

Chemotherapy-induced peripheral neuropathy (Review)

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Abstract. Neuropathy is associated with side effects of frontline chemotherapeutics, which is a prominent therapy utilized in prevalent cancers. Peripheral neuropathy negatively impacts quality of life in cancer patients and survivors. It also affects the dose plan of the treatment, thereby limiting the efficacy of the treatment. We searched the electronic database PubMed for pre-clinically and clinically controlled trials reporting neuropathy of adverse effects, a result of chemotherapy in cancer patients. It was observed clearly that many reports provide clinical evidence to rapidly growing neuropathy cases of cancer patients. Furthermore, the reports clearly showed enhanced cold pain, sensorimotor deficits, sensory innervation of the skin and sensorimotor deficits in the patients with cancer who underwent treatment mainly with the chemotherapeutic approach. The present review highlighted the current view of peripheral neuropathy during chemotherapeutic approaches.

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1. Introduction

Cancer currently is a leading cause of mortality worldwide and the number is on the increase (1). In less than 20 years, cancer has become the leading cause of mortality (2). However, with increasingly sensitive tests for detecting cancer and the administration of frontline chemotherapeutic agents, the number of cancer survivors is expected to increase to 35% from 13.7 in 2012 to 18 million by the year 2022 (3). Chemotherapeutics are effective in arresting the progression of cancer because they are often designed to differentially target and eliminate rapidly dividing cancer cells.

Despite the positive effects of chemotherapeutic approaches in the cancer-fighting arena, there are various deleterious side effects (e.g., anemia, appetite changes, constipation, diarrhea, nausea, vomiting, neurological changes, infection, fluid retention, fatigue, hair loss, infertility, pain and peripheral neuropathy) that negatively affect normal cells and structures of the body (4). Given the potential longevity of biochemical and cellular changes induced by cancer and chemotherapy, cancer survivors may require a lifetime of medical monitoring and treatment for cancer and/or drug-induced health problems and comorbidities. Of the adverse effects induced by cancer treatment, 20-100% of patients develop a condition known as chemotherapy-induced peripheral neuropathy (CIPN) (5,6). CIPN occurs when peripheral nerves are damaged, resulting in abnormal sensory function, and pain or loss of motor control. This condition sometimes leads to chemotherapy dose decrease or cessation, thereby limiting the efficacy of cancer treatment. The present review discusses the latest aspects of chemotherapy-associated peripheral neuropathy.

2. Neuropathy-associated pain

Neuropathic pain is a type of maladaptive pain produced in response to a peripheral or central nervous system (CNS) injury that persists long after the initial injury and is refractory to therapy (7). Many types of injuries and diseases cause what is broadly termed neuropathic pain. Although neuropathic conditions are similar, the underlying disease is responsible for mechanistic differences and the manifestation of symptoms. For the majority of patients, neuropathic pain is caused by focal/multifocal lesions of the peripheral nervous system (PNS) (8). In addition, generalized lesions of the PNS (polyneuropathies), lesions of the CNS, or complex neuropathic disorders also contribute towards neuropathic pain (8). Examples of focal or multifocal lesions of the PNS

that cause neuropathic pain include postherpetic neuralgia, phantom limb pain and diabetic mononeuropathy. Generalized PNS lesions that cause neuropathic pain resulted from various conditions, including diabetes mellitus, amyloidosis, alcoholism, HIV-induced neuropathy, toxic neuropathy (e.g., chemotherapy-induced), vitamin B deficiency and hereditary sensory neuropathies. Furthermore, the lesions of the CNS that have been reported to result in neuropathic pain are spinal cord injury, brain infarction (e.g., of the brainstem and thalamus), syringomyelia and neurodegenerative diseases such as multiple sclerosis. Complex neuropathic pain disorders that cause neuropathic pain refer to complex regional pain syndromes type I and II. Thus, central as well as peripheral injury may cause neuropathic pain.

3. Peripheral mechanisms of neuropathic pain

Peripheral nerve injury can lead to neuropathic pain through a change in the properties of primary afferents and the manner in which stimuli are encoded. For instance, primary afferents become hypersensitive and may fire spontaneously. Upregulation of Nav1.7, Nav1.8, Nav1.9 and potentially, Nav1.3 sodium channels may induce hyper-excitability of nociceptors after injury (9). Nav1.7 opens in response to small depolarizations near the resting potential; thus, modulation of Nav1.7 expression can dictate the ease of firing an AP. Nav1.8 is selectively expressed in dorsal root ganglion (DRG) neurons and opens to allow depolarization in the absence of voltage change. Nav1.3 is responsible for persistent sodium current and is capable of magnifying small depolarizations. Nav1.9 opens at hyperpolarized voltages near resting potential and does not inactivate, thereby potentiating depolarization. Changes in receptor expression on nociceptors can therefore alter the firing properties of nociceptors by increasing excitability and neurally encoding hypersensitivity.

Due to their electrophysiological properties, sodium channels have been linked to pain in numerous studies (9). Clinically, mutations in the *SCN9A* gene that encode Nav1.7 have been linked to several of the following disorders: Inherited erythromelalgia and paroxysmal extreme pain disorder patients, experiencing abnormally high pain levels, as compared to patients who exhibit congenital insensitivity to pain and are unable to feel pain (10). Nav1.8 mutations are associated with small-fiber painful neuropathy (11). Pre-clinical studies indicate that Nav1.9 plays a role in diabetic neuropathic pain and inflammatory pain (12). In addition to sodium channels, other channels, such as TRPV1, TRPV4 and TRPM8 are upregulated in injured nociceptors and contribute to the development of neuropathic pain (13). Other findings have suggested that molecular changes in undamaged primary afferents accompany injury and play an important role in the experience of pain (14).

4. Central mechanisms of neuropathic pain

Central sensitization plays a role in pain and particularly, in neuropathic pain. The literature suggested the involvement of a wide array of neurons, ion channels, signaling pathways, molecules and non-neuronal cells in central sensitization (15). Damage to peripheral nerves (particularly C-fibers) causes

spontaneous activity, which in turn alters secondary order neurons in the spinal dorsal horn and results in hyper-excitability via diverse molecular changes. This is accomplished through the release of the excitatory neurotransmitter, glutamate, as well as peptide neurotransmitters from primary afferents and thus, activation of NMDA receptors on secondary order neurons. Additionally, an upregulation of N-type calcium channels pre-synaptically and Nav1.3 channels post-synaptically is believed to underlie this excitability (16). In addition to upregulation in the cellular machinery producing excitability, a decrease in inhibitory mechanisms has also been observed in neuropathic pain conditions (17). This decrease may be caused by selective loss of an inhibitory class of neurons, γ -aminobutyric acid (GABA) neurons, or a loss of the potassium-chloride exporter (KCC2), which causes cells to become more excitable rather than inhibited in the presence of GABA (18). Previous results also suggested that changes in descending inhibitory pain pathways may lead to the promotion rather than the repression of pain (19). Central changes are not limited to the spinal cord and extend into the brain. Technologies including functional magnetic resonance imaging, positron emission tomography and magneto-encephalography have also facilitated the detection of pain-related changes in the brain (20).

5. Inflammatory mechanisms of neuropathic pain

Previous findings identified the involvement of innate immune mechanisms in neuropathic pain syndromes, which include the upregulation of diverse inflammatory mediators (21). Inflammatory substances may be capable of causing long-lasting pain through inducing neuroplasticity (21). This can be achieved by binding to respective receptors, thereby activating downstream signaling molecules capable of entering the nucleus and influencing gene transcription. Tumor necrosis factor- α (TNF- α) is possibly the most widely studied proinflammatory cytokine in neuropathic pain and induces the release of other anti- and pro-inflammatory cytokines. Animal models of neuropathic pain wherein the nerve is transected or crushed, produces demyelination, and degeneration of the distal axon, termed Wallerian degeneration (22). In response to this type of nerve injury, Schwann cells, mast cells, endothelial cells, and fibroblasts release TNF- α , which in turn, leads to the release of other inflammatory mediators. Release of TNF- α is also considered to be responsible for activating immune mechanisms through the recruitment of phagocytic macrophages to the site of injury (23). In Wallerian degeneration, non-resident macrophages localize to the nerve and degrade myelin, contributing to the pain phenotype (24). In addition to TNF- α , there is strong evidence of the involvement of many other diverse inflammatory mediators and cytokines in pain. Interleukin (IL)-6 plays a complex role in pain. IL-6 is detected in injured primary afferent nerve fibers, DRG, and spinal cord and peripheral administration of IL-6 causes increased mechanical hypersensitivity (25). However, IL-6 also has a role in neuronal survival as well as regeneration. IL-1 (26) and the chemokine receptors CXCR4, CCR5, CCR4, and CCR2 are upregulated following nerve injury and facilitate neuropathic pain conditions (27,28). Upon binding to respective G-protein-coupled receptors,

chemokines potentiate inflammatory and pain states through mitogen-activated protein kinase system (MAPK) signaling cascade. In addition to central neuronal changes, non-neuronal changes also occur. Thus, neuropathic pain may be initiated due to peripheral or central injury and potentiated by changes in cellular machinery and innate immune responses.

6. Bortezomib anticancer therapy and neuropathy

Bortezomib is usually administered for cancer at dose rates of 1.3 or 1.0 mg/m² by intravenous bolus or subcutaneously. The most common adverse events associated with bortezomib are fatigue, thrombocytopenia, gastrointestinal issues, and sensory neuropathy (29). In an initial study, 34% of patients reported new or worsening symptoms of neuropathy with bortezomib (30). Subsequent trials using bortezomib as a single-agent induction therapy for multiple myeloma reported treatment-emergent sensory neuropathy in 64% of patients (31). In an analysis of two bortezomib phase II studies with 256 enrolled patients, 90 patients experienced treatment-emergent neuropathy, 5% of patients discontinued treatment due to neuropathic symptoms, and 12% of patients received a dose reduction due to peripheral neuropathy (31).

Bortezomib-induced neuropathy (BIPN) is typically sensory, although motor neuropathy has also been reported (32). The incidence of peripheral neuropathy varies depending on the trial, grading scales, and detection methods of neuropathy. To increase the efficacy of bortezomib, polymodal therapy has been implemented, whereby bortezomib was combined with several other agents, including dexamethasone alone, dexamethasone and thalidomide, prednisone alone, melphalan and prednisone and lenalidomide (33). Richardson *et al* (29) reported that multiple therapies do not increase the incidence of reported neuropathy.

Neuropathy is the most clinically relevant side effect of bortezomib. Due to the prevalence of neuropathy, BIPN leads to dose reduction and/or discontinuation of therapy. The incidence of neuropathy typically increases as patients receive more cycles of chemotherapy and the cumulative dose of the drug increases (32). Furthermore, the most significant risk factor for the development of neuropathy is a previous history of neuropathy (33). Of note, BIPN is reversible: 60% of cases return to baseline levels of neuropathy within a median of 5.7 months. However, in other studies neuropathy was observed at a year following treatment (34). The etiology and mechanisms underlying BIPN are poorly understood. BIPN is debilitating and treatment-limiting and requires further investigation in animal models.

7. Bortezomib-induced neuropathy: Pre-clinical studies

Animal studies have attempted to characterize the pathophysiology of BIPN. Rats treated with bortezomib at a clinically-equivalent dose exhibit neurophysiological and histopathological differences compared to control animals (35). Sensory nerve conduction velocity is significantly reduced and the sciatic nerve in these rats exhibits damaged Schwann cells and degeneration of myelin, although recovery was observed after 4 weeks. The DRGs of these animals showed increased recruitment of satellite cells (36).

Bortezomib-treated animals also have an abundance of ubiquitin-tagged proteins in DRG neurons and signs of abnormal transcription and translation, which likely contributes to sensory neuron dysfunction (37). Taken together, these data show that bortezomib damages peripheral nerves and their cell bodies, although the underlying pathways leading to this destruction remain to be identified. In addition, despite carefully conducted animal studies, the mechanism of action for bortezomib remains to be determined.

8. Neuropathy-associated therapy and other therapies

Thalidomide is another chemotherapeutic agent in use as an anti-cancer therapeutic. Thalidomide modulates the immune system to increase natural killer cells and T-cells, inhibiting cytokine production and angiogenesis, and inducing apoptosis (38). Potential mechanisms of thalidomide-induced neuropathy include the downregulation of TNF- α , which induces demyelination and Wallerian degeneration or direct damage of the DRG (38). Symptoms included dose-dependent abnormalities in the form of distal paresthesias or dysesthesias and possible weakness. Aside from chemotherapy, autologous stem-cell therapy is usually considered an option for the treatment of MM and may prolong life if a complete response is attained (39). The severity of neuropathy induced by chemotherapeutic agents in individual patients dictates the future dose that can be administered. In order to quantify neuropathy, several grading scales have been implemented.

9. Overview of CIPN symptoms and grading scales

Primary afferent neurons and their cell bodies located in the DRG are particularly vulnerable to the toxic effects of chemotherapy because they do not have a protective blood-brain barrier that is present in the CNS. Without the blood-brain barrier, substances in the blood can freely exchange across the walls of DRG and affect primary afferents. In cancer patients, this produces an array of sensory disturbances (e.g., numbness, tingling, burning, or dysesthesias) broadly known as CIPN that affect the hands and feet in a glove and stocking distribution (40). Patients typically present with symptoms consistent with CIPN weeks or months after beginning chemotherapy treatment. Several chemotherapies are notorious for causing CIPN; however, the presentation and onset of symptoms varies depending on the drug, possibly due to mechanistic differences. CIPN is generally thought to improve after chemotherapy treatment has ended. However, the platin family of compounds (e.g., oxaliplatin, carboplatin and cisplatin) is known to exacerbate symptoms after treatment has been arrested (a phenomenon known as 'coasting') (38).

Bortezomib-treated patients most commonly describe their sensory symptoms as tingling (paresthesia), hypersensitivity (hyperesthesia), numbness (hypoesthesia), abnormal sense of touch (dysesthesia), burning, or pain and their motor symptoms as weakness (41). Although much less common, some chemotherapies such as bortezomib, may also affect the autonomic nervous system causing orthostatic hypotension, sex organ dysfunction and constipation. Previous studies have focused on different chemotherapeutics, the potential mechanisms by

which they induce neuropathy, and the quality of neuropathic symptoms induced (42).

10. Aspects of quantification of CIPN

CIPN is challenging to quantify because of the subjectivity of patient and provider reports. Thus, several grading systems have been developed in an effort to increase objectivity. Historically, three different grading scales of peripheral neuropathy have been implemented that categorize neuropathy numerically from grade 0 to grade 4. These include the World Health Organization (WHO) Common Toxicity Criteria for Peripheral Neuropathy, National Cancer Institute (NCI) Common Toxicity Criteria, and the Eastern Cooperative Oncology Group (ECOG) Grading Scale for CIPN (43). According to the WHO rating scale, a grade 0 corresponds to no symptoms of neuropathy, grade 1 corresponds to paresthesias (a tingling, tickling or prickling sensation) and/or decreased tendon reflexes, grade 2 corresponds to severe paresthesias and/or mild weakness, grade 3 corresponds to intolerable paresthesias and/or marked motor loss and grade 4 corresponds to paralysis. NCI and ECOG ratings make slight modifications to the WHO rating system. The Total Neuropathy Score is slightly different in that it rates patients with a cumulative score ranging from 0 to 32 based on deep tendon reflexes, pin sensation, vibration sense, nerve conduction, and subjective self-report of symptoms from the patient (44).

11. Quantitative sensory testing in neuropathy

Quantitative sensory testing (QST) is a sensitive, but non-invasive method of assessing the extent of neuropathy. QST is a battery of tests administered to patients that measures sensory function in several different modalities and assesses the function of discrete fiber types. Touch detection thresholds measure A β -function, temperature thresholds measure the function of different populations of A δ - and C-fibers, and sharp detection thresholds measure A δ -fiber function. A 2010 study using QST on 1,236 neuropathic pain patients in a multi-center study found both loss and gain of sensory function in patients as compared to healthy controls as well as a high degree of heterogeneity between patients in the modalities tested (45). These results emphasize the complex array of sensory phenotypes attributable to neuropathic pain syndromes that can be differentiated by testing discrete fiber types using QST.

12. Conclusions

From the abovementioned studies it is evident that, peripheral neuropathy is one of the prominent major side effects associated with chemotherapeutic agents. At present, numerous studies have focused on investigating the mechanism underlying this side effect. However, future results confirming the findings are required.

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