225 mg daily	Nausea	Cardiac disease, withdrawal syndrome with abrupt discontinuation	Tramadol, TCA	Improvement of depression
Duloxetine	30 mg once a day	60 mg twice a day	Nausea	Hepatic dysfunction, renal insufficiency, alcohol abuse	Tramadol, TCA	Improvement of depression

TCA, tricyclic antidepressant; SNRI, serotonin-norepinephrine reuptake inhibitor.

older patients.

Newer antidepressants, the SNRIs, have fewer side-effects than TCAs. Unfortunately, serotonin-selective reuptake inhibitors (SSRIs) do not relieve pain. In a randomized, double-blind crossover trial on 231 patients with taxane- or platinum-treated, cervical intraepithelial neoplasia, duloxetine (30 mg daily for 1 week followed by 60 mg daily for 4 weeks) decreased the average pain score by 1.06, compared to 0.34 in the placebo group [44]. Fifty-nine percent of patients receiving duloxetine reported some pain reduction. A recent study showed that the drug relieved musculoskeletal pain in patients with early-stage breast cancer [45]. The adverse effects are those of all SNRIs, including nausea, dizziness, headache, and dry mouth. The drug is not recommended for patients with hepatic disease

or severe renal impairment (CrCl < 30 mL/min). Venlafaxine (another SNRI) relieves diabetic neuropathic pain and fibromyalgia. A randomized, double-blind, placebo-controlled phase 3 study reported that venlafaxine was clinically active against oxaliplatin-induced, acute neurosensory toxicity [46]. However, efficacy in patients with chronic CIPN has not yet been proven. The National Comprehensive Cancer Network (NCCN) guidelines recommend venlafaxine and duloxetine, the newest SNRI [47], as the first choice for NCP patients; both drugs are effective against diabetic neuropathic pain. Also, SNRIs relieve the depression and anxiety accompanying chronic cancer pain. However, several weeks are required before adjuvant analgesic effects are evident, and somnolence, dry mouth, dizziness, and increased sweating are common side-effects.

Anticonvulsants

Anticonvulsants have been used since the 1970s to manage pain. The World Health Organization and NCCN guidelines suggest that adjuvant analgesics should be combined with opioids to relieve cancer pain. Pregabalin and gabapentin have been proposed as first-line treatments for cancer-related neuropathic pain; these new-generation anticonvulsants have fewer side-effects than older drugs such as carbamazepine and valproic acid. Anticonvulsants act by blocking the sodium channels of the affected peripheral nerves, reducing spinal, glutamatergic nociceptive transmission and enhancing the descending inhibition of spinal nociceptive transmission.

Gabapentin is currently widely used because several clinical trials demonstrated efficacy against NCP when the drug was given either alone or in combination with opioids. Pregabalin has the same mechanism of action and the same indications. This drug binds to the $\alpha 2\delta$ subunit of the voltage-gated calcium channel, reducing the levels of excitatory neurotransmitters. Although the drugs were effective against neuropathic pain of various etiologies, they have not been shown to be effective against NCP. Only one randomized controlled trial found that pregabalin was more effective, and required a lower level of a combined opioid, than gabapentin and amitriptyline, associated with a significantly lower mean VAS score [48]. However, pregabalin did not reduce the chronic pain associated with oxaliplatin therapy [49]. Gabapentinoids usually reduce anxiety and sleep disturbances in those with chronic pain and can also be helpful in patients whose pain does not respond to opioids or for whom opioid reductions are required. The maximal daily doses are 3,600 mg/day for gabapentin and 600 mg/day for pregabalin; the latter drug exhibits linear pharmacokinetics and dose-dependent absorption, thus reducing pain rapidly and is six-fold more potent than gabapentin. Common side effects include somnolence, dizziness, and edema. Renal dose adjustment is required for both drugs.

Carbamazepine, a sodium channel blocker, is used to treat trigeminal neuralgia. Common side-effects include dizziness, skin rash, hyponatremia, and leukopenia. The drug has not been proven to act against NCP, but can be cautiously used by those with neuralgic pain caused, for example, by cancer infiltration of peripheral nerves.

Opioids

Neuropathic pain responds very poorly to conventional analgesics such as opioids, paracetamol, and nonsteroidal anti-inflammatory drugs. Both the NCCN and World Health Organization guidelines recommend that combinations of opioids and adjuvant analgesics should be used to treat mixed or somatic pain even in patients with mild-to-moderate cancer pain. A patient may simultaneously experience mixed visceral and neuropathic pain in one lesion and pure somatic or neuropathic pain elsewhere. Therefore, opioids are used to control cancer-related neuropathic pain. However, NCP is not effectively controlled by opioids only. Adjuvant analgesics such as antidepressants and/or anticonvulsants are required [50]. Although combinations of opioids and adjuvant analgesics help to control NCP, the situation remains problematic, both in terms of pain relief *per se* and the management of side-effects. Moreover, the prescription rate of adjuvant analgesics to treat NCP is no higher than 20% worldwide.

Other agents

Topical 5% (v/v) lidocaine and capsaicin (8% w/v) patches effectively treat postherpetic neuralgia [51]; however, their effects on NCP remain unclear. Skin patches may be useful in patients who cannot take oral medication or who exhibit dynamic allodynia as the patches pre-

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vent skin stimulation. Based on the Grading of Recommendations Assessment, Development and Evaluation (GRADE) classification, drugs that may not be useful for patients with neuropathic pain include lacosamide, lamotrigine, oxcarbazepine, topiramate, and zonisamide [50]. Levetiracetam and mexiletine are not recommended. Apart from pharmacological management, spinal cord stimulation, scrambler therapy or even acupuncture may afford relief, and are worth exploring.

CONCLUSIONS

NCP is pain caused by direct damage to the nervous system by the cancer *per se*, or cancer treatments including chemotherapy, radiotherapy, and surgery. Burning, tingling, shooting, and electric shock-like pain, as well as decreased sensation, impaired balance and motor weakness are often associated with NCP. The prevalence of NCP is high (about 40% in both Western and Korean cancer patients) and NCP interferes significantly with the activities and quality of daily life. NCP compromises quality of life more than pure nociceptive pain. CIPN is an important form of NCP; taxanes, vinca alkaloids, and platinum compounds cause CIPN, in turn, triggering treatment delays, dose reductions, and drug discontinuation. Although the prevalence of NCP (including CIPN) is high, management is inadequate. Fewer than 50% of all NCP patients receive the adjuvant analgesics they need.

Comprehensive patient evaluation is essential. NCP should be sought during initial evaluation, at each follow-up, and whenever new pain develops. A thorough history-taking, sophisticated neurological examinations and objective neurophysiological studies, are imperative. The NPSI is useful for characterizing the type of neuropathic pain, and in the follow-up of responses to pharmacological or other therapeutic interventions.

NCP management is complex, featuring antidepressants (SNRIs; duloxetine, venlafaxine), anticonvulsants (pregabalin, gabapentin), combination opioid therapy, topical agents and the use of interventional strategies. Antidepressants and anticonvulsants are first-line adjuvant analgesics for NCP treatment. However, combinations with opioids may be helpful because many cancer patients experience mixed neuropathic and nociceptive pain. Notably, SSRIs do not aid in NCP control. Many cancer patients suffer from insomnia, anxiety, and depression. Adjuvant analgesics alleviate these psychological symptoms, thus aiding pain control. Patient education should emphasize the trial-and-error nature of treatment; pain control is difficult, adverse effects can be serious, and the time to control may be weeks-to-months. Therefore, sympathy for patients with NCP and formation of a doctor-patient rapport are critical in terms of management.

Conflict of interest

No potential conflict of interest relevant to this article was reported.

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