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Discovering Cytokines as Targets for Chemotherapy-Induced Painful Peripheral Neuropathy

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Abstract

Chemotherapy-induced peripheral neuropathy (CIPN), a dose-limiting neurotoxic effect of chemotherapy, is the most common reason for patients stopping their treatment early thereby increasing the risk of recurrence and decreased survival rate. Inflammatory cascade activation, proinflammatory cytokine upregulation, and neuro-immune communication play essential roles in the initiation and progression of CIPN. Most notably, TNF- α , IL-1 β , IL-6, and CCL2 are involved in neuropathic pain experienced by patients undergoing chemotherapy. Further elucidation of the role of these cytokines may lead to their use as biomarkers for predicting the onset of painful peripheral neuropathy and early axonal damage. Evidence is discussed for the involvement of cytokines in CIPN, the possible underlying mechanisms, and their use as potential therapeutic targets to prevent and improve the painful peripheral neuropathy related to chemotherapeutic agents.

Introduction

Receiving a full chemotherapeutic regimen is a critical factor in determining the survival of patients with cancer. However, chemotherapy-induced peripheral neuropathy (CIPN), a dose-limiting toxic effect of chemotherapy, significantly limits the dose and numbers of chemotherapy cycles in cancer treatment. According to the National Cancer Institute (NCI), CIPN is one of the main reasons that patients prematurely terminate treatment. Early termination of chemotherapy negatively affects patient outcomes as current oncology practice to use more aggressive single agent or combination regimens requires full course completion to decrease the risk of recurrence and increase survival rates.¹⁻⁴

Chemotherapeutic agents most commonly associated with neuropathy include platinum-based drugs (cisplatin and oxaliplatin), vincristine, taxanes (paclitaxel and docetaxel), epothilones, bortezomib, thalidomide, and lenalidomide. Although a variety of neuroprotective approaches have been investigated in both experimental studies and clinical trials, there is no available preventive strategy or effective treatment for chemotherapy-induced neurotoxicity because its etiology has not been fully elucidated. Therefore, defining the mechanisms underlying pain symptoms of CIPN is critical to develop preventive and treatment strategies, and to enhance quality of life in cancer survivors.

It is noteworthy that most chemotherapeutic drugs penetrate the blood-brain barrier (BBB) poorly, but readily penetrate the blood-nerve-barrier (BNB) and bind to the dorsal root ganglia (DRG) and peripheral axons.^{5, 6} Experimental studies reveal that chemotherapeutic drugs preferentially accumulate and bind in the DRG and peripheral nerves.⁷ The blood-nerve barrier is less efficient than the BBB, specifically deficient at the areas of the DRG

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and nerve terminals,⁸ which allow easier access for potential neurotoxins into the periphery. Additionally, the endoneural compartment lacks lymphatic system to remove toxins.⁹ These factors increase the peripheral nerve vulnerability to potentially toxic medications as compared to the central nervous system. There is also evidence that chemotherapy drugs may directly damage the structure of the DRG cells and peripheral nerves that cause degeneration of sensory fibers or loss of small nerve fibers in the epidermal layer.¹⁰⁻¹² Although various CIPN mechanisms based on *in vitro* and *in vivo* have been proposed, the pathogenesis of CIPN has not been fully elucidated and differs among the classes of chemotherapeutic agents (Figure 1). It is generally accepted that at the cellular level neurotoxic chemotherapeutic agents damage microtubules and interfere with microtubule-based axonal transport, interrupt mitochondrial function, or directly target DNA,¹³ and subsequently lead to peripheral nerve degeneration or small fiber neuropathy. Of interest, nerve biopsies from experimental animals and patients treated with taxol, oxaliplatin or vincristine show identical morphological changes even though these compounds have different neurotoxic targets.^{10-12, 14, 15} Peripheral nerve degeneration or small fiber neuropathy is generally accepted as the underlying mechanism in the development of CIPN.^{10, 11, 16}

However, a recent study found that paclitaxel facilitates axon regeneration in the mature CNS through its effect of microtubule stabilization.¹⁷ In view of the essential role of small nerve fibers (Aδ and C-fiber) in the transmission of pain sensation, the following findings may expand this hypothesis. First, unlike painful peripheral neuropathy due to trauma or diabetes, the neuropathic pain caused by chemotherapy agents occurs in the absence of axonal degeneration in peripheral nerves.¹⁸⁻²⁰ Furthermore, the evidence of partial reversibility of neuropathy three months after the discontinuation of paclitaxel and carboplatin is difficult to explain based on axonal degeneration in peripheral nerves²¹ and functional abnormality may be a more reasonable explanation. Second, there is no correlation between the reported pain visual analogue scale (VAS) score and quantitative sensory testing or intraepidermal nerve fiber density in patients with Fabry disease.²² Third, when neurodegeneration occurs in advanced stages of Parkinson's disease, patients showed a significant loss of epidermal nerve fibers (ENFs) and a significant loss of pain perception.²³ Similarly, in an animal model of peripheral neuropathy caused by mitochondrial dysfunction, loss of small C-fibers resulted in a reduced sensitivity and increased withdrawal latency to noxious stimuli as compared to controls.²⁴ Finally, it is worthy to note that neuropathic pain induced by taxol and cisplatin often occurs as soon as the first dose infusion but without any significant findings in intraepidermal nerve fibers (IENFs) loss.^{10, 15} Taken together, these findings may provide an additional rationale for the pathogenesis of chemotherapy-induced painful peripheral neuropathy and expand the existing hypothesis that loss of small nerve fibers (SNFs) is the sole mechanism underlying CIPN.

There are several mechanisms in which chemotherapeutic agents can cause the DRG or axonal damage leading to peripheral neuropathy (Figure 1). Although these mechanisms of chemotherapy-induced neurotoxicity differ among classes of chemotherapeutic agents, all neurotoxic chemotherapeutic agents cause a common sensory disruption leading to painful paresthesias. However, these mechanisms alone do not explain the development of acutely painful neuropathies that occur even prior to the pathological loss of axons or alterations in the diagnostic testing for neuropathy. Thus, the common sensory disruption induced by these chemotherapeutic agents may result from a shared mechanism that is most probably not associated with their antineoplastic mechanisms. Inflammatory cytokines may be the contributors and play a critical role in the common clinical symptoms and signs of CIPN, and may contribute to chemotherapy-induced painful paresthesias.

The role of proinflammatory cytokines

Proinflammatory cytokines not only contribute to axonal damages²⁵ but also modulate spontaneous nociceptor sensitivity and activity^{26, 27} by linking the immune and the peripheral nervous systems.²⁸ Using microarray analysis, qRT-PCR and protein detection in a clinical model of inflammatory pain, we recently demonstrated upregulation of the gene expression of cytokines of IL6, IL8 and CCL2 chemokine following acute inflammation.²⁹ Most interestingly, the up regulation of these gene expressions was positively correlated to patient reported pain intensity, whereas the expression of IL-1RA was negatively correlated with the pain intensity (not published). In a recent case controlled study, it was demonstrated that IL-6 and IL-8 gene expression were significantly up-regulated in the affected skin biopsies taken from patients with painful peripheral neuropathy.³⁰ These findings provide evidence that proinflammatory cytokines and chemokines are involved in the pathogenesis of acute and chronic peripheral pain in humans.

Chemotherapeutic agents induced pain is likely due to either a direct effect of the agent on nerve tissues or an effect mediated by inflammation induced by chemotherapeutic drugs. Emerging evidence indicates that proinflammatory cytokines are implicated in the pathogenesis of peripheral neuropathy. Increasing data in clinical and experimental studies support the critical role of pro-inflammatory cytokines/chemokines in the development and maintenance of painful peripheral neuropathy.^{27, 30-32} After intravenous administration of chemotherapy drugs, the neurons and surrounding satellite cells in the DRG and peripheral nerves show notable pathological changes, accompanied by allodynia and hyperalgesia. These pathological changes include a massive increase in the number of activated macrophages in the DRG, peripheral nerves and Schwann cells.³³ Activating transcription factor 3 (ATF3), a marker of nerve injury, was strongly expressed in the same locations with macrophage infiltration in neuropathic pain models of paclitaxel treatment.³³⁻³⁶ More interestingly, these ATF3-expressed cells possess pathological features, including eccentric nuclei and the accumulation of neurofilament in DRG cell soma and proximal axons that have been observed in an animal model of peripheral injury due to vincristine treatment.¹⁹ Another pathological feature of the ATF3-expressed cells treated with paclitaxel is the presence of nodules of Nageotte, which has been seen in the DRG tissue samples from patients with neuropathy following cisplatin treatment.³⁷ The increased ATF3 expression occurs in animal models as early as 1 day after paclitaxel infusion, corresponding to the same time point that patients first report pain in the course of paclitaxel-induced acute pain syndrome.^{38, 39} The initial intensity of acute pain in P-APS seems to predict the severity of burning and shooting pain associated with sensory peripheral neuropathy, specifically at the chronic stage of peripheral neuropathy.³⁹

Most interesting to note that although different chemotherapeutic agents have different mechanisms of neurotoxicity (Figure 1), almost all these agents induce up-regulation of gene expression that is associated with inflammatory and immune responses found in clinical and experimental studies. For instance, 43% of the upregulated genes from the DRG were involved in inflammatory and immune responses in an animal model of paclitaxel-induced painful peripheral neuropathy.³⁶ In a recent prospective trial, molecular-genetic profiles involved in proinflammatory and apoptosis genes including MBL2 and PPARG and PARP1, LTA and two single-nucleotide polymorphisms (SNPs) in GLI1 have been found to play an important part in the pathogenesis of early-onset vincristine-induced peripheral neuropathy and late-onset bortezomib-induced peripheral neuropathy, respectively.⁴⁰ SNPs in PARP, LTA and GLI1, which are associated with an inflammatory response, are found to implicate in early-onset vincristine-induced peripheral neuropathy.^{40, 41} Platinum compounds such as cisplatin induce ototoxicity via upregulation of gene and protein expression associated with the STAT6 mediated inflammatory pathway.⁴²

As mentioned, although both neuronal and non-neuronal cells are involved in the pathogenesis of CIPN, the molecular mechanisms underlying the neuro-immune interaction and the actions of cytokines/chemokines in the context of chemotherapy-induced peripheral neuropathy are not fully understood. In addition to the entry of immune cells into the PNS, both macrophages and T-lymphocytes communicate with neurons and their satellite cells in the DRG, as well as Schwann cells. Release of cytokines and chemokines is one of the primary mechanisms facilitating neuron-immune communication. In response to chemotherapy-induced injury, macrophage infiltration leads to a subsequent production and secretion of various cytokines (TNF- α , IL-1 β , IL-6, IL-8), chemokines (CCL2, CXC family), growth factors, and inflammatory mediators such as bradykinin, prostaglandins (PGs), serotonin and nitric oxide (NO). Schwann cells start undergoing phenotype modulation and releasing TNF- α , IL-1 β , IL-6, PGE2, ATP, leukemia inhibitory factor (LIF) and CCL2.⁴³⁻⁴³ These molecules are well known as potential mediators for the development of peripheral neuropathy²⁸ through promoting macrophage infiltration and neuroinflammation.⁴⁴ Interestingly, Schwann cells also produce anti-inflammatory factors IL-10 and erythropoietin to counterbalance the proinflammatory cytokines and protect axons from further damage.⁴⁵ In animal experiment, intrathecal injection of IL-1ra and IL-10 gene therapy attenuated paclitaxel-induced neuropathic pain by suppressing the expression of TNF- α and IL-1 β , as well as iNOS in the DRG.⁴⁶⁻⁴⁷ Together, these findings provide evidence that proinflammatory cytokines are involved in the pathogenesis of chemotherapy-induced painful peripheral neuropathy. Further elucidation and identification of the underlying mechanism(s) would be of interest and may lead to potential therapeutic targets.

Sensitization of nociceptors by proinflammatory cytokines

Inflammatory cytokines TNF- α and IL-1 β can directly stimulate and sensitize A- and C-fibers⁴⁸ and lead to spontaneous discharge from A- and C-fiber, which is involved in allodynia and hyperalgesia after nerve injury. In rats with neuropathic pain due to vincristine or paclitaxel treatment, these abnormal spontaneous discharge from A and C-fiber are associated with the both acute and chronic pathogenesis of chemotherapy-induced painful peripheral neuropathy.^{18, 49} Molecules that are known to be involved in primary afferent sensitization, e.g., transient receptor potential vanilloid 4 (TRPV4), protein kinase A and kinase C, have been shown to be involved in paclitaxel-induced peripheral neuropathic pain.^{49, 50} Suppression of A- and C-fiber spontaneous discharge by acetyl-L-carnitine (ALC), blocks the development of the painful behavior induced by paclitaxel and vincristine in an animal model.⁵¹

Numerous studies have identified cytokines/chemokines as plausible mechanisms underlying the sensitization of nociceptors and their fibers in peripheral neuropathic pain.^{28, 38} It is known that peripheral nociceptors respond directly to cytokines, chemokines and other inflammatory mediators.⁵² IL-1 β , TNF- α , bradykinin, and nerve growth factors elicit action potential discharge by increasing Na⁺ and Ca²⁺ currents at the nociceptor peripheral terminals, which results in an increased membrane excitability, and a reduction in pain threshold and peripheral sensitization. The pain sensation in distal extremities has been attributed to dysfunction of small myelinated A δ or unmyelinated C-fiber.^{14, 53-55} Thus, sensitizing uninjured adjacent nerve fibers (nociceptors) or sensory neurons by proinflammatory cytokines and chemokines may play a critical role in the development of the chemotherapy-induced painful peripheral neuropathy in cancer patients. The molecular domains of inflammatory cytokines and chemokines may be the significant contributors to the chemotherapy-induced painful peripheral neuropathy.

In taxol and vincristine animal models, sensory terminal degeneration is found to be associated with activation of cutaneous Langerhans cells, which are known to release

proinflammatory cytokines.⁵⁶ One can argue that the pain symptom induced by chemotherapeutic drugs may be directly due to sensor terminal degeneration caused by those proinflammatory cytokines or chemokines. Given the fact that that neuropathic pain induced by taxol and cisplatin often occurs much sooner than any significant findings in IENF loss after the first dose infusion,^{10, 15} pain due to sensitization of nociceptors by these inflammatory cytokines may be an early sign of neurotoxicity caused by chemotherapeutic agents. The axonal degeneration may represent the later event occurring in peripheral nerves, as a consequence of an increase in the severity of injury in nerve fibers or sensory neurons in the DRG caused by proinflammatory cytokines after chemotherapy treatment. Clinically, paclitaxel acute pain syndrome may be an early manifestation of a disorder associated with sensitization of nociceptors and their fibers by proinflammatory cytokines.³⁹ One would expect that, if the spontaneous discharge is due to chemotherapy-induced inflammation, then NSAIDs should be effective in managing CIPN related pain. However, neither ibuprofen nor celecoxib have analgesic effects on the painful chemotherapy-induced peripheral neuropathy in humans and animal models.⁵⁷ As indicated in Figure 2, inflammatory mediators that do not derive from the cyclooxygenase cascade may play a role in this painful CIPN.

Numerous studies demonstrate that matrix metalloproteinases (MMPs) play an important role in the inflammatory and degenerative processes following nerve injury. MMPs mediate BNB breakdown, myelin destruction, leukocyte recruitment and cytokine release. Absence of MMPs, such as MMP24, causes a significant increase in the density of C-fiber nerve endings in the epidermis in the skin surface of MMP24^{-/-} mice, and the MMP24^{-/-} mice are characterized by enhanced sensitivity to noxious stimuli, and proinflammatory cytokine IL-6 and PGE2.⁵⁸ In an animal model, MMP3 expression and macrophage accumulation occurs in the DRG of rats after paclitaxel treatment and these animals show the identical symptoms of peripheral sensory neuropathy-related mechanical hyperalgesia,^{33, 36} suggesting that paclitaxel-induced upregulation of MMP3 and accumulation /activation of macrophages in the DRG are associated with behavioral changes. Interestingly, the upregulation of MMP3 occurs prior to macrophage infiltration indicating that MMP upregulation may play a triggering role in subsequent macrophage accumulation and activation in the DRG.

MMP2, MMP3 and MMP9 produced by neurons and satellite cells in the DRG mediate painful chemotherapy-induced peripheral neuropathy (pain hypersensitivity) by initiation and activation of IL-1 β and TNF- α .⁵⁹ By activating TNF- α , MMPs also lead to endoneurial remodeling and Wallerian degeneration, which is also associated with neuropathic pain. Treatment with neutralizing antibody to IL-1 β and TNF- α blocked allodynia caused by MMP2 and MMP9 injections^{59, 60} and furthermore, combined treatment with antibodies to TNF- α and IL-1ra reduces neuropathic pain to a greater extent than monotherapy with either antibody.⁶⁰ Additionally, Schwann cells control demyelination by degrading myelin protein through a matrix metalloproteinase (MMP)-dependent pathway, which contributes to early pain hypersensitivity. MMP promoted macrophage recruitment and activation possibly assist in the demyelinating process.^{61, 62} Therefore, MMP could be a target to prevent or treat chemotherapy-induced painful peripheral neuropathy in clinical practice. A therapeutic agent acting as a MMP inhibitor may prove effective in treatment of neuropathic pain in humans as described below.

Reciprocal interplay between cytokines and mitochondrial dysfunction

There is recent evidence from animal studies indicating that axonal mitochondrial function is disrupted during chemotherapy treatment and axonal mitotoxicity is the primary cause of all of the neuropathic symptoms induced by paclitaxel, vincristine, oxaliplatin and bortezomib.^{14, 15, 51} Mitochondrial dysfunction is one of the main causes of

neurodegenerative diseases and is related to oxidative stress, which promotes production of proinflammatory cytokines. It is worth mentioning that mitochondrial abnormalities don't occur significantly until day 7 following initial treatment of paclitaxel,¹⁴ whereas the onset of pain symptoms can happen as early as 24 hours after treatment with paclitaxel, cisplatin or combination of paclitaxel/cisplatin treatment in humans^{39, 63} and even after a few hours in animals.⁴⁹ Furthermore, in clinical observation, the symptoms and signs induced by paclitaxel or cisplatin can be long-lasting without improvement and probably irreversible even by the end of treatment⁶³ while the abnormalities of mitochondria have resolved by day 160 after paclitaxel treatment.¹⁴ As described earlier, it has been observed in an animal model of taxane-induced neuropathy that macrophage infiltration and activation occur following nerve injury as expressed by activation of expression of ATF3 in the DRG as early as 24 hours after treatment.^{34, 35} This finding suggests that immune system activation and immune-neuron communication may be the constituent explanation for the appearance of peripheral neuropathy specifically for the early painful symptoms. Mitochondrial dysfunction in peripheral neuropathy may derive from the direct effects of proinflammatory mediators such as cytokines, chemokines, reactive oxygen species and nitric oxide. Alternatively, mitochondrial dysfunction may affect several pathways that have been implicated in increased cytokine-induced inflammation and matrix metalloproteinase (MMP) catabolism. The reciprocal interplay between proinflammatory cytokines and mitochondrial dysfunction may play a key role in the development of significant loss of small fibers induced by paclitaxel, oxaliplatin, vincristine and bortezomib as well chemotherapy-induced peripheral neuropathy. The balance between the immune system pro-inflammatory and anti-inflammatory mechanisms is the important contributor to the development of chemotherapy-induced peripheral neuropathy, specifically to the initiation and progression of painful peripheral neuropathy. Tipping the balance in favor of anti-inflammatory processes may provide a novel therapeutic opportunity to interrupt development and progression of peripheral neuropathic pain in cancer patients who receive chemotherapy treatment.

Cytokines as candidate biomarkers and therapeutic targets

Biomarkers are generally used in clinical practice as diagnostic and prognostic tools to identify diseases and to monitor disease activity and treatment response. It is clear from experimental and clinical studies that the inflammatory response cascade accompanies the development of peripheral neuropathic pain. Cytokines, chemokines, and their receptors as well as their signaling pathways are involved in the development of chemotherapy-induced painful peripheral neuropathy. Therefore, characterization of cytokine and chemokine expression after chemotherapy might yield a new insight into the development of CIPN and may lead to development of effective prevention or treatment strategies for CIPN. Unfortunately, no biomarkers are currently available to assess the extent of CIPN or to predict outcomes in CIPN. Neurologists mostly rely on clinical examination and electrophysiological studies as diagnostic criteria for CIPN. But some information cannot be obtained from clinical examination and electrophysiology, especially when nerve damage is restricted to the distal extremities, as is the case with CIPN. Neurophysiologic tests are limited to evaluate of large diameter fibers and thus correlate poorly with physical examination or patient reported paresthesias and numbness.⁶⁴ Changes in neurophysiologic findings likely lag behind the onset of CIPN pathophysiology that leads to symptoms.⁶⁵ Thus, discovery of cytokines and chemokines as candidate biomarkers has the potential to predict the onset of CIPN and identify the early damage of axons. Moreover, CIPN presents a unique manifestation of the precise time and extent of neuronal or nerve injury induced by chemotherapy drugs and provides opportunities to conduct pre-emptive trials in preclinical and clinical setting. If CIPN can be blocked or attenuated by a pre-emptive therapy, it is more likely that a full and more aggressive chemotherapy regimen can be administered and

completed, which will increase survival rate of patients with cancer and enhance these patient's quality of life.

MMP inhibitors

As discussed above, the release of proinflammatory cytokines/chemokines by activated macrophages, satellite cells in the DRG and Schwann cells may be the primary cause of the pain symptom in CIPN, which is an early sign of initial peripheral neuropathy in most cancer patients undergoing chemotherapy treatment. Therefore, targeting the production of proinflammatory cytokines may be a promising therapeutic strategy for prevention or relief of chemotherapy-induced peripheral neuropathy, especially for the pain symptom. Extracellular matrix metalloproteinases (MMPs) control the integrity of the blood-nerve-barrier, myelin protein turnover and phenotypic remodeling of glia and neurons. The specific role of MMPs in the pathogenesis of painful peripheral neuropathy is believed to relate to their control of cytokine release (Figure 2). Pharmacologic inhibition of MMPs or administration of small interfering RNA (siRNA) for MMPs produced immediate and sustained attenuation of mechanical allodynia.^{59, 66} Treatment with the MMP inhibitor GM6001 or minocycline significantly reduces the mechanical allodynia after nerve injury.^{10, 66} Minocycline, a MMP3 inhibitor, has been reported to attenuate neuropathic pain⁶⁷ by inhibition of MMP3 upregulation, macrophage accumulation and proinflammatory cytokine release in the paclitaxel-treated rats. Treatment with minocycline effectively prevents both taxol-induced mechanical hyperalgesia and IENF loss in rats.¹⁰ Its inhibitory effect on cytokine release has been reported to be associated with its suppression of the nuclear factor- κ pathway.⁶⁸ Therefore, minocycline protects against cytokine-related damage to axons and Schwann cells.⁶⁹ However, its inhibitory effect seems most effective when treatment begins prior to nerve injury⁷⁰ because that minocycline does not reverse existing hypersensitivity after nerve injury.⁷¹ Pretreatment with minocycline inhibits macrophage infiltration and activation, suppresses ATF3 expression in DRGs and partially blocks the loss of intraepidermal nerve fibers.^{10, 16} Therefore, it is not difficult to understand its preventive effect on the mechanical allodynia and hyperalgesia induced by chemotherapeutic drugs.^{16, 72} Minocycline may be a promising drug to prevent the development of CIPN in clinical practice. According to NCI at NIH, minocycline is currently under investigation for the prevention or treatment of chemotherapy-induced peripheral neuropathy.

Phosphodiesterase inhibitors

Experimental evidence suggests that the intracellular mechanism involved in nociceptor sensitization results from an activation of neuronal signaling pathways, beginning with cyclic adenosine monophosphate (cAMP) production that modulates the activity of Na⁺ channels.⁷³ Cyclic AMP plays a key role in regulation of inflammatory responses of activated macrophages. Increasing of cAMP level through either PDE4 inhibition, PDE4 gene knock-out, or cAMP agonist have been widely show to decrease the inflammatory response of macrophages to activating agent, and therefore, decreasing cytokine expression. AV411 (ibudilast), a phosphodiesterase PDE4 inhibitor, has been shown in glial cells in vitro to suppress the production of proinflammatory cytokines IL-1 β and TNF- α , and increase the production of anti-inflammatory cytokines IL-10 and neurotrophic factors in a concentration-dependent manner. In patients with multiple sclerosis, AV411 also reduces the expression of proinflammatory cytokines TNF- α and interferon (IFN)-gamma.⁷⁴ AV411, clinically used as an anti-inflammatory drug, has been increasingly recognized as an approach for treating neuropathic pain. Indeed, AV411 is efficacious in preventing the onset of mechanical allodynia and attenuating mechanical allodynia in paclitaxel-treated rat model.⁷⁵ Propentofylline, a PDE3 inhibitor, is effective in reducing neuropathic pain induced by the chemotherapy drug vincristin.⁷⁶ A recent study reported that AV411 and its analog,

AV1013, inhibit the catalytic and chemotactic function of the macrophage migration inhibitory factor (MIF), which may contribute to their therapeutic functions as well.⁷⁷ Therefore, the mechanism underlying the analgesic effect of phosphodiesterase inhibitors may derive from suppression of IL-1 β , IL-6, TNF- α and nitric oxide production and an increase of cAMP production and an increase in the expression of the anti-inflammatory cytokine IL-10.⁷⁸

Bradykinin receptor inhibitors

Selective bradykinin B2 or B1 antagonists prevented the development of vincristine-induced hyperalgesia.⁷⁹ More interestingly, simultaneous administration of indomethacin or celecoxib with selective bradykinin B1 or B2 antagonists produces an additive anti-hyperalgesic effect on the vincristine-induced neuropathic pain model,⁸⁰ whilst celecoxib alone had no effect on alleviating this type of pain.⁵⁷ These results indicate that the interaction between the activation of bradykinin receptors and cox pathways plays an important role in the development of chemotherapy-induced peripheral neuropathic pain. However, from animal models and clinical observations, NSAIDs (such as aspirin, ibuprofen and celecoxib), even at high doses, failed to produce analgesic effects once allodynia occurred. Pre-emptive analgesia with lower dose of indomethacin and celecoxib significantly suppressed vincristine-induced hyperalgesia.⁸⁰⁻⁸² Therefore, the pre-emptive strategy may play an important role in prevention of peripheral neuropathic pain induced by chemotherapeutic agents.

Melatonin

In preclinical and clinical studies, melatonin, a pineal hormone, has been shown to exert a neuroprotective effect due to its anti-inflammatory properties. Patients receiving melatonin during chemotherapy treatment with taxanes and cisplatin show a decreased incidence of neuropathy.⁸³⁻⁸⁵ Its anti-inflammatory activity arises from the inhibition of NF- κ B and Nrf2 cascades and downstream inflammatory mediators and the production of free radicals, which play a part in mediating the chemotherapy-induced neurotoxicity.⁸⁶

Conclusions

CIPN remains a common and devastating effect of many chemotherapeutic agents without effective prevention and treatment, although a wide range of pharmacologic and non-pharmacological treatment have been investigated. It is hoped that as the mechanisms underlying CIPN are better understood, more therapeutic targets will be identified. Hopefully, this review will expand understanding of the role of cytokines in the development of CIPN and provide an additional rationale for developing therapeutic targets to intervene and treat CIPN. Moreover, it is important to undertake further investigation into the natural history of CIPN associated with various classes of neurotoxic chemotherapy agents. This may provide important insights into the molecular-genetic mechanisms that can be used in the development of new strategies for the prevention and treatment of CIPN.

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Figure 1.
The proposed targets of chemotherapy-induced neurotoxicity in the peripheral nervous system.

Figure 2.

A proposed diagram of cytokine network in pathogenesis of chemotherapy-induced peripheral neuropathic pain. Chemotherapeutic drugs such as taxanes induce upregulation of Matrix metalloproteinases (MMPs) in Schwann cells, DRGs and peripheral nerves. MMPs exert the following different roles in the pathogenesis of chemotherapy-induced peripheral neuropathy: 1) MMPs are the only proteases able to degrade the blood-nerve-barrier (BNB) by disruption of extracellular matrix components of the basement membrane; 2) MMPs directly degrade the myelin sheath; 3) MMPs induce migration, infiltration and activation of inflammatory cells in DRG and peripheral nerves; 4) MMPs induce inflammatory cells to release and activate inflammatory cytokines IL-6, IL-8, IL1B, TNF-α. The latter directly or indirectly act on primary afferent neurons to induce hypersensitivity of peripheral nerves, which contribute to the peripheral neuropathic pain processing after chemotherapy infusion.