

Chemotherapy induced peripheral neuropathic pain

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Chemotherapy-induced peripheral neuropathy (CIPN) is one of the most serious complications associated with anticancer drugs. CIPN leads to a lower quality of life and dysfunction of the sensory, motor, and autonomic systems, and often causes patients to discontinue chemotherapy. It is usually misdiagnosed and undertreated due to a lack of consensus and unclear pathophysiology, for which many mechanisms have been suggested, including mitochondrial dysfunction, various pain mediators, abnormal spontaneous discharge in A and C fibers, and others. To date, no agents have been shown to effectively prevent CIPN, leading to debate as to the standard protocol. Duloxetine has demonstrated a moderate therapeutic effect against CIPN. Although tricyclic antidepressants (such as nortriptyline or desipramine), gabapentin, and a topical gel containing baclofen (10 mg), amitriptyline HCL (40 mg), and ketamine (20 mg) showed inconclusive results in CIPN trials, these agents are currently considered the best options for CIPN treatment. Therefore, further studies on the pathophysiology and treatment of CIPN are needed. (Korean J Anesthesiol 2014; 67: 4-7)

Key Words: Cancer, Chemotherapy, Pain, Peripheral neuropathy.

Introduction

Chemotherapy-induced peripheral neuropathy (CIPN) is a frequent, dose-dependent complication of anticancer drugs including platinum, taxanes, epothilones, vinca alkaloids, and newer agents such as bortezomib [1]. It not only leads to dose reduction or discontinuation of treatment but also decreases the quality of life of cancer survivors [2]. CIPN occurs in ~20% of patients given standard doses of chemotherapy and in almost 100% of patients treated with high doses.

CIPN presents clinically as deficits in sensory, motor, and sometimes autonomic function. Sensory disturbances range

from a mild tingling sensation to spontaneous burning pain and hypersensitivity to stimuli. These symptoms often affect both hands and feet and may spread into a 'glove/stocking' distribution. Symptoms are usually symmetrical distally but may be more severe unilaterally. Although dependent on the specific agent, the feet are often affected first. The incidence of CIPN depends on the dose (mainly cumulative) and type of agent; it is more common in patients with preexisting nerve damage either from previous CIPN or from other causes (e.g. diabetes). Symptoms may occur at any time during the course of chemotherapy (seen with paclitaxel), or even after termination (commonly known as "coasting") [3], which refers to neuropathic symptoms

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that present after discontinuation of anticancer treatment, and which may continue or worsen over weeks or months. This phenomenon suggests that there is ongoing neuronal damage even after discontinuation of anticancer drugs.

Although the exact pathophysiology of CIPN remains unknown, it is thought that individual chemotherapeutic agents each have a different pathophysiology [4]. Hence, the treatment must also be specific to each chemotherapeutic agent. The pathophysiology and treatment of CIPN are described in this article.

Pathophysiology

Although the mechanism of development of neuropathic pain due to chemotherapeutic drugs is unknown, various hypotheses have been suggested.

Mitochondrial dysfunction

Abnormal mitochondrial structure and function are considered a possible etiology of CIPN. The numbers of vacuolated and swollen mitochondria are significantly increased in the C fibers and myelinated axons of paclitaxel-induced peripheral neuropathy [5]. Mitochondrial caspase activation is essential for chemotherapy-induced apoptosis (vincristine, bortezomib) [6,7]. Cisplatin directly inhibits mitochondrial DNA (mtDNA) replication and transcription. Mitochondrial vacuolization and degradation are also observed in cisplatin-treated DRG in vitro and in vivo [8]. Dysregulation of intracellular calcium by mitochondrial dysfunction is involved in bortezomib-induced apoptosis and CIPN [9,10].

Therefore, correction of mitochondrial dysfunction may be considered for prevention or treatment of CIPN. This is supported by several reports that prevention of mitochondrial alterations by acetyl-L-carnitine reduces paclitaxel-induced neuropathic pain [11] and amendment of calcium channel dysregulation decreases pain behaviors [3,10].

Pain mediators

Changes in many pain mediators in the peripheral nerve, dorsal root ganglion, and spinal cord after anticancer drug treatment have been postulated. These include cytokines, growth factors, ion channels, etc. [4]. Reduction of the nerve growth factor level is correlated with the degree of cisplatin-induced peripheral neuropathy [12]. Mitogen-activated protein kinases and extracellular signal-related kinases may play important roles in CIPN; activation of these kinases is involved in chemotherapy-induced apoptosis [13].

The TNF- α level is increased in the sciatic nerves and spinal cords of a CIPN animal model [14,15]. Administration of TNF- α

neutralizing antibodies reduced vincristine-induced tactile hyperalgesia significantly [15]. When IL-1 β release was blocked in the CIPN rat model, mechanical hyperalgesia was also reduced [16]. The IL-6 level was increased in the sciatic nerve and DRG of CIPN mice, and administration of IL-6 antibodies to the sciatic nerve reduced tactile hyperalgesia significantly. Additionally, chemotherapy-induced tactile hyperalgesia was less common in IL-6 KO mice than in wild-type mice [17]. These results suggest that proinflammatory cytokines such as TNF- α , IL-1, and IL-6 are implicated in CIPN [4].

Fos expression was activated significantly in the superficial, intermediate, and deep layers of the spinal cord in a CIPN animal model [18]. Also, Fos protein was distributed more widely in the dorsal horn of a CIPN animal model than in a nerve injury animal model [19].

Abnormal spontaneous discharge in A and C fibers

Peripheral and central sensitization may be involved in the development of CIPN. Abnormal spontaneous activity in A β , A δ , and C fibers has been observed in vincristine-, paclitaxel-, oxaliplatin-, and bortezomib-induced peripheral neuropathy [20,21]. Moreover, C-fiber nociceptors showed significant hyper-responsiveness to suprathreshold tactile and thermal stimuli in a CIPN animal model [22].

Others

Paclitaxel-, oxaliplatin-, and vincristine-induced peripheral neuropathy is caused by decreased numbers of intraepidermal sensory fibers and increased numbers of epidermal Langerhans cells [23], and resembles a traumatic-nerve-injury-induced neuropathic pain model (CCI, sciatic nerve transection). The CNS has also been shown to be involved in CIPN both directly and indirectly [24].

The mechanisms of CIPN may differ from those of other types of neuropathic pain

First, hyperalgesia to mechanical and cold stimuli usually manifests in CIPN. However, heat hyperalgesia is nearly absent in a model of cisplatin-, paclitaxel-, and vincristine-induced CIPN [25]. Heat hyperalgesia is observed frequently in a model of neuropathic pain due to traumatic nerve injury (e.g. CCI, SNL, etc.).

Second, the abnormal spontaneous discharge in A β , A δ , and C fibers does not resemble the pattern seen in nerve injury-induced neuropathic pain models, as only 2–3 spikes/s are observed in CIPN rather than the 20–30 spikes/s in nerve-injury-induced neuropathic pain models [20].

Third, CIPN shares several mediators and processes with other types of neuropathic pain. Nevertheless, the efficacy of antineuropathic drugs differ [26].

These discrepancies indicate that the pathophysiology of CIPN may differ from that of nerve-injury-induced neuropathic pain.

Treatment and Prevention

Therapeutic strategies should not hinder the anticancer effects of chemotherapy. Although some data suggest that certain substances may prevent CIPN [2], no treatments have been demonstrated to prevent CIPN effectively. Thus, no accepted standard protocol exists [27].

Pregabalin may be used to decrease neuropathy after oxaliplatin treatment [28]. Duloxetine showed modest analgesic efficacy in CIPN (paclitaxel- and oxaliplatin-induced) patients compared with a placebo in a randomized clinical trial [29,30]. These data support a moderate recommendation for CIPN treatment [27]. Among antidepressants, venlafaxine has been shown to reduce the incidence of CIPN, albeit with some side effects [31]. Cannabinoids may be a new treatment option for CIPN, and should be evaluated in robust RCTs [32]. Although tricyclic antidepressants (such as nortriptyline or desipramine), gabapentin, and a topical gel containing baclofen (10 mg), amitriptyline HCL (40 mg), and ketamine (20 mg) yielded inconclusive data in CIPN trials, these agents may constitute the remaining CIPN treatment options [27].

Neuroprotectants exhibit only very weak efficacy in terms of preventing CIPN [33], but nutraceuticals, as alternatives to pharmacotherapeutics, have shown more promising results in the treatment and prevention of CIPN [34]. Vitamin E has been

used to reduce cisplatin- and paclitaxel-induced neuropathic pain [35], while menthol (a TRPM8 channel activator) has analgesic effects in carboplatin- and bortezomib-induced neuropathy [36,37]. Drugs that increase mitochondrial function have shown some efficacy in laboratory studies and may be eligible to enter clinical trials regarding the treatment and prevention of CIPN [11,38,39].

Conclusions

Anticancer chemotherapeutics can induce painful peripheral neuropathy. Symptoms range widely and can involve the sensory, motor, and autonomic systems. However, CIPN is under-assessed and undertreated and its diagnosis is somewhat complicated by the lack of a consensus on its pathophysiology and presentation. Although limited reliable evidence regarding the appropriate treatment for this condition exists, it is based on current neuropathic pain guidelines. Further studies of the differences between the pathophysiology of CIPN and those of other neuropathic pain conditions may lead to development of more effective treatment modalities. Additionally, therapeutic strategies for the management of CIPN must be validated in large-scale RCTs to satisfy the demands of evidenced-based medicine.

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