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Chemotherapy-Induced Peripheral Neuropathy: Current Status and Progress

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Abstract

As there are increasing numbers of cancer survivors, more attention is being paid to the long term unwanted effects patients may experience as a result of their treatment and the impact these side effects can have on their quality of life. Chemotherapy-induced peripheral neuropathy (CIPN) is one of the most common long-term toxicities from chemotherapy. In this review we will briefly review the clinical presentation, evaluation and management of chemotherapy-induced peripheral neuropathy, with a focus on CIPN related to platinum and taxane agents. We will then discuss current clinical models of peripheral neuropathy and ongoing research to better understand CIPN and develop potential treatment options.

Keywords

chemotherapy; toxicity; neuropathy

i. Introduction

Chemotherapy-induced peripheral neuropathy (CIPN) is damage to the peripheral nerves caused by exposure to a neurotoxic chemotherapeutic agent. It is a common serious non-hematologic adverse effect of chemotherapy. The precise incidence and prevalence of CIPN vary among agents, combinations, and studies, and many authors note significant under-reporting [1]. The Gynecologic Oncology Group (GOG) reported that with a regimen of eight cycles of carboplatin area under the curve (AUC) 6 and every three week paclitaxel at 175 mg/m² in the front-line therapy of ovarian cancer, 36% of patients 70 years and older and 20% of patients under the age of 70 experienced neuropathy of grade 2 or higher [2].

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Conflict of Interest Statement

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CIPN interferes with optimal treatment of active disease resulting in the need for dose reductions, treatment delays and even premature cessation of chemotherapy, and can lead to long-term debilitating effects that can cause increased morbidity and decreased quality of life. In a study of paclitaxel efficacy and toxicity in older women, there was an increased incidence of paclitaxel related toxic effects that increased with age. In addition, the neurosensory and neuromotor toxic effects seen in older adults were significant and concerning for potential future functional consequences, such as loss of mobility, increased falls and other disability [3].

Chemotherapy-induced peripheral neuropathy most commonly presents as a pure sensory neuropathy with symmetric symptoms typically including numbness, loss of proprioception sense, tingling, pins and needles sensation, hyperalgesia or allodynia in the hands or feet in a stocking-glove distribution [4]. Occasionally there can be damage to motor fibers resulting in a motor neuropathy, which occurs more commonly with paclitaxel and vincristine. Autonomic neuropathy is seen most commonly with vinca alkaloids and can be associated with orthostatic hypotension, severe constipation and erectile dysfunction [5]. A review of systems should be completed prior to the initiation of potentially neurotoxic chemotherapy to establish a baseline assessment of patient functionality and symptoms. CIPN is typically dose-dependent [6]. It can occur at any point after the initiation of treatment including weeks to months after treatment has ended. Late presentations are particularly common with cisplatin. CIPN is commonly associated with exposure to platinum agents (cisplatin, carboplatin, oxaliplatin), taxanes (paclitaxel, docetaxel), vinca alkaloids (particularly vincristine), epothilones (such as ixabepilone) thalidomide and bortezomib [4]. Although upfront identification of patients who will experience CIPN is difficult, risk factors include prior therapy with a neurotoxic agent, diabetes mellitus, folate/vitamin B12 deficiencies, African race, and older age [7, 8]. Patients with increased risk should be particularly carefully informed about the risks and symptoms of CIPN and monitored closely during therapy with neurotoxic agents. In some instances, it may be best to consider an alternative regimen (e.g. substitution of docetaxel or liposomal doxorubicin for paclitaxel in therapy of ovarian cancer). In addition to metabolic or medical conditions that may increase risk for CIPN, numerous genetic variants have been identified that are associated with an increased risk of developing CIPN. However, to date none of these genetic variants have been replicated in independent studies [8-10].

Unfortunately, to date there are no agents that have been successful in the prevention of chemotherapy-induced peripheral neuropathy [11]. There has also been limited progress in discovery of agents that show benefit in the treatment of CIPN. None of the available therapies reverse the neuropathy although some may ameliorate the pain. Many agents are used based on data from management of other forms of neuropathy, e.g. diabetic neuropathy [12]. However Smith et al., [12] demonstrated a benefit for duloxetine over placebo specifically in the treatment of chemotherapy-induced peripheral neuropathy.

ii. Clinical features of CIPN associated with Taxanes and Platinum Agents

Taxanes

Paclitaxel and docetaxel typically cause a sensory neuropathy described as paresthesia, numbness or neuropathic pain in the hands and/or feet. Deficits in motor function are less common, but can present in severe cases. The risk of taxane-induced peripheral neuropathy increases with cumulative dose received [6]. Some studies have reported less neurotoxicity with weekly paclitaxel dosing in comparison to 3-week dosing when the total dose is kept similar [13]. For example, in the MITO-7 study, a randomized phase 3 trial of carboplatin plus paclitaxel once a week at 60 mg/m² versus paclitaxel every three weeks at 175 mg/m² in patients with advanced ovarian cancer, 17% of patients experienced grade 2 or higher neuropathy in the every 3 week arm versus only 6% in the weekly arm. However most commonly used weekly paclitaxel regimens involve a higher cumulative dose of paclitaxel and neuropathy rates with such weekly regimens are not lower. The Japanese Gynecologic Oncology Group (JGOG) administered paclitaxel at a dose of either 80 mg/m² weekly or 180 mg/m² every three weeks (along with carboplatin AUC 6), and reported 7% grade 3 or higher sensory and 5% grade 3 or higher motor neuropathy in the weekly group versus 6% grade 3 or higher sensory and 4% grade 3 or higher motor neuropathy in the every three week group [14]. In a trial randomizing metastatic breast cancer patients to single agent paclitaxel 175 mg/m² every three weeks versus paclitaxel 80 mg/m² weekly, the patients on the weekly arm were initially given the first six infusions at 100 mg/m²; this resulted in a 30% incidence of grade 3 peripheral neuropathy, and the trial was subsequently amended to start weekly infusions at 80 mg/m² [15].

Most patients can expect symptom improvement or resolution within a 3-6 month period after the discontinuation of treatment, but more severe cases tend to be less likely to resolve [16]. Pignata et al reported on 120 ovarian cancer patients who received six cycles of front-line chemotherapy with carboplatin AUC 5 and paclitaxel 175 mg/m² every three weeks. There was a 15% probability of still having neuropathy (mostly grade 1) 6 months after completion of chemotherapy, and an 11% chance of still experiencing neuropathy at 2 years after completion of chemotherapy [17]. In one case-control study of breast cancer patients treated with weekly paclitaxel, diabetes mellitus (DM) was the only independent factor found to predict for delayed recovery. After 2 years, 68.7% of patients with DM (vs 29.2% of women without DM) still experienced CIPN, which was functionally significant (grade 2-3) in 18.2% [18].

Administration of paclitaxel can be associated with an acute pain syndrome characterized by development of myalgia and arthralgia within 1-4 days of paclitaxel infusion [19]. This is more common with higher single doses (i.e. more common with a weekly than with an every three week regimen). Severe acute pain syndrome with paclitaxel has been reported to be predictive of development of chemotherapy-induced sensory neuropathy [19].

Docetaxel is generally less neurotoxic than paclitaxel at standard dosage. The Scottish Gynaecological Cancer Trials Group front line ovarian cancer trial reported a rate of 11% grade 2 or higher neurosensory toxicity with docetaxel 75mg/m² and carboplatin AUC 5 versus a rate of 30% with paclitaxel 175 mg/m² every three weeks and carboplatin AUC 5.

Oncologic outcomes (overall and progression free survival) were not different [20]. Neuropathy rates with nab-paclitaxel appear to be similar to those seen with standard paclitaxel when the same cumulative dosage is administered [21].

Platinum

Platinum chemotherapies tend to present with a similar sensory peripheral neuropathy consisting of numbness, tingling and paresthesia in the hands and/or feet. This can also be associated with decreased vibratory sensation and loss of proprioception which can lead to gait instability [22]. Platinum chemotherapies are unique in their ability to be associated with worsening CIPN that occurs after the discontinuation of the platinum agent, a phenomenon called “coasting.” They can also be associated with Lhermitte’s syndrome, the occurrence of an electrical sensation radiating from the neck to the extremities with neck flexion [22, 23]. Oxaliplatin is associated with cold-triggered neuropathic symptoms. Carboplatin is much less neurotoxic than either cisplatin or oxaliplatin [22].

Other chemotherapeutic agents associated with CIPN

Vinka alkaloids such as vinorelbine are also sometimes used in the treatment of gynecologic malignancies. They can cause a peripheral neuropathy that is primarily sensory [4]. However autonomic dysfunction is also common with this class of agents. This can present as severe constipation, and prophyllactic stool softeners are sometimes used.

iii.Pathophysiology of CIPN

Taxanes

Mitochondrial abnormalities are a major mechanism of CIPN across all of the various chemotherapeutic agents. The taxane family of chemotherapeutics, including paclitaxel, inhibits tubulin depolymerization [24, 25], thereby interfering with the stabile/labile balance of microtubules[25], including the axons of neurons. Swollen and vacuolated mitochondria are commonly observed in the axons of sensory nerves in animal models of CIPN caused by paclitaxel [26]. By interfering with microtubule dynamics, paclitaxel has been shown to interfere with calcium signaling in mitochondria and the endoplasmic reticulum (ER) by opening of the mitochondrial membrane permeability pore, leading to calcium triggered calcium release from the ER [27]. The mitochondrial permeability transition pore (mPTP) is a multi-molecular complex containing the voltage-dependent anion channel (VDAC), which spans the mitochondrial outer membrane. Isolated mitochondrial membrane fragments that contain the VDAC also contain β -tubulin [28]. The paclitaxel-evoked opening of the mPTP has also been shown to cause calcium release from mitochondria which may facilitate cellular injury. Paclitaxel induces injury of sensory neurons, morphological and biochemical alterations in dorsal root ganglion (DRG) satellite cells, hyperplasia/hypertrophy of macrophages in the peripheral nervous system, and increased microglial and astrocyte activation within the spinal cord. Collectively, these pathologic changes may contribute to the sensory dysfunction and pain that accompanies the development of paclitaxel-induced neuropathy[29].

Platinum Agents

DRG represent the main structure that is targeted by the deposition of platinum compounds, thereby generating neurotoxicity [30]. Two putative mechanisms are primarily involved in platinum-induced neurotoxicity, and DRG neuron apoptosis is the common cornerstone [31]. First, platinating agents are able to alter the tertiary structure of DNA by forming intra-strand adducts and inter-strand crosslinks [32, 33]. Moreover, it has been documented that the neuronal apoptosis on DRG could be triggered by oxidative stress, mitochondrial dysfunction with a release of the cytochrome-c pathway, independence of Fas receptor activation, or by increased activity of p53, p38, and ERK1/2 [30, 34]. Oxaliplatin-induced neurotoxicity induces a distinct form of chronic neurotoxicity that is induced by the morphologic and functional changes in the DRG cells, resulting from the local deposition and accumulation of oxaliplatin. On the other hand, the acute form of oxaliplatin-induced neurotoxicity is thought to be caused by a dysfunction of nodal axonal voltage-gated Na⁺ channels, likely resulting from the oxalate chelating effect on both Ca²⁺ and Mg²⁺ [34]. Cisplatin forms adducts with mitochondrial DNA resulting in direct mitochondrial DNA (mtDNA) damage that is a novel mechanism for cisplatin-induced CIPN. Mitochondrial dysfunction has also been observed in axons following CIPN caused by oxaliplatin and bortezomib [28, 35] and bortezomib, like paclitaxel, has been shown to lead to mitochondrial calcium release leading to activation of the apoptotic cascade [28].

iv. Pharmacogenomics of CIPN

Taxanes

Identifying genetic or molecular markers predictive of patients with a high risk of neurotoxicity development from a given chemotherapeutic agent could significantly impact the quality of life of cancer survivors. Clinical risk factors are discussed above. There have been some candidate gene approaches to evaluate single nucleotide polymorphisms (SNPs) in genes involved in the pharmacokinetic and pharmacodynamic properties of neurotoxic drugs, but no reliable biomarker has thus far been identified to detect patients at high risk of developing CIPN [10]. Variants in genes relevant to drug disposition, metabolism and drug action can influence the patient's exposure and sensitivity to the drug [10]. For paclitaxel, most studies focus on mutations in biologically relevant candidate genes such as CYP2C8, CYP3A4, CYP3A5 and ABCB1 [10, 23]. Hertz et al. [10] demonstrated an association between the CYP2C8*3 variant and a two-fold increase in risk for paclitaxel-induced peripheral neuropathy across racial groups. Interindividual variability has also been found in the therapeutic target of paclitaxel, β -tubulin II α (TUBB2 α) mRNA expression and two genetic variants in the promoter region of the gene are involved in this variation. Genotyping patients treated with paclitaxel showed that these variants are associated with paclitaxel neuropathy risk [36]. In addition, genome wide association studies (GWAS) were performed to identify genetic markers predictive of peripheral neuropathy in the paclitaxel arm of Cancer and Leukemia Group B 40101 in which patients were assigned to receive varied cycles of AC (doxorubicin plus cyclophosphamide) or paclitaxel as well as Eastern Cooperative Oncology Group (ECOG) 5103 a trial in which patients treated with AC were followed by a paclitaxel arm or two different arms with bevacizumab and chemotherapy. A SNP in FGD4, a congenital peripheral neuropathy gene, FZD3 and EPHA5 were identified

to be associated with a severity or dose at onset of paclitaxel-induced sensory peripheral neuropathy in patients with both European and African ancestry [9]. In another study integrating LCL cytotoxicity SNPs and paclitaxel-induced neurotoxicity SNPs, a gene named RFX2 was identified to be associated with increased risk of paclitaxel-induced neurotoxicity [37]. In a similar integration method using Asian cell lines and patient cohorts, when focusing more on Asian specific genes, decreased AIPL1 was found to result in decreased sensitivity of neurons to paclitaxel. In addition, breakpoint cluster region protein (BCR) was also identified to protect the neurons from paclitaxel induced toxicity [38]. Furthermore, using the CALGB 40101 patient cohort, paclitaxel-induced peripheral neuropathy was found to be heritable. The set of genes that drive heritability of paclitaxel induced neuropathy was found to be implicated in axonogenesis and, more specifically, the regulation of axon outgrowth [39].

More recent work has identified a panel of candidate SNPs associated with increased risk of grade 3-4 paclitaxel-induced peripheral neuropathy in patients of European descent [8]. Only two SNPs were found to be statistically significant and these did not overlap with any of the previously implicated SNPs from the CALGB 40101 study [9]. Interestingly, one of the significant SNPs alters the GPR177 gene, also called Wnt. Wntless (Wnt) is in the same family as an already implicated gene, frizzled (FZD3) [9], which may suggest the importance of the Wnt pathway in paclitaxel-induced peripheral neuropathy [8]. In the same study, African American race was a strong predictor for grade 2-4 paclitaxel-induced peripheral neuropathy [8]. Further understanding of germline variations associated with increased risk of CIPN will likely help to guide clinical practice in the future.

Platinum

Few studies have addressed genetic susceptibility to long-term cisplatin neurotoxicity. One early study focused on glutathione-S-transferases (GSTs), which are expressed in dorsal root ganglia and may protect against cisplatin-generated overproduction of reactive oxygen species [40]. Among 238 testicular cancer survivors, self-reported neurotoxicity using the validated Scale for Chemotherapy-Induced Long-Term Neurotoxicity was assessed according to functional polymorphisms in GSTP1 and GSTM1 in lymphocyte DNA [40]. The 37 patients expressing GSTP1-GG were statistically significantly less symptomatic for distal paresthesias compared with those with GSTP1-AA and GSTP1-AG [40]. Other study comparisons were in terms of the total Scale for Chemotherapy-Induced Long-Term Neurotoxicity score, which also includes self-reported hearing loss and tinnitus. An investigation of polymorphisms in GSTs and several DNA repair genes in 104 ovarian cancer patients given cisplatin and cyclophosphamide found that neuropathy (measured in terms of National Cancer Institute criteria) was less frequent among women with the GSTM-null or GSTM3 AGG/AGG genotypes [41]. According to recent reviews [23, 42], there have been no other reported pharmacogenomic studies of CIPN in which cisplatin was given alone or in combination with a non-neurotoxic chemotherapeutic agent [42]. Clinical GWAS has also been performed in colon cancer patients treated with oxaliplatin to identify genetic predictors of oxaliplatin-induced neuropathy. Patients with GSTP1 T/T genotype treated with oxaliplatin were more susceptible to neurotoxicity and therefore more likely to discontinue therapy [43]. Several SNPs were identified and the TAC1 gene in particular was

found to be significantly associated with neuropathy [44]. A recent study published a GWAS cohort of oxaliplatin-treated colorectal cancer patients, aimed at validating SNPs identified in previous oxaliplatin GWAS [44] as determinants of oxaliplatin induced neuropathy. Interestingly, this GWAS did not validate the previously established variants after multiple comparisons [45]. The lack of validation of SNP variants associated with neuropathy highlights the importance of replication studies with meta-analysis for validation of GWAS findings

viii. Models to study CIPN

Current animal models

Traditional methods for studying neuronal damage due to chemotherapy have largely relied on animal and cell-line models [46]. Often these models demonstrated many of the neuropathological changes seen in the human disease. Most of these models also exhibited typical electrophysiological abnormalities expected in CIPN, such as reduced nerve action potentials and in some cases reduced conduction velocities. Careful behavioral examination of these animals revealed findings consistent with neuropathic pain [47]. Unsettling in the field, however, are the significant differences in outcome measures used, and pathological, electrophysiological, and behavioral abnormalities observed in different laboratories. There are many causes of such discrepancies, and these include the genetic background of the animal used, mode of administration of neurotoxic chemotherapy (intravenous vs intraperitoneal), dose and duration of drug administration, and extent and detail of outcome measures used in the evaluation of peripheral neuropathy [48]. In addition to the rat models of paclitaxel CIPN, various mouse models have also been developed [47, 49]. These models predominantly used morphological assessments, including epidermal nerve fiber density [50] as the primary outcome measures. These models have been successfully used to evaluate potential therapeutic compounds [49, 50] but have not resulted in effective new therapies to treat CIPN.

CIPN studies have been performed in rat pheochromocytoma cell lines, PC12 or NS1, as model systems to evaluate neurite outgrowth in response to neurotoxic chemotherapy drugs, such as paclitaxel [37, 51], vincristine [51], oxaliplatin [52, 53] and cisplatin [51, 54]. Several studies have used the rat *in vitro* and *in vivo* models to investigate potential neuroprotective agents against paclitaxel [51], oxaliplatin [53] and cisplatin [54] induced peripheral neuropathy. The mechanism by which oxaliplatin elicits its neurotoxicity and the effect of calcium and magnesium against this toxicity has also been studied using the rat model [52]. The limitations are that the cells are derived from a neuroendocrine rat tumor and cells require treatment with nerve growth factor for neurite outgrowth (the measure used to study effects of treatment), and a randomized clinical trial found that calcium and magnesium infusions were not effective in reducing the neurotoxicity of oxaliplatin [55].

Novel stem cell-derived models

While stem cell technology, such as induced pluripotent stem cells, has revolutionized the field of “*in vitro* disease modeling” [56], there is a paucity of published work using these differentiated cells for studies of drug toxicity such as CIPN. Human fibroblasts were

reprogrammed into nociceptor neurons and the neurons exhibited sensitization to the chemotherapeutic drug oxaliplatin, modeling the inherent mechanisms underlying painful CIPN [57]. Recently, a potential model to evaluate CIPN by employing human neurons reprogrammed from commercially available induced pluripotent stem cells has been published [58]. The authors reported reproducible differences in morphological characteristics including neurite outgrowth phenotypes, cellular viability and apoptosis following treatment with four distinct chemotherapeutic drugs: vincristine, paclitaxel, cisplatin and hydroxyurea (negative control). This model was also used to demonstrate functional consequences of gene knockdown on neuronal sensitivity to chemotherapeutics of genes identified through clinical genome-wide association studies (GWAS). Studies to date that have used these neurons include: 1) knockdown of a gene encoding paclitaxel target TUBB2 α caused decreased neurite outgrowth after paclitaxel treatment (concordant with findings from a patient study connecting decreased expression of the gene with promoter alleles that associate with increased risk of paclitaxel-induced peripheral neuropathy [36]; 2) decreased expression of *CEP72* (encoding centrosomal protein 72kDa) resulted in decreased relative total outgrowth, number of processes, and number of branches upon vincristine treatment. This supported clinical findings of genome-wide significance of rs924607, a SNP in the promoter region of *CEP72* and its association with vincristine-induced acute peripheral neuropathy [59] and; 3) a gene identified in an Asian-specific GWAS, BCR (breakpoint cluster region), was validated using iPSC-derived neurons with knockdown corresponding to increased sensitivity to paclitaxel induced damage to neurons [38].

The use of a relevant tissue model that represents neurons and recapitulates the key neuropathy features will be key to developing novel therapies to overcome neuropathy (Figure 1). Important questions regarding whether these neurons represent the donor individual and whether *in vitro* phenotypes recapitulate clinical phenotypes (e.g., CIPN) are still unanswered. Furthermore, determining whether inter-individual variation is greater than intra-individual variation in chemotherapeutic sensitivity using this model will be an important next step for genotype-phenotype studies.

v. Clinical Assessment Tools for CIPN

Evaluation of patients with CIPN currently consists of clinical assessment that is usually performed by a physician, nurse practitioner or other clinical staff using a traditional clinical grading scale or patient reported measures (Table 1). The most commonly referenced physician-based clinical grading scales include the National Cancer Institute Common Terminology Criteria for Adverse Event (NCI-CTCAE—currently version 4), World Health Organization, ECOG and Ajani criteria [7] [60]. In general, these scales tend to be organized in ordinal fashion with sensory or motor neuropathy symptoms receiving a grade of 0 to 5, with grade 0 representing the absence of symptoms and grades 4 and 5 representing the most severe symptoms or symptoms that result in death, respectively.

Limitations with this form of clinical assessment of CIPN have been identified and discussed extensively in the literature [1]. In particular the subjective nature of this type of assessment leads to a high degree of inter-rater variability. There is also a significant degree of variability between physician-based symptom rating and patient reported self-assessment

scores, with physician-based clinical assessment tools showing decreased sensitivity in picking up symptoms of chemotherapy adverse events identified by patients on patient-reported outcomes instruments [1].

Critiques of the NCI-CTCAE include its lack of reference to descriptions of clinically significant CIPN and its failure to give specific criteria or parameters to distinguish each level of grading [7]. There is also concern that some aspects of CIPN are not adequately captured with this scale, such as CIPN related pain [60]. NCI-CTCAE v5.0, which is currently under production, should have a focus on improved definitions of neuropathy specifying limitations in instrumental activities of daily living (ADLS) versus self-care ADLS (CTCAEv5 draft 6/2015).

Other physician-based assessment tools such as the Ajani scale and Total Neuropathy Scale were developed and modified in an attempt to improve detection and grading of CIPN. Additional features such as morbidity range and quantitative evaluation of CIPN through neurophysiologic exam were added with the intent to improve detection of CIPN and guide clinical practice [60].

Multiple patient-based assessments have been developed to help improve evaluation and detection of CIPN. The FACT/GOG-Ntx is a two-part assessment consisting of a quality of life measure (FACT-G) and an 11-item neurotoxicity scale. Validation of scale showed the four-item sensory component could be used as a quick and effective measure for identifying patients with clinically significant CIPN [61]. The EORTC-QLQ-CIPN20 is another frequently PRO tool and has been validated for the detection of CIPN [62] [1]. The NCI has recently developed the PRO-CTCAE which focuses on 78 of the 790 adverse events in the CTCAE for patient self-report. This tool has been validated in a multicenter study conducted at both academic and community oncology settings showing higher PRO-CTCAE scores in the groups receiving active cancer treatment and expected to have worse symptoms regardless of ECOG-PS score [63]. Other PRO tools, such as the Patient Neuropathy Questionnaire (PNQ) and Chemotherapy Induced Neurotoxicity Questionnaire (CINQ) include more detailed assessment of quality of life by assessing how CIPN affects daily activities [64] [65].

Objective measures have been studied and used for the evaluation of chemotherapy-induced peripheral neuropathy. Nerve conduction studies (NCS) measure the amplitude and conduction of compound sensory and motor action potentials (CSAPs and CMAPs, respectively) and show a correlation of a reduced CSAP in patients with CIPN [6]. Nerve conduction studies are considered the gold standard in evaluation of CIPN but are rarely used in the clinical oncology setting due to the need for specialized equipment, specially trained personnel and discomfort to patients. An alternative to NCS is nerve excitability studies, which have been shown to detect oxaliplatin-induced peripheral neuropathy prior to the detection of neuropathy with NCS and the development of clinical symptoms [66]. Other forms of objective evaluation include quantitative sensory testing (QST) which quantifies changes in sensory perception by determining the threshold for sensory stimuli [7]. This can be assessed through vibration threshold detection, thermal detection and sharpness detection. In theory, many of these procedures can be performed in the clinic with

little training, such as vibration threshold detection with the use of tuning forks, however they are rarely used in clinical practice and the results of these studies have not been validated or determined to be relevant to medical decision making.

vi. Prevention of PN

Dose reduction, use of alternate chemotherapy, or temporary cessation of chemotherapy have been the primary strategies implemented for the management of CIPN. Although a number of agents have been investigated for their efficacy in preventing CIPN (Table 2) with some minimally positive studies, none have shown sufficient benefit or evidence of benefit for standard use in clinical practice. The limitations in the studies of these agents include small sample size, lack of placebo-controlled arms and in some cases, unblinded study design. The 2014 ASCO Guidelines on the Prevention and Management of Chemotherapy-Induced Peripheral Neuropathy did not recommend any agent for the prevention of CIPN [11]. The NCI clinical trials website list current active studies evaluating agents such as combination Vitamin B12 and Vitamin B6, combination Vitamin D and Omega-3 and low polyamine diet [67]. Preclinical studies evaluating cisplatin, oxaliplatin and vincristine-treated mice, have suggested a role for PARP inhibitors as a therapeutic agent in the prevention in CIPN [68].

vii. Treatment of CIPN

Multiple agents have been evaluated as potential treatments for CIPN, but have not convincingly shown a benefit in improving established CIPN (Table 3). Even agents that are successful in managing diabetic neuropathy have shown less than desired improvements in CIPN, supporting a possible difference in pathophysiology of CIPN. Duloxetine, a serotonin and norepinephrine dual reuptake inhibitor, is the one agent convincingly shown in a randomized trial to improve the symptoms of established CIPN [12]. In a phase III trial examining the effects of duloxetine on CIPN, patients with oxaliplatin induced peripheral neuropathy in particular experienced better outcomes with duloxetine than patients with taxane induced neuropathy [12]. The pathophysiology of platinum induced neuropathy is very different from taxane induced neuropathy, however the mechanism as to why duloxetine is more effective in ameliorating oxaliplatin induced neuropathy, is not clear. It is known that the serotonin and norepinephrine reuptake inhibitors block neurotransmitters which results in decreased pain transmission[55]. Narcotics are needed in some cases.

Noninvasive measures of managing CIPN can also be considered as an adjunct to medical management. Techniques such as physical and occupational therapy help with improvement in overall functional status and fine motor skills that may be affected by CIPN. Other complementary and alternative medicine (CAM) techniques have been recommended for the management of cancer related pain including acupuncture. Although the exact mechanism of action is unknown, studies have shown an improvement in pain symptoms greater than that expected with placebo effect alone [69]. A more extensive review of the clinical management of painful CIPN was recently published in this journal [70].

iv. Conclusion

CIPN represents an important challenge due to the lack of treatment that can effectively prevent or mitigate this adverse effect of some of the most common and effective chemotherapy agents. The effects of CIPN can be severe, leading to premature discontinuation of therapy and chronic effects of neurotoxicity. Efforts to find medications to prevent or treat CIPN have not yielded many options. An improved understanding of the pathophysiology of CIPN and genes/genetic variants associated with predisposition to CIPN will assist in the development of neuroprotective agents and novel therapies with improved toxicity profiles.

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Highlights

- CIPN is a common adverse effect of neurotoxic chemotherapies and tends to occur in a dose dependent fashion.
- Multiple proposed pathophysiologic changes occur at the cellular level, making it difficult to identify a single approach to prevent CIPN.
- We cannot predict patients that will have CIPN, but genetic variants have been found that indicate increased susceptibility.

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Potential of iPSC derived neurons

Figure 1. Potential of iPSC derived models

Recent technological development allows for the development of induced pluripotent stem cells (iPSCs) and differentiation to neurons for drug development, mechanistic evaluation and toxicity testing to ultimately improve health.

Table 1

Commonly Used Assessment Tools for CIPN

	Assessment tool	Test Format	Description of Test
Physician –based assessments [5] [29] [30] [32]	NCI-CTCAE v4	Physician-based assessment	-neuropathy graded on scale 1-4 - focus on inhibition of ADLS -critiqued for lack of sensitivity c/w patient reports
	WHO scale	Physician-based assessment	-neuropathy graded on scale 1-4 - focus on inhibition of ADLS
	Ajani scale	Physician-based format	-neuropathy grade associated with morbidity range that provides guidance on future therapy -focus on difficulty with ambulation as measure of functional capacity
	Total neuropathy Scale	Physician-based assessment	-evaluation of autonomic sx, vibration perception, neurophysiological exam
Patient-based assessments [31] [34] [35] [36] [37]	FACT/GOG-Ntx	11-item subscale of FACT/GOG	-positive findings correlate to NCI-CTC grade > or =1 -critiques for evaluation of astereognosis and ototoxicity [61] -4 item neurosensory can be used alone, highly reflective of CIPN
	EORTC QLQ-CIPN20	20-item subscale of EORTC QLQ	-combined assessment of QoL and CIPN -highly correlated with NCI-CTC
	PNQ	2-item Questionnaire	-specific focus on symptoms of CIPN -if symptom present, assessed for its interference with specific daily activities -weak correlation with FACT/GOG-Ntx and NCI-CTC [61]
	CINQ	Questions presence of symptoms in upper and lower extremities and face	-if symptoms present, patient asked to rate degree of bother and effect on daily activities -Highly correlated with FACT/GOG-Ntx

Table 2

Pharmacologic Agents Associated with Prevention CIPN [15]

	Pharmacologic Agent	Neurotoxic Chemotherapy	Limitations of Studies/Agents
Limited Benefit	Amifostine	Platinum and taxane, (specifically carboplatin/paclitaxel)	-benefits not consistent across studies -significant toxicity from agent: nausea, vomiting, lightheadedness [/] -some reports of associated dermatologic, cardiovascular and neurologic toxicity [/]
	Glutamine	Oxaliplatin	-small sample size -unblinded study -lack of placebo-control
	Glutathione	Platinum	-small sample sizes -in consistent results across studies
	Oxcarbazepine	Oxaliplatin	-small sample size -lack of placebo-control
	Venlafaxine	Oxaliplatin	-small study size -results not reproduced
No Proven Benefit or Harmful	Acetyl-L-Carnitine	Platinum	Worsening of CIPN
	Amitriptyline	Vinca Alkaloids, platinum or Taxanes	Drug associated toxicities
	Calcium and Magnesium	Oxaliplatin	Convincingly negative large phase 3 study
	Diethyldithiocarbamate (DDTC)	Platinum	-Increased toxicity and early treatment dc in treatment arm -lower cumulative cisplatin doses
	Glutathione	Specifically for Paclitaxel/carboplatin	Convincingly negative study
	Nimodipine	Cisplatin	Worse outcomes in active arm
	Org 2766	Cisplatin or Vinca alkaloids	-Multiple studies with negative results -possible worse outcome for active arm
	Retinoic acid	Cisplatin + Paclitaxel	drug toxicity
	Recombinant human leukemia inhibitory factor (rhuLIF)	Paclitaxel + Cisplatin	Worse neuropathy endpoints in active therapy arm
	Vitamin E	Taxane or platinum	Convincingly negative studies

[/] due to significant side effect profile, ASCO guideline recommend against use although some studies showed benefit on neuropathy

Table 3

Selected Pharmacologic Agents Evaluated for Treatment of CIPN [15]

Pharmacologic Agent	Neurotoxic Chemotherapy	Recommendation
Acetyl-L-Carnitine		Not recommended – prevention trial a/w increased CIPN
Duloxetine	Taxane or Platinum	Recommended - Positive trial for oxaliplatin or paclitaxel neuropathy
Gabapentin	Vinca alkaloids, platinum, or taxanes	Not recommended – Negative trial, but effective in other forms of neuropathy
Lamotrigine	Vinca alkaloids, platinum, or taxanes	Not recommended – Negative trial
Nortriptyline/Amitriptyline	Vinca alkaloids, platinum (cisplatin), or taxanes	Not recommended – small trials, not powered but favor treatment arms
Topical (amitriptyline, ketamine, ± baclofen)	Vinca alkaloids, platinum, taxanes, or thalidomide	Not recommended – suggestion of improvement in active treatment arm, but not statistically significant