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National Cancer Institute-supported chemotherapy-induced peripheral neuropathy trials: outcomes and lessons

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Abstract

Chemotherapy-induced peripheral neuropathy (CIPN) is one of the most common and debilitating complications of cancer treatment. Due to a lack of effective management options for patients with CIPN, the National Cancer Institute (NCI) sponsored a series of trials aimed at both prevention and treatment. A total of 15 such studies were approved, evaluating use of various neuro-modulatory agents which have shown benefit in other neuropathic pain states. Aside from duloxetine, none of the pharmacologic methods demonstrated therapeutic benefit for patients with CIPN. Despite these disappointing results, the series of trials revealed important lessons that have informed subsequent work. Some examples of this include the use of patient-reported symptom metrics, the elimination of traditional—yet unsubstantiated—practice approaches, and the discovery of molecular genetic predictors of neuropathy. Current inquiry is being guided by the results from these large-scale trials, and as such, stands better chance of identifying durable solutions for this treatment-limiting toxicity.

Keywords

Chemotherapy; Peripheral neuropathy; Cancer; Clinical trials

Introduction

Advances in chemotherapy have resulted in improved survival for many patients with cancer. A chief concern, both during and after treatment, is the presence of chemotherapy-related

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side effects. Among the most debilitating of these toxicities is chemotherapy-induced peripheral neuropathy (CIPN), a well-established adverse effect of several commonly used agents, including platinum compounds, taxanes, vinca alkaloids, and proteosome inhibitors. In the treatment phase, CIPN can limit therapeutic options for patients and result in reduction of dosing; in the aftermath of treatment, it can have a profound effect on quality of life during survivorship [1].

CIPN is predominantly a sensory phenomenon, with symptoms arising in a cumulative dose-dependent manner and occurring in a “stocking-glove” distribution. For most patients, symptoms tend to improve after cessation of chemotherapy, although there are subtle differences in the natural history of CIPN, due to the different mechanism of action of each agent. With platinum compounds, as many as 30 % of patients experience worsening of neuropathy for a few months following completion of therapy, and a sizable cohort report persistent symptoms lasting years [2, 3]. Paclitaxel-associated CIPN usually improves in the months following treatment cessation [4, 5], but still has been associated with long-term persistence of some degree of neuropathy in up to 80 % of patients, with roughly a third of these patients reporting severe symptoms [6].

Both the immediate and long-term CIPN symptoms have prompted multiple investigations designed to prevent and/or treat this toxicity. In the setting of a growing number of cases, and a dearth of successful management strategies, the National Cancer Institute (NCI) sponsored a series of trials evaluating several therapies for the prevention and/or treatment of CIPN. The present article reviews the findings from such trials and identifies lessons to be carried forward in future work.

NCI-supported CIPN trials

Prevention trials

MDA-CCC-03-27 (alpha-lipoic acid; initiated 2004; manuscript published 2014)—Pursuant to preliminary data supporting its efficacy in the treatment of neuropathy unrelated to chemotherapy [7, 8], alpha-lipoic acid (ALA) was tested as a prophylactic agent for patients undergoing platinum-based chemotherapy in a randomized, double-blind, placebo-controlled manner [9] (Table 1). Two-hundred forty-three patients, who had metastatic disease and many of whom had received prior treatments, were recruited for randomization, with an intention for subjects to receive ALA 600 mg (or placebo) three times daily for 24 weeks, alongside platinum-based chemotherapy regimens. It was expected that this sample size would have been adequate to detect significant differences between treatment groups with 90 % power, though this was limited by considerable patient withdrawal and treatment noncompliance. Degree of CIPN was measured using the Functional Assessment of Cancer Therapy/Gynecologic Oncology Group-Neurotoxicity (FACT/GOG-Ntx) scale, functional tests designed to assess limitations imposed by neuropathy (e.g., time to button six-hole shirt), and the Brief Pain Inventory (BPI) partial form. Only 29 % of patients completed the study, with comparable drop-out rates in both study arms; no statistically significant differences were observed in pain scores or functional outcomes. As a secondary outcome of the study, tumor response was measured at 24 weeks

utilizing standard response criteria, with no statistically significant differences observed between the two groups.

NCCTG-N04C7 (calcium and magnesium; initiated 2004; manuscript published 2011)—Based on supportive findings published in a retrospective review [21], the practice of administering calcium and magnesium alongside oxaliplatin-based regimens gained popularity, with hopes of preventing the development of CIPN. The North Central Cancer Treatment Group (NCCTG) developed N04C7, a placebo-controlled, double-blinded trial to evaluate this approach. The primary neuropathy assessment tool was the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE; version 3.0). A second neuropathy assessment tool used an oxaliplatin-specific scale focused on reversibility of symptoms between treatment cycles and involved a score assigned based on investigator judgment. The third assessment technique was a series of patient-reported outcome questions, requiring patients to quantify the extent of the problem posed by their neuropathy symptoms. After 102 patients were enrolled, the trial was prematurely closed due to concerns from a separate report that suggested disease response rates were decreased among subjects receiving calcium and magnesium with chemotherapy. This concern was later discovered to be unfounded. Based on the limited number of patients assigned to either arm, the study was determined to possess 80 % power to detect a 27 % difference in the incidence of grade 2 or greater neurotoxicity. The results from the patients who did complete N04C7 were promising, with improvement noted in neuropathy symptoms as measured by NCI CTCAE and oxaliplatin-specific scales. This prompted the decision to perform a confirmatory phase 3 trial [10].

NCCTG-N08CB (calcium and magnesium; initiated 2008; manuscript published 2014)—Designed to confirm results from the prematurely discontinued NCCTG-N04C7 trial, NCCTG-N08CB was developed as a randomized, double-blind, three-arm study evaluating the role of calcium and magnesium in the prevention of oxaliplatin-induced peripheral neuropathy [14]. In one arm, patients received calcium/magnesium before and after oxaliplatin; in another arm, patients received placebo before and after oxaliplatin; and in the final arm, patients received calcium/magnesium before and placebo after oxaliplatin. The primary neuropathy assessment tool was the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire-Chemotherapy-Induced Peripheral Neuropathy 20 (EORTC QLQ-CIPN 20). Other measures included an investigator-determined score utilizing NCI-CTCAE version 4.0 and an oxaliplatin-specific scale. In total, 353 patients were randomized, which was estimated to provide at least 80 % power to detect a difference in incidence of at least grade 2 toxicity from 40 % in the placebo arm to 20 % in either of the infusion arms. There were no significant differences in neuropathy measures among the three groups. The negative results of this trial provide definitive evidence that intravenous calcium and magnesium do not prevent oxaliplatin-induced neuropathy.

NCCTG-N05C3 (vitamin E; initiated 2006; manuscript published 2011)—Building on several small studies suggesting a neuroprotective role for vitamin E [22–25], the NCCTG conducted a randomized, double-blind, placebo-controlled study of vitamin E

versus placebo in patients undergoing platinum or taxane-based chemotherapy [11]. The primary endpoint was incidence of grade 2+ sensory neuropathy according to NCI CTCAE version 3.0. One hundred eighty-nine patients were randomized to receive vitamin E or placebo while initiating cytotoxic chemotherapy, providing an adequate sample size for at least 80 % power to detect difference in the primary endpoint from 25 % in the placebo group to 10 % in the vitamin E group. In contrast to small, randomized and non-randomized trials, no differences were observed between study arms in incidence of neuropathy symptoms, time to onset of neuropathy, or dose reductions due to neuropathy.

SWOG-S0715 (acetyl-L-carnitine; initiated 2009; manuscript published 2013)— Acetyl-L-carnitine (ALC) is a natural compound that has been associated with neuronal protection in both animal models [26, 27] and human studies of various peripheral neuropathies [28–30]. These data prompted a randomized, double-blind placebo-controlled trial evaluating ALC for prevention of taxane-induced CIPN in women undergoing adjuvant breast cancer therapy [12]. The intervention was conducted over a 24-week period, during which the experimental group received ALC 3000 mg daily; CIPN scores were assessed at 12 and 24 weeks. The FACT/GOG-Ntx was the main neuropathy outcome measure, with NCI CTCAE version 3.0 neuropathy score serving as a secondary endpoint. A total of 409 patients were evaluable, which was estimated to be sufficient for 80 % power to detect a three-point difference in neuropathy scores between groups. There was no evidence that ALC altered CIPN scores at 12 weeks; however, CIPN scores appeared adversely affected at 24 weeks in the ALC arm. The mean observed FACT/GOG-Ntx subscale was 5.3 points lower in the intervention group compared to 3.6 points lower than in the placebo group, representing significantly more self-reported neuropathy symptoms in the ALC arm. Although these results suggest a harmful effect of the supplement for this patient population, the clinical significance has remained unclear.

NCCTG-N08CA (glutathione; initiated 2009; manuscript published 2014)—As a naturally occurring antioxidant that reduces toxic accumulation of platinum within the dorsal root ganglion, glutathione was proposed as an agent that might counteract the underlying mechanism of neurotoxicity with platinum-based chemotherapy. Building on promising results from several pilot and controlled trials [31–36], NCCTG-N08CA was developed to assess the efficacy of glutathione as a preventive agent in patients receiving platinum/taxane combination chemotherapy, as measured by the EORTC QLQ-CIPN 20 sensory subscale. One hundred eighty-five patients receiving carboplatin and paclitaxel were randomized to additionally receive either placebo or an infusion of 1.5 g/m^2 glutathione over 15 min before chemotherapy [13]. It was estimated that this number would be sufficient for 90 % power to detect a difference of six points in the EORTC QLQ-CIPN 20 sensory subscale between the two arms. No differences were observed between groups in the incidence of neuropathy symptoms, time to development of CIPN, the degree of the paclitaxel acute pain syndrome (proposed to be a form of acute neuropathy) [4, 37], or toxicity. In patients with gynecologic malignancies, there was no significant difference between the two arms in terms of time to progression of CA-125 levels, which was used as a surrogate for disease progression.

GOG-0257 (acetyl-L-carnitine; initiated 2012; withdrawn)—A protocol to evaluate ALC in a randomized, controlled study was developed by the Gynecology Oncology Group (GOG). Although initially approved by the NCI, the study was withdrawn following the release of results from SWOG-S0715, which revealed a potentially deleterious effect of ALC on CIPN severity [12].

Treatment of established CIPN

NCCTG-93-95-92 (nortriptyline; initiated 1995; manuscript published 2002)— Based on data supporting the use of tricyclic antidepressants as treatment for a variety of neuropathic pain syndromes [38–40], the NCCTG developed a small, randomized placebo-controlled clinical trial to evaluate nortriptyline for CIPN. The visual analogue scale (VAS) and a verbal descriptor scale (VDS) were used to characterize neuropathy symptoms. The study included 51 evaluable patients, which was found to be sufficient for 80 % power to detect a 10 % change in the VAS. Patients were randomized to receive nortriptyline or placebo over a 4-week period, followed by a 1-week washout and subsequent crossover. Improvement in VAS was non-significant prior to the crossover and significant after crossover, although this occurred in the presence of a strong carryover effect. The authors concluded that the effect of nortriptyline in this setting was potentially modest at best for a small minority of patients [15].

NCCTG-N00C3 (gabapentin; initiated 2002; manuscript published 2007)— N00C3 was a randomized, double-blind, placebo-controlled crossover trial evaluating the efficacy of gabapentin in the management of patients with CIPN [16]. The rationale for this trial was based both on the drug's benefit in other neuropathic pain settings and its common use for treatment of CIPN in practice. The primary efficacy measure was patient-reported average daily pain, as quantified by a numerical rating scale (NRS) ranging from 0 to 10, and the Eastern Cooperative Oncology Group (ECOG) neuropathy scale. The study was designed to provide 80 % power to detect differences in average pain scores of 0.63 standard deviations. One hundred fifteen patients with CIPN due to platinum compounds, taxanes, or vinca alkaloids were randomized to receive gabapentin (target dose, 2700 mg/day) or placebo for a 6-week period, followed by a 2-week washout prior to crossover. CIPN pain scores improved by 20–30 %, irrespective of treatment group; there was no significant advantage demonstrated with the administration of gabapentin.

NCCTG-N01C3 (lamotrigine; initiated 2003; manuscript published 2008)— Lamotrigine is another drug that had shown promise in the treatment of certain neuropathic pain conditions [41–44]. This prompted the NCCTG to conduct a multicenter, double-blind, placebo-controlled trial, comparing the efficacy of lamotrigine (target dose, 300 mg/day) to placebo in a similar patient population to the one enrolled in the N00C3 gabapentin study [17]. Neuropathy symptoms were similarly assessed via the NRS and ENS, as co-primary endpoints. The study was designed to have 80 % power to detect differences in average pain scores of 0.57 standard deviations for each primary endpoint. One hundred thirty-one patients were enrolled and received lamotrigine or placebo over a 10-week period. As was the case with the gabapentin trial, CIPN pain scores moderately improved in both treatment and placebo groups; lamotrigine conferred no significant benefit.

MDA-CCC-02-23 and GOG-0192 (amifostine; no publications)—The MDA-CCC-02-23 (phase II) and GOG-0192 (phase III) clinical trials were similarly designed to evaluate amifostine for the treatment of platinum-related peripheral neuropathy. Results from these studies have not been published; the trials were closed early due to poor accrual.

URCC-06-05 (topical ketamine/amitriptyline cream; initiated 2007; manuscript published 2014)—A trial of topical analgesia for CIPN was performed by the University of Rochester Cancer Center Community Clinical Oncology Program (URCC CCOP), which randomized 462 patients with established CIPN following completion of chemotherapy (stratified as taxane and non-taxane) to receive either a placebo or up to 4 g of topical 2 % ketamine plus 4 % amitriptyline (KA) cream twice daily to each area of pain [18]. The primary method of neuropathy symptom assessment was an 11-point NRS (0–10), with the average daily score at 6 weeks serving as the primary endpoint. It was estimated that the study would provide approximately 80 % power to detect mean differences of 1.15 points on the NRS. At both the 3 and 6-week assessments, the KA treatment failed to significantly reduce pain, numbness, or tingling scores. Patients in the taxane subset reported significant reductions in these CIPN measures compared with their non-taxane counterparts, regardless of whether they received the investigational versus placebo treatment.

NCCTG-N06CA (topical baclofen/amitriptyline/ketamine cream; initiated 2008; manuscript published 2011)—Another study evaluating use of a topical agent was initiated in 2008 as a double-blind, randomized, placebo-controlled trial. This trial studied a formulation of baclofen 10 mg, amitriptyline HCL 40 mg, and ketamine 20 mg in a pluronic lecithin organogel (BAK-PLO) [19]. Two hundred and eight patients with a history of neuropathy secondary to neurotoxic chemotherapy (mostly platinum agents and taxanes, and a few with thalidomide) were randomized to apply the intervention gel or a placebo vehicle, twice a day for 4 weeks. The primary endpoint was change in neuropathy symptoms as measured by the EORTC QLQ-CIPN 20 sensory subscale from baseline to 4 weeks. It was expected that the study would have 80 % power to detect a half standard deviation difference between study arms. A trend toward improvement in sensory neuropathy scores favored the BAK-PLO arm (p=0.053). A significant decrease in the motor subscale of the EORTC QLQ-CIPN 20 instrument (a secondary study endpoint) was also seen. Given the trend toward benefit, the lack of toxicity, and the absence of significant systemic absorption of the study agents, the authors recommended a follow-up trial utilizing higher doses of the topical agents.

CALGB-170601 (duloxetine; initiated 2008; manuscript published 2013)—The results from a randomized, placebo-controlled, crossover trial evaluating the efficacy of duloxetine for the treatment of CIPN related to taxane or platinum agents were published in 2013 [20]. Two hundred thirty-one patients were stratified according to neurotoxic agent exposure (taxane or platinum agent) and randomized to receive duloxetine (target dose, 60 mg daily) or placebo for 6 weeks, followed by a 1-week washout before crossover. The primary endpoint was change in average pain as measured by Brief Pain Inventory-Short Form (BPI-SF) scores. Based on the sample size, the study had 90% power to detect a 0.98 point change between the two groups. Patients who received duloxetine in the initial period

experienced a significantly larger decrease in pain score (mean change score= −1.06 versus −0.34, $p = 0.003$). The magnitude of the benefit from duloxetine was modest, and appeared to be more prominent with neuropathy caused by oxaliplatin, compared to paclitaxel, in a subset analysis. There was a significantly higher incidence of CTCAE grade 2 or greater fatigue in the duloxetine arm, but otherwise the medication was well-tolerated.

Natural history trial

N08C1 (paclitaxel; initiated 2008; manuscripts published in 2011 and 2012)— The NCI approved a clinical trial designed to better understand the natural history of paclitaxel-induced neuropathy. This was accomplished using patient-reported outcome measures, primarily the EORTC QLQ-CIPN 20 instrument. To date, two manuscripts have been published from this work detailing the natural history of acute and chronic paclitaxel-induced neuropathies [4, 5].

Discussion

To date, only a single NCI-sponsored study, evaluating use of duloxetine as treatment for established CIPN, has provided clearly positive results. The remaining seven neuropathy prevention trials and seven treatment trials have failed to provide an evidence-based approach to solving this problem, despite rational choices of agents that had shown promise in previous, smaller trials. It must be acknowledged upfront that uniform comparison of the various agents used for treatment of CIPN is hampered by varying trial methodologies, specifically with regard to the differing assessment tools utilized to characterize neuropathy symptoms. Still, in each individual trial, the results provided by study agents have been sobering.

Prevention and treatment of CIPN continues to be a high priority given the number of anti-cancer agents with neurologic toxicities and the ever increasing population of cancer survivors with this debilitating side effect of therapy. Further, traditionally used neuromodulatory agents employed in the treatment of other neuropathy conditions possess risks of their own in the form of side effects, which are potentially even more deleterious in a vulnerable population. A considerable portion of cancer patients who develop CIPN are older adults in whom agents such as nortriptyline and gabapentin must be used with caution given the risk for falls and related adverse effects. Therefore, the absence of benefit demonstrated in this series of trials is important and heightens the imperative for appropriate prevention and treatment strategies. Additional, valuable lessons have been learned, which in turn, have influenced the development and conduct of future CIPN studies. The series of trials has allowed for a deeper understanding of the nature of CIPN and has contributed meaningfully to the development of the ASCO CIPN practice guidelines [45].

Among the most important lessons to come from these trials pertains to study design and outcome measurement. For example, some early studies were inadequately powered to detect significant differences in high grade neuropathy among treatment groups. Additionally, early trials often relied on clinician-assessment of neuropathy, with methods such as CTCAE criteria, which have been shown to be less sensitive than patient reported outcomes. Newer trials have included patient-reported outcomes as the primary endpoints

with instruments such as the EORTC QLQ-CIPN 20 or FACT/GOG-Ntx to more accurately characterize the incidence and severity of neuropathy [46, 47].

The NCI-supported trials have also exposed the inefficacy of some traditional practice approaches, thereby facilitating the abandonment of therapies that are unnecessary, costly, and potentially harmful. The use of calcium and magnesium for the prevention of oxaliplatin-induced neuropathy is one such example of a previously widespread approach which was shown to lack efficacy when studied in a clinical trial. Prior to the results of NCCTG-N04C7, up to 40 % of oxaliplatin infusions in this country were given with concurrent calcium and magnesium. This practice was based largely upon clinical data from non-randomized trials or small data sets from randomized trials. When the definitive trial was published [14], illustrating that calcium and magnesium administration did not actually decrease oxaliplatin-induced neuropathy, it virtually abolished this practice [48]. Without these unnecessary infusions, patients are saved time in the chemotherapy suite, and pharmacists and nurses are freed to do more valuable work; this conservation of resources was considered to be of sufficient impact that it was selected as one of ASCO's clinical practice highlights of the year in 2013.

It is now apparent that there is considerable heterogeneity among the various forms of neuropathy. Treatments that are effective for diabetic and HIV-related neuropathies, such as tricyclic antidepressants, gabapentin, and ALA, do not appear to provide benefit in the setting of CIPN. Understanding this difference has allowed for focus of basic science study on CIPN, separate from other types of neuropathy. Additionally, there appears to be differences in CIPN manifestations related to the various inciting agents. Valuable comparisons between oxaliplatin and paclitaxel neuropathies have arisen from this these trials [49], as measured by the same patient reported outcome tool—the EORTC QLQ-CIPN 20 instrument. An enhanced understanding of the natural history of CIPN can improve clinical practice by allowing providers to better predict outcomes and manage patient expectations. It might also allow for better insights into the pathologic mechanisms of chemotherapy neuropathy induced by different chemotherapeutic agents.

Lastly, samples collected from these trials have allowed for investigation into potential molecular genetic predictors of neuropathy. The large set of patient data collected from these studies provided an opportunity to differentially assess genetic variants from patients who developed neuropathy compared with those who did not. Next-gen genomic DNA sequencing associated Charcot-Marie-Tooth disease (hereditary neuropathy) related genes to CIPN in the N08C1 study [50]. Importantly, key results could be retested in N08CA, in which the same PRO-based CIPN phenotyping had been performed, validating the lead finding [51]. A literature review on taxane-associated neuropathy single nucleotide polymorphisms (SNPs) was conducted, and then a validation study was conducted in samples from the N08C1 paclitaxel neuropathy natural history trial; a manuscript describing these findings is currently under review (Beutler, personal communication, October 2015). Additional genetic based research is ongoing from samples on these and other trials. Genetic studies have also been performed in chemotherapy efficacy trials that collected neuropathy phenotyping as part of the standard toxicity data typically using CTCAE. Baldwin et al. reported the first genome-wide association study (GWAS) in the CIPN field on patients from

CALGB 40101 [52], identifying CIPN SNPs (some of which were candidates as they did not pass genomewide significance), and some have since been validated in other cohorts, including N08C1. The CALGB 40101 study was exceptionally well-executed, setting a high standard for similarly designed work. Compared to other fields of genetics, which have been well developed for decades (such as the genetics of diabetes or dyslipidemia), studies on the genetic basis of CIPN are still in a comparably early stage, with potential key discoveries remaining to be made. The effect sizes of confirmed SNPs have generally been only very modest and therefore not clinically actionable. However, most large studies performed to date have focused on common and moderately rare SNPs (i.e., those typically represented on older standard GWAS array designs). Whether truly rare genetic variants with a strong impact on CIPN risk exist will have to be determined in future studies, which will most likely rely on next-gen sequencing for additional discoveries.

The potential clinical impact of genetics on CIPN is not only limited to improved risk prediction in individual patients. Genetic variants may also be lead observations in the process of identifying therapeutic targets for CIPN, i.e., in the development of agents to prevent CIPN. Human genetic studies have recently become a driving force in novel target identification and drug development in other areas of medicine. In some cases, rare variants were found to have great clinical consequence and led to the development of drugs mimicking or blocking effects identified by genetic studies. In CIPN, this potential can be realized best by accruing larger, well-phenotyped cohorts and moving from older genetic analysis technology (PCR for SNPs and GWAS arrays) to genome sequencing approaches, potentially implementing whole genome sequencing in large cohorts, as the cost of this technology is expected to decrease further over the coming years.

Future prospects

CIPN remains a prominent clinical problem for patients receiving common cytotoxic chemotherapy regimens. The lessons learned from the NCI-sponsored trials have been multifold and meaningful, but the direction of scientific focus regarding this highly debilitating disease will be different moving forward. First, efforts should be made to standardize CIPN assessment methods, with an emphasis on use of patient-reported scales. Many CIPN symptoms are inherently subjective, and thus, accurate quantification is understandably limited. Still, a variety of assessment tools currently exist in clinical practice. Among these are scales based primarily on investigator judgment, such as the World Health Organization (WHO) scale, ECOG scale, NCI CTCAE, and Ajani scale. Although easy to use, such assessment techniques suffer from inter-observer disagreement. Other, primarily patient-reported functional assessments have been more recently developed and include the FACT/GOG-Ntx, the FACT-Taxane scale, the peripheral neuropathy scale (PNS), oxaliplatin-specific neuropathy scale, scale for chemotherapy-induced long-term toxicity (SCIN), patient neuropathy questionnaire (PNQ), and the EORTC QLQ-CIPN 20. The EORTC QLQ-CIPN 20 has been validated in a clinical setting [47] and was utilized in several of the later NCI CIPN trials. Our experience with this tool suggests it is a reasonable choice for subsequent CIPN studies, but further work comparing the various options would be helpful.

Trials which more aggressively investigate the molecular mechanisms of neurotoxicity associated with various new and old chemotherapy agents are needed. A basic understanding of these mechanisms and improved communication between basic scientists and clinician experts to translate molecular findings into clinical advances is crucial to the future of this scientific inquiry. Smaller trials in the pre-clinical and clinical settings are necessary to develop targeted treatment approaches worth evaluating with formal phase III randomized trials. With a better understanding of mechanisms, identification of molecular predictors, and appropriate use of outcome measures, novel prevention of CIPN and treatment of established CIPN will, hopefully, become available. In this way, precision medicine can extend to the prevention and treatment of toxicities such as CIPN.

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Table 1

Summary of NCI-supported CIPN prevention and treatment trials

Study	Year of approval	Design	Agent	Population	Number of patients	Results
Prevention trials						
MDA-CCC-03-27 [9]	2004	Phase III, randomized, double-blind, placebo-controlled	Alpha lipoic acid	Patients receiving cisplatin or oxaliplatin	243	No difference in FACT-NTX, BPI score, pain or functional testing at 24 weeks
NCCTG N04C7 [10]	2004	Phase III, randomized, double-blind, placebo-controlled	Intravenous CaMg	Patients receiving oxaliplatin	102	Study stopped early due to an errant concern regarding CaMg; preliminary data from this study looked promising
NCCTG-N05C3 [11]	2006	Phase III, randomized, double-blind, placebo-controlled	Vitamin E	Patients receiving oxaliplatin, cisplatin, carboplatin or taxanes	207	No difference in grade 2+ neuropathy; no difference in time to neuropathy; no difference in patient reported CIPN scores 6 months following treatment
SWOG-S0715 [12]	2009	Phase III, randomized, double-blind, placebo-controlled	Acetyl-L-carnitine	Breast cancer patients receiving taxanes	409	No difference in CIPN at 12 weeks with the 11-item neurotoxicity component of the FACT-Taxane scale; increased CIPN at 24 weeks in the intervention arm
NCCTG-N08CA [13]	2009	Phase III, randomized, double-blind, placebo-controlled	Glutathione	Patients receiving taxanes	185	No difference measured by EORTC-CIPN20 sensory subscale and the CTCAE, version 4.0 following 6 cycles; increased time to CIPN favoring placebo
NCCTG-N08CB [14]	2009	Phase III, randomized, double-blind, placebo-controlled	Intravenous CaMg	Patients receiving oxaliplatin	353	Convincing lack of benefit in terms of CIPN prevention
GOG-0257	2012	Phase III, randomized, double-blind, placebo-controlled	Acetyl-L-carnitine	N/A	N/A	Withdrawn following results of SWOG 0715
Treatment trials						
NCCTG-93-95-92 [15]	1995	Phase III, randomized, double-blind, placebo-controlled, cross-over	Nortriptyline	Pre-existing neuropathy related to chemotherapy treatment	51	No significant difference in quality of life measures and impact of symptoms on daily activities

Study	Year of approval	Design	Agent	Population	Number of patients	Results
NCCTG-N00C3 [16]	2002	Phase III, randomized, double-blind, placebo-controlled, cross-over	Gabapentin	Pre-existing neuropathy related to chemotherapy treatment	115	No difference between groups in pain measured by several at 6 and 14 weeks
NCCTG- N01C3 [17]	2003	Phase III, randomized, double-blind, placebo-controlled	Lamotrigine	Pre-existing neuropathy related to chemotherapy treatment	131	No difference in pain measured by several neuropathy scores
MDA-CCC-02-23 and GOG-0192	2003	N/A	Amifostine	Patients 2–12 months post taxane therapy with neuropathy	N/A	Closed due to poor accrual
URCC-06-05 [18]	2007	Phase III, randomized, double-blind, placebo-controlled	Topical amitriptyline and ketamine	Pre-existing neuropathy related to prior chemotherapy treatment	462	No difference in pain, numbness, and tingling scores at 6 weeks
NCCTG-N06CA [19]	2008	Phase III, randomized, double-blind, placebo-controlled	Topical BAK	Pre-existing neuropathy related to prior chemotherapy treatment	208	Mean decrease in EORTC-CIPN20 sensory scale for the BAK arm compared to placebo arm; also, decrease in motor subscale
CALGB-170601 [20]	2008	Phase III, randomized, double-blind, placebo-controlled, cross-over	Duloxetine	Pre-existing neuropathy related to prior taxane of platinum chemotherapy treatment	231	Decrease in pain score in the duloxetine group compared to those receiving placebo at 6 weeks

FACT-NTX Functional Assessment of Cancer Therapy-Neurotoxicity, *BPI* Brief Pain Inventory, *CaMg* calcium and magnesium, *EORTC-CIPN20* European Organization for Research and Treatment of Cancer-Chemotherapy-Induced Peripheral Neuropathy 20, *CTCAE* Common Terminology Criteria for Adverse Events, *BAK* baclofen, amitriptyline HCl, and ketamine