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RESEARCH

Identifying participants' preferences for modifiable chemotherapy-induced peripheral neuropathy prevention clinical trial factors: an adaptive choice-based conjoint analysis

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Abstract

Purpose There are no recommended treatments for chemotherapy-induced peripheral neuropathy (CIPN) prevention. Recruitment to CIPN prevention clinical trials is challenging because it is difficult to enroll patients between the time of cancer diagnosis and the initiation of neurotoxic chemotherapy. The purpose of this exploratory-sequential mixed-methods study was to determine patients' preferences that could affect the choice to participate in CIPN prevention clinical trials.

Methods First, twenty cognitive interviews were conducted with adults who completed less than three neurotoxic chemotherapy infusions to clarify clinical trial attributes and levels thought to be important to patients when deciding whether to enroll in CIPN prevention trials (i.e., type of treatment, clinical tests, reimbursement, survey delivery; length of visits, timing of follow-up, when to begin treatment). Second, another eighty-eight patients completed an adaptive choice-based conjoint analysis survey that incorporated the finalized attributes and levels. Each level was assigned a part-worth utility score using Hierarchical Bayes Estimation. The relative importance of each attribute was calculated.

Results The attributes with the highest relative importance values were type of treatment (27.1%) and length of study visits (20.2%). The preferred levels included non-medicine treatment (53.49%), beginning treatment after experiencing CIPN (60.47%), email surveys (63.95%), assessments that include surveys and clinical exams (39.53%), under 30-min visits (44.19%), $50/week reimbursement (39.53%), and 1-month post-chemotherapy follow-up visits (32.56%).

Conclusions Patients' preferences for participation may be included in the design of future CIPN prevention clinical trials to potentially bolster study enrollment.

Keywords Neoplasms · Peripheral nervous system diseases · Qualitative research · Surveys and questionnaires · Choice behavior

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Introduction

The symptoms of chemotherapy-induced peripheral neuropathy (CIPN) include bilateral, upper/lower extremity sensory (e.g., numbness, tingling, neuropathic pain) and/or motor impairments [1] following neurotoxic chemotherapy administration that may negatively affect physical functioning [2–4]. According to clinical practice guidelines set forth by the American Society of Clinical Oncology, there are no recommended interventions to prevent CIPN [5]. The main treatment for CIPN mitigation during treatment is chemotherapy dose reduction; this is suboptimal as patients may not be receiving adequate chemotherapy dosages to treat their cancer [6]. Thus, there is an urgent need for the development of novel treatments for CIPN prevention.

In addition to the lack of evidence surrounding the underlying mechanisms of neuropathy, a limitation to determining new treatments for CIPN prevention is the overall poor study quality of previously conducted randomized clinical trials [7, 8]. For example, Lee et al. (2019) conducted a systematic review to characterize internal threats to validity of Phase III CIPN prevention or management trials between 1990 and 2018. The authors reported that 16/17 (94%) Phase III CIPN prevention clinical trials had two or more internal threats to validity (e.g., confounding variables, lack of reliable measurement or statistical validity) [9]. To improve CIPN clinical trial design, the Analgesic, Anesthetic, and Addiction Clinical Trial Translations, Innovations, Opportunities, and Networks Consortium on Clinical Endpoints and Procedures for Peripheral Neuropathy Trials released several recommendations for CIPN clinical trial design [7, 8]. Several of the recommendations allow for investigators to choose among several options (e.g., types of measures; primary or secondary prevention design) [7]. Due to the amount of resources necessary to conduct clinical trials, a greater understanding of factors that may influence patients' participation in clinical trials (e.g., type of outcome assessments, intervention delivery, reimbursement) are needed to help facilitate recruitment and retention in future CIPN prevention clinical trials.

The conjoint analysis, a method originally used in market research [10], is a theory driven [11], choice-based approach in which participants are asked to choose the most desirable choice between two or more scenarios that contain multiple characteristics and associated values [12]. Based on participants' selections, the investigator may evaluate trade-offs between crucial characteristics of the scenarios that likely drive the participants to select the most desirable choice. Choice-based approaches recently have been used to evaluate patient preferences for chronic pain treatment and/or clinical trial design [13–16], but no studies to our knowledge have implemented choice-based approaches to elucidate the factors that patients consider most important when deciding to participate in a CIPN prevention clinical trial.

The purpose of this study was to determine modifiable clinical trial characteristics that influence patients' likelihood to participate in CIPN prevention clinical trials using cognitive interviewing and adaptive choice-based conjoint analysis methodology.

Patients and methods

Design, sample, and setting

The primary aim was investigated using an exploratory, sequential, mixed-methods design. First, we conducted cognitive interviews to gain feedback about the attributes and associated levels that may be appealing to participants when deciding to participate in a CIPN prevention clinical trial. Attributes are defined as a characteristic of a product or concept (i.e., CIPN prevention clinical), while levels are defined as a value of a given attribute [17]. Information gleaned from these interviews were used to ensure relevance and clarity of the attributes and levels for the adaptive choice-based conjoint analysis (ACBC) survey. Second, we conducted an ACBC analysis to determine modifiable CIPN clinical trial characteristics that likely influence participants' likelihood to participate in clinical trials. Patients were recruited from the hematological oncology, sarcoma, breast oncology, or gastrointestinal disease centers at Dana-Farber Cancer Institute. Patients were eligible if they were (1) 18 + years of age and spoke/read English, (2) scheduled to receive neurotoxic chemotherapy for the treatment of cancer, and (3) had not received more than two neurotoxic chemotherapy infusions. The study was approved and regulated by the Dana-Farber/Harvard Cancer Center Office of Human Research Studies (19–535). Written informed consent and/or verbal informed consent (i.e., related to need for social distancing due to the COVID-19 pandemic) was obtained from all participants.

Measures

At the time of the interview or survey, participants self-reported demographic information and completed the Patient-Reported Outcomes Version of the Common Terminology Criteria for Adverse Events (PRO-CTCAE™) Numbness and Tingling Severity and Interference Items**.** The PRO-CTCAE™ CIPN severity and interference items ask participants to self-report the severity of their numbness and tingling in their hands or feet at its worst in the past 7 days and the degree to which CIPN symptoms interfered

with activities of daily living (0–4; higher scores represent worse CIPN severity and interference, respectively) [18–20]. Study staff abstracted information about participants' cancer type, cancer stage, and chemotherapy regimen from the electronic medical record following the interview or survey.

Procedures and analysis

Consented patients were enrolled to the cognitive interviewing phase or the conjoint analysis phase. All participants received a $10 gift card for completing the cognitive interview or conjoint analysis survey. The following describes procedures and analyses specific to the cognitive interviewing or conjoint analysis phases, respectively.

Cognitive interviewing phase Given the dearth of knowledge surrounding factors that patients consider most important when deciding to participate in CIPN prevention clinical trials, a broad literature review [12] was conducted to generate the initial list of potential attributes and levels hypothesized to be important to participants when deciding whether to enroll in a CIPN prevention clinical trial. The principal investigator searched the literature for studies that conducted conjoint analyses or discrete choice experiments to determine patients' preferences for non-surgical treatment/prevention of chronic, acute, or cancer pain from 2013 to 2018. Findings from 14 articles [13–16, 21–30] were used to generate attributes that could be feasibility modified in a clinical trial focused on CIPN prevention. Next, the co-investigators revised the initial list of attributes using recommendations from the most recent CIPN prevention trial design guidelines [7, 8]. The initial list of attributes presented to participants included (1) type of new treatment, (2) when to begin the new treatment, (3) timing of study visits, (4) how to complete surveys, (5) type of clinical tests, (6) length of study visits, (7) allowed to take other pain medications during the study, (8) reimbursement for study participation, (9) type of side effects from the new treatment, (10) possibility that the new treatment makes chemotherapy less effective, (11) percent of participants who will get neuropathy without any preventative treatment, and (12) timing of follow-up study visits after the completion of chemotherapy.

Patients who consented to the cognitive interviewing phase participated in 60-min, individual, cognitive interviews [31]. All cognitive interviews were conducted by the principal investigator (RK), a PhD prepared nurse-scientist. The principal investigator had prior experience with qualitative research from his other research studies, and he pilot tested the Cognitive Interview Guide (Table 1) with his mentor (DB) before conducting any cognitive interviews with participants. All interviews occurred face-to-face at an outpatient chemotherapy infusion appointment or via telephone and were audio recorded.

Prior to each cognitive interview, the principal investigator explained the purpose of the interview and the definition, importance, and workings of clinical trials for neuropathy, but stressed to the participant that they were not being asked to join a clinical trial about neuropathy. During each cognitive interview, participants completed four activities. First, participants were presented with the attributes identified via literature review to likely be important to participants when deciding to enroll in a CIPN prevention clinical trial and were asked to rank the attributes in order of importance. Second, participants were presented with a description of all the levels associated with each attribute and were asked to select the level within each attribute that would be most appealing when deciding to enroll in a CIPN prevention clinical trial. Third, participants reviewed three hypothetical clinical trials containing varying levels for each attribute and were asked if they would be willing to participate in each respective trial (i.e., yes/no). Fourth, participants reviewed five sets of three hypothetical clinical trials and were asked to select one trial in which they would be most willing to participate. After each section, the principal investigator asked questions to determine how the participant came to a selection among the various levels and if the attributes and levels were easily understood.

After each interview, the principal investigator listened to the audio recording and simultaneously wrote notes to summarize the discussion. After approximately every five cognitive interviews, the principal investigator and JG, a pain scientist with expertise in CIPN clinical trial design, met to discuss the participants' feedback, revise the attributes and associated levels, and determine if thematic saturation was obtained. Decisions to revise the attributes and levels were made based on (1) whether participants could understand the attribute or level and (2) what attributes and levels were selected as most important by the participants. The revised attributes and levels were retested in the next round of cognitive interviews, and once again, the principal investigator and JG met to revise the attributes and levels. This iterative process was planned to continue for five cycles or until saturation of themes was reached.

Conjoint analysis phase Following the cognitive interview phase, the finalized list of attributes and associated levels were administered within an electronic ACBC survey (Sawtooth Software, Inc; Provo, UT) [32] to an additional cohort of participants who met the eligibility criteria. The ACBC survey consists of several section. First, participants were prompted to select the preferred level associated with each attribute. Second, hypothetical CIPN prevention clinical trials were presented, and participants were asked whether they would be willing to participate in each trial (i.e., yes or no). During this section, participants were periodically prompted to select the levels associated with each attribute

Table 1 Cognitive interviewing guide

Activity	Description	Questions
1	The following lists several attributes, or characteristics about how, when or what types of treatments are used in clinical trials. These could be different in each trial. Please rank these factors from most to least appealing when deciding whether you would enroll in a clinical trial about CIPN prevention. Please use a rank of "1" for the most appealing attribute and a rank of "12" for the least appealing attribute. After you rank the attributes, I will ask you questions about your preferences	Can you please describe this attribute in your own words? What did you think about when you ranked this attribute? How did you decide to rank the attribute this way? Can you tell me reasons you would feel uncomfortable telling us honestly how you rank this attribute? How could we describe this attribute better?
2	The following lists several choices for each attribute that could be different in each trial. For example, the attribute, "timing of study visits," has two choices: "before each chemotherapy infusion" or "in the days after each chemotherapy infusion." Now we would like you to choose the choice for each attribute that would be most appealing to you when deciding whether to enroll in a clinical trial about preventing CIPN	Can you please describe your selection in your own words? What did you think about when you answered this question? How did you decide to pick that choice? Can you tell me reasons you would feel uncomfortable telling us honestly how you would select a choice for this attribute? Do one of these choices seem better/worse than the rest? If so, why? How could we describe the particular choices better?
3	Now that you're familiar with these characteristics, we are going to combine them into sample clinical trials. If you look at Part 3, you'll see that on the left side, the attributes that you saw earlier are listed. Now each column represents a sample clinical trial, rather than different choices for each characteristic. This is how our future study will look to participants, but we want to make sure that this is understandable. I am going to ask you to look over each possible clinical trial and tell me whether you would consider participating in each one. Please try to make your decisions as quickly as possible, without compromising your ability to consider each trial	Describe what you were thinking when you decided to (not) participate in [study X] Is there something that we could change in [study X] that would make you more likely/less likely to participate?
4	There are five sets of trials that I am going to ask you to consider. I am going to ask you to please look over the 3 trials in each set and pick the ONE that you'd most prefer to join. Please do this for Set A (repeat for B–E) and mark your answer below the table and let me know as soon as you have made your decision	Describe what you were thinking about when you chose the trial you did? What were your overall thoughts of the attributes? Did you feel like having that much information on one page was overwhelming? Do you have any other suggestions?

This table describes the activities that participants were asked to complete during the cognitive interview and the types of questions the interviewer asked participants after each part of the interview

that were most and least desirable, respectively. Third, participants were presented with three hypothetical clinical trial scenarios and were asked to choose one trial that they would rather participate in based on the presented attributes and associated levels. Such hypothetical clinical trial scenarios are called "tournament tasks" and were presented in random order to each participant. The winning clinical trial from each tournament task advanced to subsequent tournament tasks until a final "winning" clinical trial was identified.

Statistical analysis

Sample size considerations To obtain an estimate of a sufficient sample size for the ACBC experiment, Sawtooth Software recommends that enough participants are included so that each level is seen at least two times, but preferably three times, per respondent. The "Test Design" feature within Sawtooth Software (i.e., simulates multiple test respondents who answer the questions randomly) projected that a sample size of 150 participants was sufficient for every participant to see each level a minimum of three times. Thus, the initial recruitment goal was 150 participants for the ACBC experiment. However, due to slow recruitment and COVID-19-related research stoppages, recruitment was ceased after 88 participants were enrolled. With a sample of 88 participants, results indicated that each participant saw each level at least twice.

Sawtooth Software analysis First, we conducted a counting analysis in which the Sawtooth Software tabulated the frequency of how often each level was preferred among the other levels within each attribute, selected as a "must have" in the clinical trial, selected as "unacceptable" to have in the clinical trial, or included in each individual's "winning" clinical trial. Next, each level within each attribute was assigned a part-worth utility score or the participant's desirability of a level within each attribute [17]. Part-worth utility scores were estimated using Hierarchical Bayes Estimation. Third, the relative importance of each attribute was calculated [17]. The relative importance scores for each attribute sums to 100 and may be used to determine which attributes are most important to participants when deciding to participate in a CIPN prevention clinical trial [17]. Finally, we simulated a "typical" CIPN prevention randomized controlled trial and varied the levels within the attributes that had the top three relative importance scores from the ACBC survey for an "alternative" CIPN randomized controlled trial [13, 17]. Participants' preferences for trial participation between the two hypothetical trials were compared in choice simulations using Sawtooth Software. In choice simulations, Sawtooth Software uses the raw part-worth utility data to predict the percent of respondents projected to select the typical or alternative clinical trial. The typical randomized controlled trial for CIPN prevention included prescription medicine that is known to have mild side effects, treatment that begins before chemotherapy, surveys that are completed in-person, at the clinic, clinical tests that include surveys + blood draws, 30–60-min study visits, $25 per week reimbursement, and 3-month post-chemotherapy follow-up study visits.

Results

Participant flow and characteristics

Participant recruitment and data collection occurred from 2/12/2020 to 11/19/2020. Fig. 1 describes participant flow through the study. Overall, 20 and 88 participants were evaluable for analysis in the cognitive interview and ACBC analysis phases, respectively. Table 2 describes the demographic characteristics of the analyzed sample for each phase.

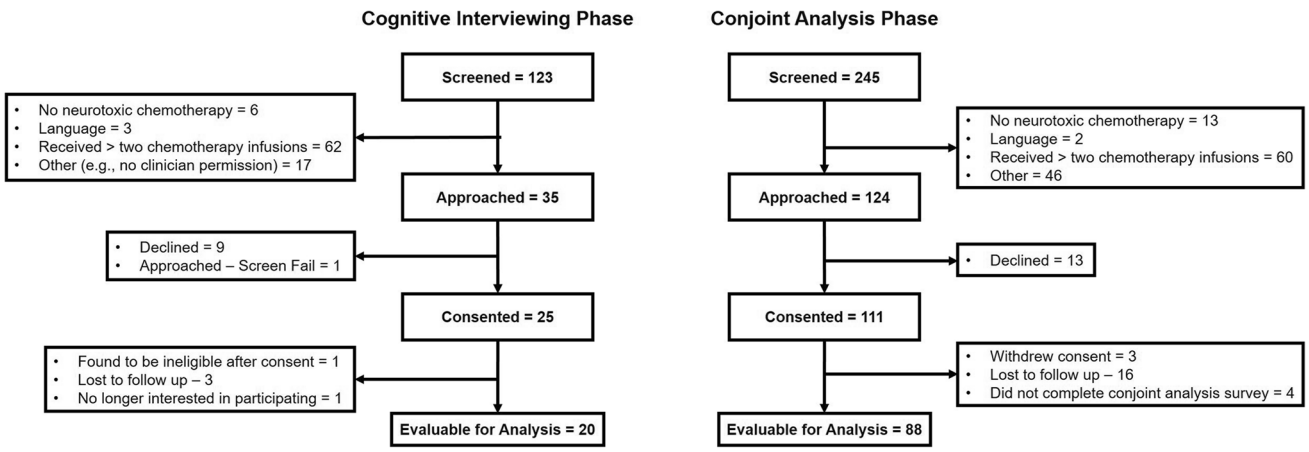

Fig. 1 Participant flow through the cognitive interviewing and conjoint analysis phases, respectively

Table 2 Demographic characteristics of the enrolled sample at baseline

Characteristic	Cognitive interviewing ($N=20$)	Conjoint analysis ($N=88$)
Age at baseline	($n=19$)	($n=86$)
Median (*range*)	52 (34–78)	54 (21–74)
Gender		($n=87$)
Female	14 (73.7%)	67 (77%)
Male	5 (26.3%)	20 (23%)
Race		
Asian	0	3 (3.4%)
Black or African American	0	2 (2.3%)
White	18 (94.7%)	82 (93.2%)
Unknown or do not wish to report	1 (5.3%)	1 (1.1%)
Ethnicity	($n=18$)	($n=83$)
Hispanic or Latino	3 (16.7%)	1 (1.2%)
Not Hispanic or Latino	15 (83.3%)	82 (98.8%)
Education		($n=87$)
Completed high school	2 (10.5%)	6 (6.9%)
Some college or technical training	4 (21.1%)	26 (29.9%)
University undergraduate degree	7 (36.8%)	29 (33.3%)
University post graduate degree	6 (31.6%)	26 (29.9%)
Marital status		
Single	1 (5.3%)	12 (13.6%)
Married/partnered	18 (94.7%)	68 (77.3%)
Divorced	0	5 (5.7%)
Widowed	0	3 (3.4%)
Employment status		($n=87$)
Working full-time	8 (42.1%)	30 (34.5%)
Working part-time	0	6 (6.9%)
Working at home	3 (15.8%)	1 (1.1%)
Working, but on medical leave	1 (5.3%)	19 (21.8%)
Not working	3 (15.8%)	18 (20.7%)
Retired	4 (21.1%)	13 (14.9%)
Prior research study participation		
Zero	14 (73.7%)	54 (61.4%)
One	1 (5.3%)	16 (18.2%)
Two	3 (15.8%)	12 (13.6%)
Three	1 (5.3%)	3 (3.4%)
Four	0	2 (2.3%)
Five or more	0	1 (1.1%)
PRO-CTCAE[a] severity		
0 – None	12 (63.2%)	47 (53.4%)
1 – Mild	4 (21.1%)	25 (28.4%)
2 – Moderate	3 (15.8%)	14 (15.9%)
3 – Severe	0	2 (2.3%)
4 – Very severe	0	0
PRO-CTCAE[a] interference		
0 – Not at all	14 (73.7%)	66 (75%)
1 – A little bit	4 (21.1%)	14 (15.9%)
2 – Somewhat	1 (5.3%)	6 (6.8%)
3 – Quite a bit	0	2 (2.3%)
4 – Very Much	0	0
Cancer type		
Lymphoma	4 (20%)	11 (12.5%)
Breast	11 (55%)	41 (46.6%)
Gastrointestinal	4 (20%)	35 (39.8%)
Sarcoma	1 (5%)	1 (1.1%)
Cancer stage		
Stage I	3 (15%)	17 (19.3%)
Stage II	7 (35%)	21 (23.8%)
Stage III	5 (25%)	19 (21.6%)
Metastatic	3 (15%)	21 (23.9%)
Unknown	2 (10%)	10 (11.4%)
Chemotherapy type		
Paclitaxel	7 (35%)	23[b] (26.1%)
Docetaxel	5 (25%)	14 (15.9%)
Vincristine	3 (15%)	3 (3.4%)
Vinblastine	1 (5%)	6 (6.8%)
Oxaliplatin	3 (15%)	30 (34.1%)
Cisplatin	0	3 (3.4%)
Multiple	1 (5%)	9 (10.2%)
Chemotherapy status at baseline		
Planned, not yet started	2 (10%)	10 (11.4%)
Currently receiving	18 (90%)	78 (88.6%)

[a]*PRO-CTCAE*, Patient-Reported Outcomes Version of the Common Terminology Criteria for Adverse Events

[b]One participant was receiving paclitaxel protein-bound

Attribute and level revisions following the cognitive interview process

Following twenty interviews (*n range* = 4–6 interviews each cycle, for four cycles), the attributes and levels had been revised four times, and the investigators agreed that thematic saturation had been reached. The final list of attributes and levels that were incorporated into the ACBC survey are presented in Table 3. The attribute, "type of side effect you may experience from the new treatment," was ultimately deleted because its levels were discordant with the levels for "type of new treatment for neuropathy (e.g., unlikely that there would be side effects with non-pharmacological treatments)." Instead, the severity of potential side effects was incorporated into the wording of the levels regarding prescription medicine under the attribute, "type of new treatment for neuropathy." The attributes "possibility that the experimental treatment makes the chemotherapy less

Table 3 Relative Importance and part-worth utility scores of the attributes and levels ($N = 88$)

Attributes and associated levels	Relative importance[a]	Average utility[b]
Type of new treatment for neuropathy	27.14 ($SD = 11.31$)	
Prescription medicine (that is known to have mild side effects)		26.70 (59.41)
Prescription medicine (that is known to have moderate side effects)		−79.98 (45.84)
Non-medicine like exercise or mindfulness		53.28 (87.35)
Length of study visits	20.23 ($SD = 9.89$)	
Under 30 min		49.68 (38.99)
30 min to 1 h		38.96 (23.35)
1 to 2 h		−12.82 (19.18)
2 to 3 h		−75.83 (46.25)
How to complete surveys for the study	12.05 ($SD = 4.98$)	
In person, at clinic		−30.98 (26.27)
Telephone		−11.57 (21.73)
Email		42.55 (22.82)
Type of clinical tests for the study	11.24 ($SD = 4.16$)	
Surveys only		6.98 (32.50)
Surveys + blood draw		−14.0 (32.38)
Surveys + clinical exam of arms and legs (like reflexes)		14.36 (30.75)
Surveys + physical test (like walking)		−7.34 (25.48)
Timing of follow-up study visits after the completion of chemotherapy	10.70 ($SD = 5.08$)	
None		−21.10 (26.52)
1-month post-chemotherapy		13.28 (33.84)
3-month post-chemotherapy		15.07 (17.41)
6 months to a year post-chemotherapy		−7.25 (31.39)
When to begin the new treatment for neuropathy	9.64 ($SD = 6.76$)	
Before any chemotherapy starts		−13.83 (38.98)
After you experience neuropathy		13.83 (38.98)
Reimbursement for study participation	8.99 ($SD = 3.73$)	
None		2.65 (33.33)
Travel expenses only		−6.65 (26.35)
$25 per week		1.64 (21.19)
$50 per week		2.36 (24.83)

[a]Presented as percentages. All relative importance scores sum to 100%

[b]Average utility scores are zero centered. Higher scores for a level within an attribute represent higher desirability. A negative value does not necessarily indicate that the level was unattractive. Utility scores for levels within a particular attribute cannot be compared to levels within different attributes[17]

effective" and "percent of participants who will get CIPN without any preventative treatment" were removed because participants consistently did not understand these attributes and associated levels. The attribute, "timing of study visits," was removed because participants were unclear as to whether the level, "before each chemotherapy infusion" referred to any time before the infusion or at the clinic on the day of the infusion. Lastly, the attribute, "allowed to take other pain medications during the study" was removed because participants were mixing up pain/neuropathy medications with medications in general when responding and many patients are not on neuropathy pain medications at the beginning of chemotherapy. Otherwise, minor wording changes to the other attributes were instituted in response to participant feedback after each round of interviews.

Adaptive choice-based conjoint (ACBC) analysis

Eighty-eight participants completed the ACBC analysis survey. Table 3 describes the relative importance of each attribute and the average utility of levels within the clinical trial attributes. Type of new treatment for neuropathy was the attribute with the highest relative importance (27.14%), followed by length of study visits (20.23%), and how to complete surveys for the study, respectively (12.05%). The

remaining four attributes had relative importance scores that ranged from 8.99 to 11.24%.

The results of the tournament tasks revealed that the levels most frequently included in participants' "winning" CIPN prevention clinical trial included (1) non-medicine treatment, (2) beginning the new treatment for neuropathy after experiencing CIPN, (3) email surveys, (4) assessments that include surveys and clinical exams of arms and legs, (5) under 30-min study visits, (6) $50 per week reimbursement, and (7) 1-month post-chemotherapy follow-up study visits (Table 4). A subset of participants reported that using a non-medicine treatment for CIPN would be a requirement to join a neuropathy prevention trial ($n = 17$, 19.32%). Conversely, some participants reported that using a prescription medicine known to have mild ($n = 17$, 19.32%) or moderate side effects ($n = 34$, 38.64%) and/or 2–3-h long study visits ($n = 32$, 36.36%) would be unacceptable when considering whether to join a CIPN prevention trial.

Results from the choice simulations revealed in comparison to a typical CIPN prevention trial, 1) 85.8% (95% CI: 82.1–89.5%) would prefer an alternative trial that involved email surveys than a typical trial with in-person surveys, (2) 55.7% (95% CI: 50.3–61.2%) would prefer an alternative trial with under 30-min study visits than a typical trial with 30–60-min study visits, and (3) 54.9% (95% CI: 46–63.8%) would prefer an alternative trial that involved non-medicine than a typical trial with a prescription medicine (i.e., mild side effects).

Table 4 Composition of the "winning" concept from the choice tournament section ($N = 86$)[a]

Attributes and associated levels	Frequency (%)[b]
Type of new treatment for neuropathy	
Prescription medicine (that is known to have mild side effects)	37 (43.02%)
Prescription medicine (that is known to have moderate side effects)	3 (3.49%)
Non-medicine like exercise or mindfulness	46 (53.49%)
Length of study visits	
Under 30 min	38 (44.19%)
30 min to 1 h	36 (41.86%)
1 to 2 h	6 (6.98%)
2 to 3 h	6 (6.98%)
How to complete surveys for the study	
In person, at clinic	11 (12.79%)
Telephone	20 (23.26%)
Email	55 (63.95%)
Type of clinical tests for the study	
Surveys only	26 (30.23%)
Surveys + blood draw	13 (15.12%)
Surveys + clinical exam of arms and legs (like reflexes)	34 (39.53%)
Surveys + physical test (like walking)	13 (15.12%)
Timing of follow-up study visits after the completion of chemotherapy	
None	17 (19.77%)
1-month post-chemotherapy	28 (32.56%)
3-month post-chemotherapy	21 (24.42%)
6 months to a year post-chemotherapy	20 (23.26%)
When to begin the new treatment for neuropathy	
Before any chemotherapy starts	34 (39.53%)
After you experience neuropathy	52 (60.47%)
Reimbursement for study participation	
None	22 (25.58%)
Travel expenses only	15 (17.44%)
$25 per week	15 (17.44%)
$50 per week	34 (39.53%)

[a]Data is available from 86 participants for this analysis because two participants did not complete all the tournament tasks

[b]Higher frequency represents higher desirability of a selected level

Discussion

To our knowledge, this is among the first studies to use ACBC analysis to elicit participant preferences for clinical trial attributes when deciding whether to join a CIPN prevention clinical trial. The type of new treatment for neuropathy was the most important factor participants considered when deciding whether to participate in a CIPN prevention clinical trial. An approximately equivalent number of participants preferred non-pharmacological treatments or pharmacological treatment with mild side effects, while several participants selected pharmacological treatment with moderate side effects as unacceptable. Our findings suggest that participants were most interested in treatments that did not lead to additional side effects, which is not surprising given that patients are already experiencing side effects from cancer treatment [33]. Ultimately, investigators' choices of experimental treatments for CIPN prevention should be targeted to underlying hypothesized mechanisms of how CIPN develops [7].

Prior conjoint analysis research has demonstrated that participants with chronic pain are less likely to participate in clinical trials that include invasive clinical tests (e.g., skin biopsy or ice-water sensory testing) or frequent, in-person study visits [13]. Our results are consistent with past research in that blood draws and physical tests were the least desirable options in our sample. In addition, participants highly desired email surveys and shorter study visits. The onset of the COVID-19 pandemic has required investigators to identify new ways to deliver research procedures and interventions virtually [34, 35] and could serve as a guide to streamline study procedures in future research to decrease participant burden. However, attempts to minimize participant burden should also be balanced with strategies to maintain study rigor and adequately measure treatment response. For example, while "surveys only" was an option for the attribute of "type of clinical tests for the study," participants most frequently selected "surveys + clinical exam of arms and legs" as the top choice for this attribute. The use of patient-reported outcomes and clinician-rated neuropathy outcomes (e.g., reflexes, vibration, muscle strength, physical function) is recommended for use in CIPN prevention clinical trials [7].

While higher reimbursement was preferred, reimbursement for study participation was the least important attribute participants considered when deciding whether to enroll in a CIPN prevention clinical trial. Payment for study participation has been identified as an important attribute for individuals with chronic pain when deciding to participate in clinical trials [13]. It is unclear why reimbursement for study participation was less important to patients receiving chemotherapy. CIPN prevention clinical trial participation may be less of a burden for patients receiving chemotherapy because they are already spending many hours at oncology outpatient centers for cancer treatment. Inadequate compensation for research participation may decrease recruitment and retention and increase the possibility that participants are being exploited for their time and effort [36, 37].

There are several limitations to this research. First, despite a literature review and cognitive interviews with participants, it is possible that some clinical trial characteristics were not included in the ACBC survey that may have significantly influenced ACBC survey results or some participants did not fully understand the attributes or levels included in the ACBC survey. Second, the external generalizability of the study findings is limited given that recruitment occurred at one institution and the participant sample was homogenous with regard to race, ethnicity, and gender. Third, it is also possible that our results lacked a high degree of precision at the individual level because the results indicate that each level was shown twice, but not three times, to each participant when completing the ACBC survey. Fourth, some participants were experiencing CIPN at the time of the cognitive interview or conjoint analysis survey, which may have influenced their answers to the questions in comparison to participants who had not yet experienced CIPN. Finally, given that participants were selecting preferences for CIPN prevention clinical trial attributes based on hypothetical clinical trial scenarios, it is possible that participants may exhibit different preferences when actually presented with an opportunity to participate in a CIPN prevention clinical trial.

Recruitment to CIPN primary prevention clinical trials is particularly challenging because it is difficult to enroll patients between the time of cancer diagnosis and the initiation of neurotoxic chemotherapy [7]. Study results highlight several trial characteristics that may be important to participants when deciding to enroll in a CIPN prevention clinical trial. Investigators designing CIPN prevention trials in the future may incorporate clinical characteristics preferred by participants to increase participant interest and enrollment.

Author contribution RK: conceptualization; methodology; formal analysis; investigation; writing, original draft; funding acquisition. DB: conceptualization, methodology, writing—review and editing. JM: conceptualization, writing—review and editing. KR: conceptualization, writing—review and editing. ES: conceptualization, writing—review and editing. KT: conceptualization, writing—review and editing. JG: conceptualization; methodology; writing, review and editing; supervision.

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Data availability The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Declarations

Ethics approval This study was performed in line with the principles of the Declaration of Helsinki. Approval was granted by the Dana-Farber/Harvard Cancer Center Office for Human Research Studies (Protocol: 19–535; 11/22/2019).

Consent to participate Informed consent was obtained from all individual participants included in the study.

Consent for publication Not applicable.

Conflict of interest RK has received personal fees (consulting) from Strategy Inc., Spark Healthcare, Fors Marsh Group, Osmol Therapeutics, Inc., and the Comprehensive and Integrative Medicine Institute and serves on the scientific advisory board of Wellium. JM has served as an advisor/consultant to Merck Pharmaceutical and COTA Healthcare. JG has received grant funding from the National Institutes of Health, compensation for grant reviews from the US Department of Defense, and consulting income from Algo Therapeutix, Asahi Kasei Pharma, Eikonizo Therapeutics, GW Pharma, Magnolia Neurosciences, Orthogonal Neurosciences, Science Branding Communications, SK Life Science, and Saluda Medical.

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