Trial designs for chemotherapy-induced peripheral neuropathy prevention

ACTTION recommendations

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Abstract

Chemotherapy-induced peripheral neuropathy (CIPN) is a common and potentially dose-limiting side effect of neurotoxic chemotherapies. No therapies are available to prevent CIPN. The small number of positive randomized clinical trials (RCTs) evaluating preventive therapies for CIPN provide little guidance to inform the design of future trials. Moreover, the lack of consensus regarding major design features in this area poses challenges to development of new therapies. An Analgesic, Anesthetic, and Addiction Clinical Trial Translations, Innovations, Opportunities and Networks (ACTTION)–Consortium on Clinical Endpoints and Procedures for Peripheral Neuropathy Trials (CONCEPPT) meeting attended by neurologists, oncologists, pharmacists, clinical trialists, statisticians, and regulatory experts was convened to discuss design considerations and provide recommendations for CIPN prevention trials. This article outlines considerations related to design of RCTs that evaluate preventive therapies for CIPN including (1) selection of eligibility criteria (e.g., cancer types, chemotherapy types, inclusion of preexisting neuropathy); (2) selection of outcome measures and endpoints, including those that incorporate alterations in chemotherapy dosing, which may affect the rate of CIPN development and its severity; (3) potential effects of the investigational therapy on the efficacy of chemotherapy; and (4) sample size estimation. Our hope is that attention to the design considerations and recommendations outlined in this article will improve the quality and assay sensitivity of CIPN prevention trials and thereby accelerate the identification of efficacious therapies.

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Glossary

ACTTION = Analgesic, Anesthetic, and Addiction Clinical Trial Translations, Innovations, Opportunities and Networks; **CIPN** = chemotherapy-induced peripheral neuropathy; **ClinRO** = clinician-rated outcome measure; **CONCEPPT** = Consortium on Clinical Endpoints and Procedures for Peripheral Neuropathy Trials; **DOOR** = Desirability of Outcome Ranking; **EORTC-CIPN20** = European Organisation for Research and Treatment of Cancer–CIPN20; **FACT-Taxane** = Functional Assessment of Cancer Therapy–Taxane; **FDA** = Food and Drug Administration; **LOCF** = last observation carried forward; **NCI-CTCAE** = National Cancer Institute–Common Terminology Criteria for Adverse Events; **PRO** = patient-reported outcome; **QST** = quantitative sensory testing; **RCT** = randomized clinical trial; **TNS** = Total Neuropathy Score; **TNS-SF** = TNS–short form; **TNSc** = TNS–clinical.

Chemotherapy-induced peripheral neuropathy (CIPN) is a common and potentially dose-limiting side effect of neurotoxic chemotherapy agents (e.g., taxane- or platinum-derived compounds). According to a recent meta-analysis, it occurs in between 58% and 78% of patients who receive neurotoxic chemotherapies, depending on the agent, and lasts at least 6 months after termination of chemotherapy in 30% of patients.[1] CIPN symptoms include burning/shooting pain, tingling, cramping, numbness, and weakness in the hands and feet. CIPN symptoms are associated with impaired balance and walking, falls, and decreased health-related quality of life.[2–5] No therapies are currently available to prevent CIPN.[6] The randomized clinical trials (RCTs) used to evaluate preventive therapies for CIPN have been generally small and have included variable eligibility criteria and primary endpoints.[7] Two possible reasons exist for the high rate of failed trials in this area: (1) a lack of clear understanding of the causal mechanisms of CIPN has inhibited development of efficacious therapies to prevent CIPN; and (2) current research designs provide insufficient assay sensitivity to identify efficacious therapies. Regardless of which is the main cause for trial failure, the absence of replicated positive RCTs supporting therapies for CIPN prevention provides limited guidance as to the optimal design of future trials. This lack of positive trial examples and the absence of consensus among clinical investigators on major trial design features pose challenges to clinical development of new therapies for this unmet medical need.

Methods

The Consortium on Clinical Endpoints and Procedures for Peripheral Neuropathy Trials (CONCEPPT) of the Analgesic, Anesthetic, and Addiction Clinical Trial Translations, Innovations, Opportunities and Networks (ACTTION) public–private partnership convened a meeting in March 2017 to discuss current challenges and develop design considerations for clinical trials of therapies for CIPN prevention. An international group of neurologists, oncologists, pharmacists, clinical trialists, statisticians, and regulatory experts from academia, government agencies, and the pharmaceutical industry attended the meeting. Participants were selected based on their research, clinical, or regulatory expertise relevant to CIPN and clinical trial design in order to reflect a broad representation of relevant disciplines and perspectives while limiting the meeting size in order to promote productive and efficient discussion. To facilitate discussion, a set of background lectures was presented at the meeting by participants; presentations and the meeting transcript are available at actt-ion.org/conceppt.

This article outlines design considerations and provides recommendations for the design of CIPN prevention trials. The considerations are centered on areas in need of improvement identified in the systematic review that was performed in preparation for the meeting.[7] They are based on the background presentations, extensive discussion at the meeting, and subsequent review of the manuscript drafts by the meeting attendees/coauthors. Our hope is that incorporation of these design considerations will improve the assay sensitivity of CIPN prevention trials, thus accelerating the identification of efficacious preventive therapies for this important, unmet public health need.

Considerations/recommendations

Prevention trial design

Efficacious therapies for CIPN prevention should ideally maximize chemotherapy adherence, which may improve cancer treatment outcomes and prevent long-term neuropathy. Two approaches to prevention exist for CIPN. Each type of prevention approach and corresponding trial design has advantages and disadvantages. Primary prevention involves initiating the therapy prior to the start of chemotherapy treatment. Secondary prevention involves initiating the therapy after mild neuropathy signs or symptoms from chemotherapy are detected in order to prevent worsening. Primary prevention has a higher likelihood of being efficacious than secondary prevention if the preventive therapy has no or limited ability to reverse or slow established damage. However, a primary prevention trial may be logistically challenging because recruitment, consent, randomization, and initiation of the investigational therapy must occur prior to the initiation of chemotherapy—a time when establishing a cancer treatment plan is the priority for patients and oncologists. Allowing participants to receive a single dose of neurotoxic chemotherapy prior to receiving the investigational CIPN prevention therapy could mitigate this logistic hurdle,

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although such a trial is not a true primary prevention trial and some nerve damage may occur prior to initiation of the investigational therapy. Secondary prevention trials might be logistically easier because the therapy would not be initiated prior to the start of chemotherapy. However, in order to ensure that the patients do not have existing neuropathy from other causes, it would be best to screen all patients for neuropathy prior to the start of chemotherapy. Any pre-chemotherapy screen for neuropathy should be relatively brief and ideally performed at an already scheduled oncology visit. Primary prevention trials expose participants who will never develop neuropathy to an investigational therapy, which is not the case for secondary prevention. Which type of trial would require more participants is not straightforward to determine and might be different depending on the type of chemotherapy and trial endpoints (figure).

In order to definitively determine that an intervention is preventive and not a symptomatic therapy, the outcomes must be assessed after the investigational therapies have been withdrawn. Acknowledging this limitation, we use the term prevention in this article to indicate the initiation of the therapy prior to the start of chemotherapy or the appearance of moderate to severe neuropathy in order to distinguish these trial designs from those that evaluate the efficacy of treatments for established moderate to severe CIPN.

Eligibility criteria

Chemotherapy types

Restriction of entry criteria to a single class of neurotoxic chemotherapy agent (e.g., platinum-derived compounds) is recommended. Preventive therapies may have different efficacy depending on the chemotherapy mechanism of action. If the investigational therapy is hypothesized to prevent neuropathy from multiple chemotherapy classes, a trial could include multiple classes; however, such a trial could fail to show a treatment effect if the therapy is only truly efficacious for neuropathy in a subset of the treatment classes. In addition, restricting entry to one or a few dosing regimens of a single chemotherapy agent can limit variability in CIPN characteristics and severity and thus improve assay sensitivity. If more than one dosing regimen is allowed, stratification of randomization based on the planned regimen is recommended.

Cancer types

Ideally, to increase homogeneity, a CIPN prevention trial would include a single type of cancer. However, considering feasibility and generalizability challenges, the consensus of the meeting participants was that inclusion of multiple cancer types could be considered. For drugs that have not yet been studied in patients receiving chemotherapy, the US Food and Drug Administration (FDA) recommends including patients with metastatic cancer (see section on mitigating risk). For subsequent efficacy studies, including patients with early-stage cancer would likely minimize participant dropout from cancer recurrence or death.

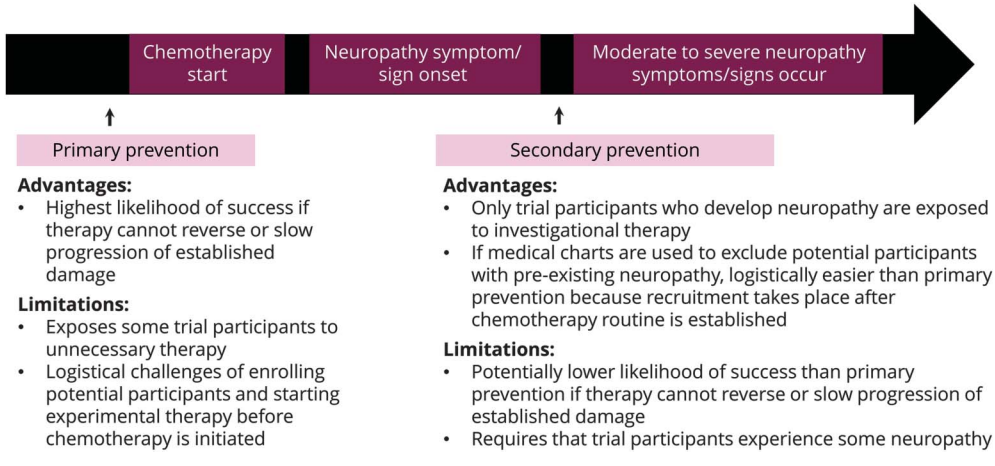
Non-neurotoxic chemotherapy

Considering that exclusion of patients who had previously received non-neurotoxic chemotherapy would limit recruitment and generalizability with no obvious advantages, including such patients is recommended.

Preexisting neuropathy, comorbid conditions associated with neuropathy, and previous neurotoxic treatments

Excluding patients with preexisting neuropathy of even minimal severity ensures that the RCT is evaluating the preventive effects of the treatment on neuropathy that is purely induced by chemotherapy (i.e., not the effects on preexisting neuropathy that is exacerbated by chemotherapy or the natural progression of preexisting neuropathy). Such a homogenous population could increase the assay sensitivity of a trial if the mechanism of the therapy is unique to neuronal damage caused by chemotherapy in the absence of any preexisting

Figure Advantages and limitations of primary and secondary prevention approaches



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damage. However, one study suggests that mild preexisting neuropathy may be a risk factor for more severe CIPN.[8] Thus, excluding patients with mild preexisting neuropathy could decrease the incidence of CIPN in the trial and increase the number of participants needed for adequate power. Furthermore, excluding these patients would decrease the generalizability of the results to the population of patients who may be most in need of preventive therapy.

In order to balance the efficiency of the trial and generalizability of the results, most authors agreed on the following recommendation: exclude patients with probable preexisting neuropathy, but consider including (1) patients with possible neuropathy and (2) patients who are at higher risk than the general population of having subclinical neuropathy because they have received previous neurotoxic treatments or have stable comorbid conditions associated with neuropathy. Generating entry criteria to identify patients with "mild" neuropathy may be challenging. One approach could be to exclude patients who have probable preexisting neuropathy but include patients with possible preexisting neuropathy as defined by the Toronto Diabetic Neuropathy Expert Group.[9] For studies in which a neurologist is not available at all sites, this would require standardizing neurologic assessments for determination by an oncologist, nurse, or clinical coordinator. Assessments of preexisting neuropathy must occur prior to the patients receiving any chemotherapy, regardless of the type of prevention design. Excluding these patients from a secondary prevention trial may not be feasible. Although less than ideal, one option for a secondary prevention trial would be to base these entry criteria on medical records.

Concomitant medications

Concomitant medications that are known to cause neuropathy (e.g., certain HIV drugs) should not be allowed in CIPN prevention trials. Although no drugs are proven to prevent CIPN, based on evidence from other neuropathic pain conditions and experience in clinical practice, certain drug classes (e.g., serotonin norepinephrine reuptake inhibitors) could mask CIPN-associated pain and affect trial outcomes. However, prohibiting these drugs could impede recruitment and generalizability and present an ethical dilemma as cancer patients may require these medications for pain associated with cancer or other treatments (e.g., surgery). If concomitant analgesics are allowed, requiring consistent dosages throughout the trial and daily medication logs should be considered.

CIPN assessment

Standardization of the timing of neuropathy assessments in relation to the chemotherapy treatments (e.g., 1–5 days after each chemotherapy treatment cycle or directly before each treatment cycle) is recommended to minimize variation in neuropathy severity due to this timing. When designing the timing of assessments, it is also important to consider the hypothesized mechanism of the investigational therapy; for example, whether it is hypothesized to prevent severe acute CIPN symptoms that occur shortly after chemotherapy treatments or longer term cumulative CIPN or both. It is also important to coordinate study assessments with clinical visits whenever possible to minimize participant burden. Our recent systematic review found that standardization of this timing was rarely reported.[7]

Since no successful development programs exist for CIPN prevention, previous trials of demonstrably efficacious interventions cannot inform the choice of primary outcome measure or relative assay sensitivity of different outcome measures. Patient-reported outcomes (PROs) of CIPN-related symptoms should always be included in clinical trials. Measures of clinician-rated neuropathy signs (ClinROs) (e.g., vibration and pinprick sensation assessments) and function measures (e.g., balance) are also encouraged. For trials designed to support regulatory approval, choice of outcome measures, including PROs, ClinROs, and function measures, and the timing and frequency of assessments should be discussed with the FDA early in the development process to ensure that the trial provides rigorous and interpretable data that can be used for regulatory purposes.

Patient-reported outcomes

Many PROs have been developed for CIPN in general and for CIPN from specific chemotherapy agents (e.g., oxaliplatin[10]). Development of the European Organisation for Research and Treatment of Cancer–CIPN20 (EORTC-CIPN20) and the Functional Assessment of Cancer Therapy–Taxane (FACT-Taxane) utilized multiple methods to enhance content validity, including soliciting input from patients, clinician experts, and the available literature.[11] The construct validity (i.e., correlation with other measures of neuropathy; ability to distinguish between groups of patients treated with neurotoxic and non-neurotoxic chemotherapies) and responsiveness to change (i.e., from before to after administration of neurotoxic chemotherapies) of the EORTC-CIPN20 and FACT-Taxane have been demonstrated in multiple studies.[12–17] The constructs covered by the 2 measures are fairly similar. Recent studies suggest that removal of some items and modifications to the wording of others may improve the internal consistency and content validity of the EORTC-CIPN20.[13,14,18] Although inclusion of a common measure in future trials would be advantageous to facilitate meta-analyses, we lack sufficient evidence to recommend one over the other. For example, although these measures have been shown to detect increases in neuropathy over time after administration of chemotherapy,[13,14,19] the sensitivity of either measure to detect small or moderate differences in the severity of CIPN is unknown. In addition, depending on the chemotherapy agents included in the trial or the mechanism of action of the investigational therapy, primary outcome measures other than the EORTC-CIPN20 and FACT-Taxane may be more appropriate. Future research investigating the utility of various PROs for different chemotherapies and different types of CIPN (e.g., low vs high severity; paresthesias or dysesthesias vs pain; predominantly small vs large fiber) will inform selection of outcome measures for future RCTs. Future studies to improve

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the scaling properties of the PROs and ClinROs using contemporary psychometric techniques such as Rasch analysis would also be informative.[20]

Clinician-rated sign outcome measures

To our knowledge, the National Cancer Institute–Common Terminology Criteria for Adverse Events (NCI-CTCAE) and the Total Neuropathy Score (TNS) and its modified versions (e.g., TNS–clinical [TNSc] and TNS–short form [TNS-SF]) [21–24] are the only measures with a clinician-based sign component that have been used to assess neuropathy in patients with CIPN. The purpose of the NCI-CTCAE is to assess adverse events during chemotherapy. It performs poorly as an outcome measure, with low interrater reliability and poor sensitivity to change.[25] Thus, it is not an appropriate primary outcome measure.

The TNS includes clinician-rated items related to vibration, pinprick, muscle strength, and reflex as well as patient-reported symptoms, nerve conduction assessments, and quantitative sensory testing (QST). The TNSc and TNS-SF do not include the nerve conduction assessments or the QST. The TNSc had good test retest reliability and interrater reliability when administered by examiners who were not neurologists (e.g., nurses),[15] suggesting that it can be included in clinical trials conducted in busy cancer clinics.

Other ClinROs that have been developed for use in peripheral neuropathy conditions with similar presentation (e.g., diabetic peripheral neuropathy) may also be appropriate for use in CIPN. ClinROs that emphasize sensory neuropathy may be most appropriate because sensory deficits are often more common than motor deficits in CIPN.[26] Unlike the TNS, the Modified Toronto Clinical Neuropathy Score,[27] Inflammatory Neuropathy Cause and Treatment Score,[28] Early Neuropathy Score,[29] and Utah Early Neuropathy Score[30] all heavily weight sensory neuropathy domains, with items that evaluate large and small fiber sensory neuropathy making up at least 80% of the total possible score from clinician-rated signs. Studies to investigate the psychometric properties of these measures for evaluating CIPN of different severities and from different agents are encouraged so that these measures will be available for future CIPN prevention trials.

Function measures

Although patient-reported interference with function is included in most PRO measures of CIPN, we identified only 2 trials in our systematic review that included objective function measures[7] (e.g., pegboard test[31]). Potentially useful, brief, and easy to administer established neuropathy-related function tests include the Grooved Pegboard test,[32] brief Bumps Detection test,[33] hand grip strength test using a hand-held dynamometer,[34] and the miniBEST balance test[35] or timed 1-leg, tandem, semi-tandem, and together leg stands. The Grooved Pegboard and brief Bumps Detection tests have been used in longitudinal studies for early detection of CIPN and to evaluate baseline predictors of CIPN.[8,36]

Endpoints

Many trial endpoints that can be used to test different scientific hypotheses are available for CIPN prevention trials. It is important to consider which trial endpoints are the most clinically meaningful to patients and also which provide superior assay sensitivity. Future research to increase our understanding of the relative effect of CIPN on patients' lives during and after chemotherapy will be critical to inform the clinical meaningfulness of different endpoints. For example, many patients may only choose to initiate a preventive therapy if it would decrease neuropathy that lasts at least 1 year after chemotherapy. Such research should include patients as active partners as well as research participants.[37]

When selecting endpoints for CIPN prevention trials, it is important to consider that modifications to the planned chemotherapy regimen after randomization can affect the occurrence and severity of neuropathy at specific timepoints; these effects might increase variability or create systematic measurement error in different endpoints. For example, if the participants in the control group receive less chemotherapy due to early development of neuropathy than the participants in the investigational group, the overall neuropathy severity measured at the end of the trial may be lower in the control group than the investigational group. In such a case, if only neuropathy severity is included as an endpoint, a trial may fail to demonstrate a true treatment effect that allows more cancer patients to receive a full course of chemotherapy and possibly obtain better cancer outcomes. In regards to assay sensitivity, the advantages and limitations of potential endpoints are discussed below and summarized in table 1.

Endpoints that incorporate only neuropathy

Possible neuropathy endpoints include (1) the severity of neuropathy at a specified timepoint or cycle number; (2) a summary score of neuropathy severity over multiple timepoints throughout chemotherapy; (3) the occurrence of neuropathy of a specified severity at any point during chemotherapy treatment; and (4) the occurrence or severity of neuropathy at a specified timepoint after completion of chemotherapy.

Severity endpoints that are assessed on a continuous scale (e.g., EORTC-CIPN20) have several advantages. They contain more information than dichotomous (i.e., yes vs no) endpoints and, therefore, potentially have greater assay sensitivity. Severity endpoints that incorporate assessments from multiple timepoints include more information than those that only include one timepoint, which may further increase assay sensitivity. In addition, neuropathy severity endpoints do not require identification of a cutoff to define occurrence of neuropathy. Although the occurrence of neuropathy endpoint has been used frequently in past studies,[7] many of these studies utilized the NCI-CTCAE, which has poor interrater reliability,[25] to identify the occurrence of neuropathy. Future studies could utilize the Toronto Criteria[9] or a cutoff score in a PRO or ClinRO to identify the occurrence of neuropathy.

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Table 1 Advantages and limitations of endpoints

	Advantages				Disadvantages			
	Continuous/ rank order (potentially higher power)	Not adversely affected by participants discontinuing chemotherapy due to neuropathy	Incorporates amount of chemotherapy received	Captures variation of neuropathy throughout chemotherapy	Dichotomous (potentially lower power)	Neuropathy assessment required after participants alter or prematurely discontinue chemotherapy	Requires prespecified cutoff for clinically meaningful neuropathy	Requires assumptions[a] about the rank of desirability of outcomes
Neuropathy endpoints								
Severity of neuropathy at specified timepoint	✓					✓		
Summary of severity of neuropathy at multiple timepoints	✓			✓		✓		
Occurrence of neuropathy		✓			✓		✓	
Neuropathy + chemotherapy endpoints								
Percentage of planned chemotherapy dosage until occurrence of neuropathy	✓	✓	✓				✓	
DOOR	✓	✓	✓	Maybe[b]		Maybe[b]		✓
Joint rank approach	✓	✓	✓	Maybe[b]				✓

[a] When the data are available, assumptions can be replaced with data-driven selection.
[b] Depends on the strategy used to assess neuropathy severity within the endpoint.

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Identification of valid cutoffs in these measures to identify clinically meaningful CIPN is a high priority future research area.

The occurrence of neuropathy endpoint has one important advantage: participant discontinuation of chemotherapy treatment after presenting with the prespecified severity of neuropathy will not adversely affect this endpoint. In contrast, with endpoints that assess neuropathy severity at particular timepoints, participants who alter their planned chemotherapy because of neuropathy before they complete the planned assessments might have lower neuropathy at the assessment timepoints than they would have if they had continued on their chemotherapy regimen as planned. If the investigational therapy is truly efficacious, patients in the placebo group might be more likely to alter their chemotherapy regimen due to neuropathy than patients in the active therapy group and potentially be rated as having less severe neuropathy at the assessment timepoint than they did when they altered their chemotherapy. Assuming that such participants would continue to be assessed in the study even though they had discontinued chemotherapy, the trial results could be biased toward the null with a neuropathy severity outcome if the estimand is the treatment effect assuming continuation of the chemotherapy regimen by all participants. A potential alternative is to impute subsequent neuropathy severity assessments with the last neuropathy assessment that occurred prior to the participant's discontinuation of chemotherapy, similar to the last observation carried forward (LOCF) method to accommodate missing data. Other imputation models that acknowledge the possible increase in neuropathy severity if chemotherapy had been completed while incorporating uncertainty in the actual severity may provide a better alternative than LOCF.[38,39] If, as discussed below, the chosen endpoint is after chemotherapy completion, similar models could also be considered to account for the coasting phenomenon (i.e., increasing severity of CIPN after discontinuation of chemotherapy) that occurs with some chemotherapies.

Endpoints that evaluate neuropathy severity at a specified timepoint after completion of chemotherapy will likely minimize the variability in neuropathy caused by different durations since the last chemotherapy cycle. Considering that prevention of CIPN that is unlikely to resolve on its own would be ideal, longer times post chemotherapy (e.g., 1 year) may be most clinically meaningful. However, a meta-analysis by Seretny et al.[1] found that the CIPN prevalence for all chemotherapies combined was 68% (95% confidence interval [CI] 58%–78%) within 1 month postchemotherapy, 60% (95% CI 36%–82%) 3 months postchemotherapy, and 30% (95% CI 6%–54%) 6 months or later postchemotherapy. Thus, it is important to balance the declining prevalence, which will increase the required sample size, with the potential increase in clinically meaningfulness of outcomes at 1 or 2 years post chemotherapy.

Endpoints that incorporate neuropathy and chemotherapy dosage received

The percentage of the planned chemotherapy dosage that a participant received before presenting with a certain severity of neuropathy has similar advantages and limitations to the occurrence of neuropathy endpoint. It also has the added advantage that it accounts for the amount of chemotherapy that the participant was able to take prior to developing neuropathy. Furthermore, it is continuous and may be more responsive to change than the occurrence of neuropathy endpoint.

Another strategy to incorporate neuropathy and chemotherapy dosage in a single outcome is to use a composite endpoint, for example, a Desirability of Outcome Ranking (DOOR) approach.[40] This strategy ranks patients according to how they fared on multiple dimensions at once rather than investigating each dimension separately.[41] In this case, the multiple dimensions might be neuropathy severity assessed in one of the ways described above and the percentage of planned chemotherapy that the participant was able to receive. This strategy requires assumptions regarding the rank of the desirability of outcome combinations, preferably informed by data. For example, one possible ranking scheme would be the following (1 is most desirable; 4 is least desirable): (1) participant completes all planned chemotherapy; (2) participant completes at least 75% but less than 100% of planned chemotherapy; (3) participant completes between 50% and 74% of planned chemotherapy; and (4) participant completes less than 50% of planned chemotherapy. Within each of these 4 ranks, participants would be ordered (from best to worst outcome) based on the severity of their neuropathy. The cutoffs of completion of 75% and 50% of planned chemotherapy regimens are arbitrary in this example. Data that are or become available regarding the amounts of chemotherapy that correspond to certain likelihoods of positive oncology outcomes (e.g., progression-free survival) should be used to inform the DOOR cutoffs.

Another assumption made in the above example ranking system is that completing chemotherapy is of higher priority than minimizing neuropathy. For example, it is not certain whether patients would prefer to complete all of their chemotherapy with severe neuropathy or to complete 75% of their planned chemotherapy with mild neuropathy. These preferences might depend on whether the cancer is curable, and for curable cancers, the available information regarding the degree to which decreasing the total chemotherapy dosage affects the likelihood of a cancer cure. Future research to evaluate clinicians' and patients' priorities regarding chemotherapy completion and neuropathy for different cancer types and stages would increase the validity of this type of endpoint.

Another option for a composite endpoint that combines neuropathy severity and chemotherapy completion would be to use a joint rank approach similar to that used in some amyotrophic lateral sclerosis RCTs.[42,43] Participants would be ranked from worst to best outcomes first by the time to the first alteration of their planned chemotherapy regimen and then by neuropathy severity for patients who completed all of the planned chemotherapy on schedule. As with the example

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DOOR endpoint presented above, this endpoint prioritizes completion of chemotherapy over minimizing neuropathy severity, but by considering only the time until the first alteration of the chemotherapy regimen it sacrifices information regarding the cumulative dosage of chemotherapy received throughout the duration of follow-up. Regardless of which type, composite endpoints may help address the challenge of 2 competing, clinically important outcomes that a CIPN prevention therapy would ideally improve.

Missing data

Participants who prematurely discontinue chemotherapy for reasons unrelated to neuropathy (e.g., nausea) present a missing data challenge for CIPN prevention trials regardless of the endpoint. These participants may or may not have developed neuropathy if they had continued their chemotherapy treatment. If a large number of participants prematurely discontinue or decrease planned dosages of chemotherapy before developing neuropathy, however, the ability of the study to detect a treatment effect (i.e., assay sensitivity) could decrease. In response to this occurrence, it may seem reasonable to eliminate from the analyses participants who did not reach a prespecified minimum cumulative dosage of chemotherapy that is thought to cause neuropathy. However, because the investigational therapy could affect whether participants receive this dosage of chemotherapy, the elimination of these patients could bias the treatment effect estimates. Methods to account for missing data should be used in intention-to-treat analyses.[44,45] Sensitivity analyses that make various assumptions regarding whether the participants who prematurely terminated chemotherapy would have developed neuropathy if the planned chemotherapy regimen had been completed are encouraged.

Mitigating risk of investigational therapy inhibiting chemotherapy effects

Data characterizing the mechanism of action for any novel investigational therapy and data establishing that the mechanism of an investigational therapy is not likely to interfere with the chemotherapy's mechanism of action should be collected. One or more proof-of-concept animal studies (e.g., mouse xenograft) are recommended to identify any obvious inhibition of the chemotherapy-related antitumor effects. In these animal studies, the investigational therapy should be concurrently administered with the same chemotherapy agents that will be included in human trials.[46,47] Given the uncertainties in preclinical data, the FDA generally recommends that the first study in cancer patients be in a population with metastatic disease to ensure that patients with potentially curable disease are not exposed to a therapy that could inhibit chemotherapy efficacy.

Sample size considerations

The required sample size for prevention trials is generally larger than for treatment trials because not everyone who is randomized will develop the condition.[48] The small sample size of previously published prevention trials (i.e., median [interquartile range] 68 [39–150][7]) may have contributed to the lack of significant results. Identifying a sufficiently large sample size requires an understanding of the variability of the primary outcome measure or how many patients will develop the primary endpoint that will be used in the study (e.g., develop CIPN of a prespecified severity). Improvements in the accuracy of CIPN incidence rates from studies that use various outcome measures as well as meta-analyses that generate summary incidence estimates by chemotherapy type will help to inform more accurate estimates of sample size requirements. Similarly, studies that investigate the percentages of patients who discontinue or delay chemotherapy treatment, due to neuropathy or other causes, for particular cancer and chemotherapy types will help inform sample size estimations for studies that incorporate information about the degree of completion of the chemotherapy regimen in the endpoints.

Inclusion of patients who are more likely to develop CIPN or discontinue chemotherapy due to neuropathy can decrease the necessary sample sizes for CIPN prevention trials. Although previous studies have investigated clinical risk factors for CIPN, many of the studies were relatively small with inconsistent results.[1] Measurement of baseline characteristics that could predict neuropathy in future prospective longitudinal studies or RCTs will help to identify important risk factors for CIPN. Collection of the following baseline characteristics should be considered: age, sex, diabetes status, HIV status, alcoholism status, previous exposure to neurotoxic therapies, neuropathy function tests (e.g., bumps test[33]), intraepidermal nerve fiber density, nerve condition studies, quantitative sensory *testing*, and laboratory testing (e.g., HbA1C, vitamin B_{12} levels, immunofixation electrophoresis).

Although better understanding of the natural history of CIPN will inform future studies, current gaps in knowledge need not be a barrier to conducting CIPN prevention trials at present. Methods of sample size reestimation based on examination of data in a planned interim analysis can help address uncertainties in assumed values of nuisance measures (e.g., SD) in the initial sample size estimation.[49] This type of interim analysis can decrease the chances of conducting a study that has inadequate power due to, say, the incidence of neuropathy in the placebo group being lower than expected based on information available prior to the trial.

Efficacious therapies to prevent CIPN would not only improve patients' quality of life, but may improve cancer-related outcomes if the frequency of complete and timely delivery of chemotherapy is increased. Consideration of the recommendations presented in this article and summarized in tables 2 and 3 might improve the quality and assay sensitivity of future CIPN clinical trials and thereby accelerate the identification of new therapies.

Author contributions

Jennifer S. Gewandter presented one of the talks at the consensus meeting, co-led the consensus discussion, wrote the first draft of the manuscript, and harmonized multiple rounds of input from coauthors. Joanna Brell presented one of the

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Table 2 Recommendations for chemotherapy-induced peripheral neuropathy (CIPN) prevention trial designs

Selecting type of prevention design
• Consider the advantages and limitations regarding study design and clinical application for primary and secondary prevention outlined in the prevention trial design section and figure
• Consider the mechanism of action of the investigational therapy when weighing these advantages and limitations
Entry criteria
Chemotherapy type
• Limit to one class of chemotherapy (e.g., taxanes)
• Include a limited number of chemotherapy regimens
Cancer type
• Include only similar cancer types
• Consider limiting to one cancer type, if feasible, especially in early proof-of-concept studies
• Avoid cancer types that may lead to relatively high withdrawal (e.g., pancreatic cancer)
Previous non-neurotoxic chemotherapy
• Do not exclude patients who have previously received chemotherapy that is not known to be neurotoxic
Preexisting neuropathy, comorbid conditions related to neuropathy, or previous neurotoxic treatments
• Exclude patients with probable neuropathy (see text for suggestions to operationalize)
• Consider advantages and limitations of including patients with possible neuropathy, comorbid conditions associated with neuropathy, and who have previously received neurotoxic treatments but do not have probable neuropathy
Concomitant medications
• Consider advantages and limitations of allowing concomitant medications
• Require consistent dosages if concomitant analgesics with efficacy in neuropathic pain are allowed
Outcome measures
• Include PROs and ClinROs to measure neuropathy as well as functional measures to evaluate the effect of neuropathy
• See the CIPN assessment section for considerations regarding choice of measures
Endpoints
• Consider the advantages and limitations of selected endpoints (table 2 and endpoints section)
Mitigating risk of investigational therapy inhibiting chemotherapy effects
• Perform sufficient animal studies to identify possible effects of the investigational therapy on the chemotherapy efficacy; use the chemotherapy classes that will be included in the human studies
• Consider metastatic cancer populations for first-in-cancer patient studies
Sample size considerations
• Sample size calculations should be based on current best estimates of CIPN incidence and severity for the class of chemotherapy and type of cancers to be included in the study
• Consider preplanned interim analyses to reevaluate the sample size calculation based on estimates of nuisance parameters from the study data

Abbreviations: ClinRO = clinician-rated outcome; PRO = patient-reported outcome.

talks at the consensus meeting, was an active participant in the consensus discussion, and provided feedback on multiple drafts of the manuscript. Guido Cavaletti presented one of the talks at the consensus meeting, was an active participant in the consensus discussion, and provided feedback on multiple drafts of the manuscript. Patrick M. Dougherty presented one of the talks at the consensus meeting, was an active participant in the consensus discussion, and provided feedback on multiple drafts of the manuscript. Scott Evans presented one of the talks at the consensus meeting, was an active participant in the consensus discussion, and provided feedback on multiple drafts of the manuscript. Lynn Howie presented one of the talks at the consensus meeting, was an active participant in the consensus discussion, and provided feedback on multiple

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Table 3 Research priorities to improve chemotherapy-induced peripheral neuropathy (CIPN) prevention randomized clinical trial designs

Research to investigate the following areas is encouraged:
• Validation of PROs, ClinROs, and function outcomes for different types of CIPN (e.g., from different chemotherapies; low vs high severity; paresthesias or dysesthesias vs pain; predominantly small vs large fiber)
• Identification of evidence-based cutoffs for (1) mild, moderate, and severe CIPN and (2) subclinical, clinically apparent, and clinically meaningful CIPN using PROs, ClinROs, and function measures
• Identification of baseline demographic and clinical characteristics that predict the development of CIPN
• Estimation of incidence rates of neuropathy induced by different chemotherapies using different measures with validated cutoffs (once such cutoffs are identified)
• Estimation of incidence of chemotherapy delay and discontinuation due to CIPN and other causes for different chemotherapy types
• Ascertainment of relative patient priorities regarding chemotherapy completion vs prevention of CIPN in populations of different cancer types and stages (e.g., to inform DOOR rankings)

Abbreviations: ClinRO = clinician-rated outcome; DOOR = Desirability of Outcome Ranking; PRO = patient-reported outcome.

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