Support Care Cancer
DOI 10.1007/s00520-013-1981-6

ORIGINAL ARTICLE

Comparison of two chemotherapy-induced peripheral neuropathy measurement approaches in children

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Received: 24 May 2013 / Accepted: 11 September 2013

Abstract
Purpose Chemotherapy-induced peripheral neuropathy (CIPN) is a common side effect of cancer treatment in children; however, measurement of CIPN has been hampered by limitations in available tools, which may impact prevalence estimates. The purpose of this study was to assess the relative ability of the Common Terminology Criteria (CTCAE) rating process to detect sensory and motor neuropathy as compared to administration of the pediatric modified Total Neuropathy Score (peds-mTNS).
Methods The ped-mTNS was administered to 60 children/adolescents ages 5–18 undergoing treatment for acute lymphocytic leukemia, lymphoma, or non-CNS solid tumors. CTCAE v3.0 scores for the same time point were abstracted from the medical record by a separate trained rater. Comparisons were made between scores using descriptive statistics, correlations, and specificity and sensitivity calculations.
Results The median ped-mTNS score was 9 (32 possible), while the median sensory and motor CTCAE ratings were 0 and 2, respectively (4 and 5 possible, respectively). There was no correlation between ped-mTNS and combined sensory and motor CTCAE scores. The only ped-mTNS item with significant correlation to CTCAE scoring was strength testing. Medical record abstraction of CTCAE scores failed to identify sensory neuropathy in 40 % and significant motor neuropathy (manual muscle test grade 3 or worse) in 15 % of subjects.
Conclusions Prospective measures of CIPN using the ped-mTNS identified a far greater proportion of subjects with peripheral neurotoxicity as compared to CTCAE v3.0 sensory and motor neuropathy ratings, and thus we recommend the use of a specific measure of CIPN such as the ped-mTNS.

Keywords Neurotoxicity · Cancer · Pediatrics

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Introduction

Chemotherapy-induced peripheral neuropathy (CIPN) is a common yet frequently under-reported side effect of cancer treatment in both adult and pediatric patients [1]. Many children treated for cancer receive chemotherapeutic agents, such as vincristine, cisplatin, and methotrexate, which have known neurotoxic effects (for reviews on this topic see references [2–5]). In addition to potentially limiting the dose of chemotherapy a patient may receive, CIPN can have immediate and long-term effects on physical function and quality of life [6–8]. In recent years, more emphasis has been placed on reducing the overall toxicity of treatment [9] and thus measurement of treatment-related side effects such as CIPN has become a more important outcome for both clinical trials and patient care.

Currently, clinicians and scientists most often use the definitions and scoring system provided by the National Cancer Institute in the Common Terminology Criteria for Adverse Events [10] (CTCAE; Table 1) to assess CIPN in children and adolescents. Examples of recent clinical trials that have used this methodology include Children's Oncology Group trial

Published online: 27 September 2013

ADVL0916 [11] and the Therapeutic Advances in Childhood Leukemia and Lymphoma (TACL) study trial T2005-003 [12]. The CTCAE was developed as a comprehensive grading system for adverse events occurring during or after cancer treatment in all body systems [13]. Version 3.0 of the CTCAE consists of over 330 scales that can rate adverse events in 26 different body systems. When neuropathy is found to be present by a healthcare practitioner, it can be rated on the sensory and/or motor neuropathy subscales (Table 1). These scales use a 1–5 rating to indicate the severity of a side effect, with higher numbers indicating increasing perceived disability, and a rating of 5 indicating death from that side-effect. In some of the CTCAE scales, such as the sensory neuropathy scale, death from that event is not a possibility and thus a score of 5 is not applicable for that specific subscale. While study subjects can be graded at any rating level available for that adverse event, many trials only require the reporting of high level (grade 3 or greater) toxicities. In many institutions, including the one where this study was conducted, physicians will grade life-threatening or medically complex adverse events, but clinical research associates under the direction of principle investigators review the medical records of subjects on clinical trials for grading more minor and non-life threatening adverse events such as neuropathy. While this system provides consistent guidelines for the documentation of adverse events, it has been questioned if this rating scale is sensitive enough to document the more subtle signs of neuropathy that are often found in this population [7, 8, 14–18].

Recently, we adapted and validated a measure of CIPN for use in school-aged children and adolescents (5–18 years of age) undergoing treatment for non-central nervous system (CNS) malignancies. The pediatric-modified Total Neuropathy Score (ped-mTNS; Table 2) is a combined subjective and objective measure of nerve function. It has sound psychometric properties [7] and has been demonstrated to be feasible for clinical use [19], but is currently not widely adopted in clinical practice. To assess the relative ability of the peds-mTNS to detect sensory and motor neuropathy as compared the current practice of clinical examination and documentation followed by medical record review utilizing the CTCAE scale to evaluate CIPN, we analyzed the associations between scores on the two measures in children and adolescents undergoing cancer treatment for non-CNS tumors.

Methods

Patients with a diagnosis of acute lymphoblastic leukemia (ALL), lymphoma, or other solid tumor except for CNS tumors attending oncology clinic visits from July 1, 2008 to August 1, 2011 at Children's Hospitals and Clinics of Minnesota were invited to participate. Patients with neurologic deficits or developmental delay present prior to cancer diagnosis were not eligible. Among the 83 eligible patients, 4 declined participation and 13 were not approached for recruitment due to scheduling issues. Of the 66 patients recruited into the study, 60 (72.3 % of those eligible) completed the ped-mTNS measures and had a physical examination within 24 h by an oncology practitioner and are included in the analysis. Six subjects were lost due to scheduling issues. Recruitment materials, consent forms, and testing procedures were reviewed and approved by the institutional IRB. Informed consent/assent was obtained from parents/children prior to testing.

The ped-mTNS was administered by a physical therapist, as previously described [7] (Table 2). A score of 5 or greater on the ped-mTNS was used to define the presence of neuropathy based on previously published data of children and adolescents who had never been diagnosed with cancer or received neurotoxic chemotherapy [7]. Children with ALL were measured within 2 weeks of the end of delayed intensification and patients with lymphomas or solid non-CNS tumors were measured 3–4 months after the initiation of chemotherapy. Within 24 h of ped-mTNS testing, as part of routine clinical care, a physical examination was completed by an oncology practitioner (physician, physician assistant, or nurse practitioner) including review of the neurologic system for signs and symptoms of sensory and/or motor neuropathy and recorded in the medical record. The practitioner was blind to the participant's

Table 1 The Common Toxicity Criteria for Adverse Events (CTCAE) version 3.0 grades [10]

CTCAE	1	2	3	4	5
Neuropathy Motor	Asymptomatic weakness on examination only	Symptomatic weakness interfering with function but not interfering with ADL	Weakness interfering with ADL; bracing or assistance to walk (e.g. cane or walker) indicated	Life-threatening, disabling	Death
Neuropathy Sensory	Asymptomatic loss of tendon reflex or paresthesias (including tingling) but not interfering with function	Sensory alteration or paresthesias interfering with function but not interfering with ADL	Sensory alteration or paresthesias interfering with ADL	Disabling	Not applicable

ADL activities of daily living

Table 2 Ped-mTNS individual items and scores

Ped-mTNS item	Testing method	Criteria for higher item score	% with deficit noted (score >0)	Median and range of scores on item
Subjective symptoms				
Sensory symptoms	Scripted questions	Proximal spread of symptoms	30 %	0 (0–3)
Motor symptoms	Scripted questions	Perceived difficulty with tasks	50 %	0.5 (0–4)
Autonomic symptoms	Scripted questions	Symptom frequency	38 %	0 (0–4)
Clinical testing				
Light touch	Semmes-Weinstein monofilaments	Proximal spread of sensory loss	50 %	0.5 (0–4)
Pin sensation	MediPin	Proximal spread of sensory loss	50 %	0.5 (0–2)
Vibration sensation	Biothesiometer	Proximal spread of sensory loss	38 %	0 (0–4)
Distal strength	MMT of distal extremities	Severity of weakness	98 %	2 (0–4)
Deep tendon reflexes	Achilles and patellar DTR	Severity and proximal spread	100 %	3 (1–4)

MMT manual muscle testing, *DTR* deep tendon reflexes

score on the ped-mTNS. Cases where chemotherapy was administered between testing and examination were excluded. One medical record abstractor, specifically trained to perform CTCAE scoring, reviewed all medical records and assigned CTCAE v3.0 sensory and motor scores according to the published criteria based on clinician documentation of signs and symptoms [10]. Clinicians at the participating institution are familiar with the assessment of adverse events using CTCAE criteria, and thus routinely create their documentation to facilitate appropriate scoring by clinical research associates. The CTCAE does not prescribe the specific method in which each system must be examined, and thus, as is current practice, clinicians were allowed to choose their examination method for each system. In all cases, the neuromuscular system was reviewed by the practitioner as evidenced by results being recorded in the electronic medical record under the systems review. In cases where signs and symptoms of neuropathy were noted, a score of from 1 to 5 on the CTCAE scale was chosen based upon the criteria. In cases where the clinician indicated in the medical record that neuromuscular system was "normal", participants were given a 0 score, indicating that no neuropathy was present. Individual item scoring and composite score for the ped-mTNS was completed as per Gilchrist et al. (Table 2) [7]. Because the ped-mTNS is a composite scale of sensory and motor function, a combined CTCAE sensory plus motor score was calculated by adding the two scale scores together to allow for comparison.

Descriptive statistics, including frequencies and percentages, and medians and ranges were used to characterize the study population. The associations between scores on the ped-mTNS and CTCAE were evaluated with Spearman correlations using SPSS version 20. Specificity and sensitivity of the CTCAE sensory and motor ratings was completed using single examination items (light touch testing and manual muscle testing) from the ped-mTNS utilizing published values [20, 21].

Results

Participants ranged in age from 5 to 18 years. The most common oncology diagnosis was ALL, followed by other solid tumors, which included patients with Wilms' tumor, rhabdomyosarcoma, Ewing sarcoma, and hepatoblastoma (Table 3). Fifty-nine of the 60 patients received vincristine, with a mean cumulative dose of 15.9±8.0 mg/m^2 (range 1.8–39.0). Three subjects received cisplatin with a mean dose of 290.0±121.2 mg/m^2 (range 150.0–360.0). Two subjects received both vincristine and cisplatin. Twenty-nine participants received intrathecal methotrexate, including all but three of the subjects treated for ALL. Only one patient had received cranial radiation at the time of assessment, which could have been a confounding factor as it can also cause direct damage to neurons [22]. Twenty-nine of the 60 subjects (48 %) were enrolled on a treatment-related clinical trial.

The median ped-mTNS score was 9, with scores ranging from 2 to 19 (scores possible 0–32, higher scores indicate more impairment; Fig. 1a). Individual item median scores, ranges and percent of subjects displaying a deficit on each item of the ped-mTNS are displayed in Table 2. The median sensory CTCAE score was 0 with a range of 0–3 (possible scores 0–4). Eighty percent of subjects (48 of 60) had no signs or symptoms of sensory neuropathy recorded in their medical

Table 3 Subject demographics

	Cases (N=60)
Age (years)	10.7±3.9
Gender (% male)	40 %
Diagnosis:	
ALL	50.0 %
Lymphoma	23.3 %
Other solid tumors	26.7 %

ALL acute lymphoblastic leukemia

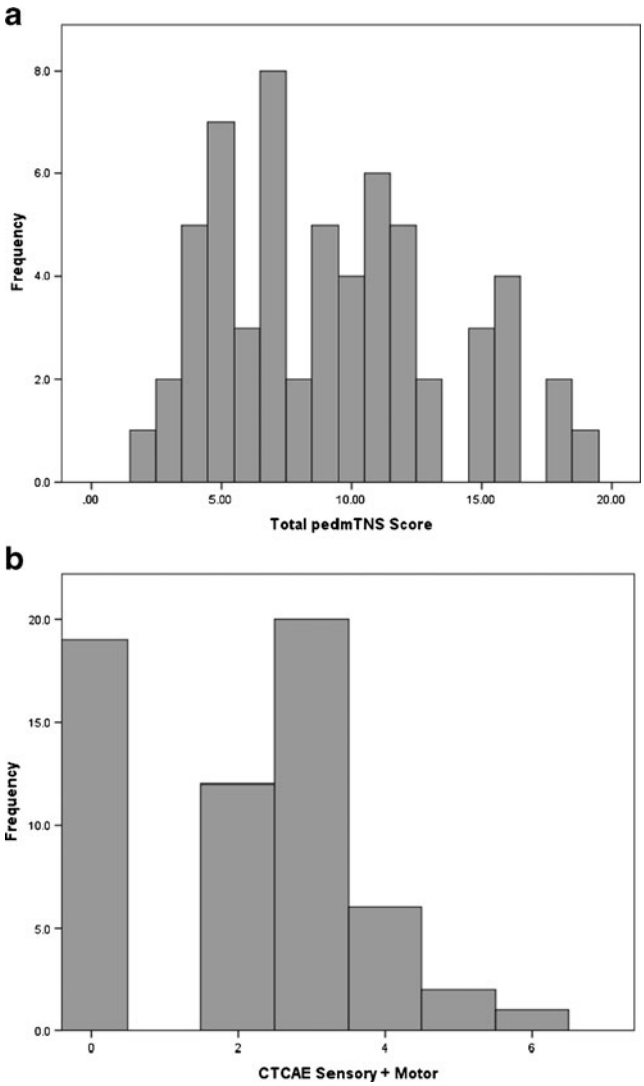

Fig. 1 Histograms of ped-mTNS (**a**) and CTCAE combined sensory and motor (**b**) scores

record and a normal result entered under the neurologic examination, and thus they received a 0 score for the sensory portion of the CTCAE. Of the remaining 20 % of subjects with positive findings of sensory neuropathy on the CTCAE, 5 subjects received a score of 1 (asymptomatic), 6 received a score of 2, and only one individual received a score of 3 (see Table 1 for full definitions). The median motor CTCAE score was 2, with a range of 0–3 (possible scores 0–5). Nineteen of the 60 subjects (32 %) had no recorded signs or symptoms of motor neuropathy in the medical record and had normal findings reported in the neurologic portion of their oncology exam. Two individuals had a CTCAE motor score of 1 (asymptomatic), while 15 and 24 subjects received motor neuropathy scores of 2 and 3 (symptomatic motor neuropathy) respectively (see Table 1 for full definitions). No individuals received scores of 4 or greater on either the sensory or motor CTCAE ratings that would indicate a life-threatening or disabling neuropathy.

When sensory and motor CTCAE scores were added for each individual, a median score of 2 was obtained with a range of scores from 0 to 6 (0–9 points possible; Fig. 1b). No significant difference was found for ped-mTNS scores or CTCAE ratings between those individuals participating ($n=29$) and not participating in treatment-related clinical trials ($n=31$). Examination of the score distributions on the ped-mTNS and CTCAE combined score (Fig. 1) reveals that no participants received the lowest possible score on the ped-mTNS, and only 8 subjects received a ped-mTNS score of 4 or lower indicating no neuropathy, while nearly one third ($n=19$) of participants received a 0 (no deficit) on the combined CTCAE score.

There was no correlation between the ped-mTNS scores and combined sensory and motor CTCAE scores (Fig. 2, Table 4). Notably, in subjects that had no recorded signs or symptoms of sensory or motor neuropathy on the CTCAE scoring, ped-mTNS scores ranged from 3 to 16 (Fig. 2). Since 16 of the 19 subjects (84 %) who received a zero overall score on the CTCAE sensory and motor neuropathy scales had scores of 5 or greater on the ped-mTNS (indicating neuropathy), most of these subjects had some degree of neuropathy that was missed by CTCAE scoring. No single item recording sensory neuropathy signs or symptoms on the ped-mTNS was correlated with sensory CTCAE score (Table 4), nor was there a correlation between combined sensory item scores (sensory symptoms, light touch, vibration, and pin sensitivity) and CTCAE sensory scores. There was not a correlation between motor symptoms on the ped-mTNS and the motor CTCAE score. There was however, a moderate association between strength testing on the ped-mTNS and the motor portion of the CTCAE (Table 4) and also a moderate correlation ($r_S=0.32$, $p=0.01$) between combined motor symptom and strength scores on the ped-mTNS and ratings of motor neuropathy on the CTCAE.

Specific examination of the sensory components of the tests revealed that although 80 % (48 of the 60 subjects) received a grade 0 on the sensory portion of the CTCAE, only half of these subjects (24 of the 48) tested within normal limits for light touch sensation according to published values [20]. Using the CTCAE scoring system to capture this clinical event would leave 40 % (24 of the 60) of the children with unidentified light touch abnormalities. Among children with unidentified light touch deficits, six had significant deficits that extended past their feet and through most of their lower extremities. Using the quantitative light touch sensory evaluation from the ped-mTNS as the standard indicated that the sensitivity of the sensory score from the CTCAE was only 0.2, while specificity was 0.8. Similarly, 38 % (18 of the 48) of the patients who received a grade 0 on the sensory portion of the CTCAE demonstrated abnormalities of vibration sensation and 12 of these subjects had deficits that extended past the foot and into the leg.

On the motor portion of the CTCAE only one of the 19 individuals who received a grade 0 (no deficit) had normal strength of great toe extensors, ankle dorsiflexors, finger

abductors, and wrist extensors as defined by manual muscle testing [21]. Nine of the 19 individuals identified as having no motor neuropathy had manual muscle test grade of 3 or lower indicating the inability for the muscle to resist more than gravitational force and thus the CTCAE failed to reveal pronounced motor neuropathy in 15 % of the population (9 of the 60 tested). Using the manual muscle testing of the distal extremities on the ped-mTNS as the standard indicates that the motor score from the CTCAE has a sensitivity of 0.7 and a specificity of 1.0. Only one participant in this study had normal strength when evaluated with manual muscle testing.

Discussion

It is becoming clear that peripheral neuropathy can persist in survivors of childhood cancers [8, 15] and it has the potential to impact overall quality of life. Accurate assessment of all components of peripheral neurotoxicity is important if clinicians and researchers intend to focus on decreasing side effects and improving quality of life for children and adolescents undergoing cancer treatment. Treatment for CIPN-related impairments, such as medical intervention for painful neuropathy and rehabilitation for strength and balance deficits, can be offered only if neuropathy is detected [23]. In this study, we have demonstrated that in a cohort of school-aged children undergoing treatment with vincristine and/or cisplatin for non-CNS tumors, using the ped-mTNS to assess CIPN identified a far greater proportion of subjects with peripheral neurotoxicity as compared to CTCAE v3.0 sensory and motor neuropathy ratings completed by chart review. Medical record abstraction of CTCAE sensory scores failed to identify sensory neuropathy in 40 % of the population tested. Although motor neuropathy according to the CTCAE was more frequently noted in the medical record than sensory neuropathy, this system failed to reveal pronounced motor neuropathy (manual muscle test grade 3 or worse) in at least 15 % of children. Higher scores on the ped-mTNS indicating increasing severity or extent of neuropathy signs and symptoms were also not associated with increasing scores on the CTCAE scale.

In the population examined, sensory toxicity was more dramatically under-reported using the CTCAE than motor toxicity. A large proportion of the population studied demonstrated sensory toxicity through clinical measures of light touch, vibration, and pin sensation. While clinical assessment of sensory integrity may not be a routine part of oncology practice, even those children and adolescents who expressed sensory symptoms on subjective questioning on the ped-mTNS were likely to have received a 0 grade on the CTCAE. In part, this may be due to reluctance on behalf of the patients and their families to express their concerns about side effects if it may impact treatment decisions. Alternately, oncology practitioners may not be asking patients about their sensory symptoms and accurate reporting of sensory neurotoxicity may be improved by incorporating standardized questions into the clinical examination or medical records template.

Motor toxicity as reported on the CTCAE was associated with strength testing and combined strength and motor symptom scores on the ped-mTNS, although motor finding were still under-reported. This finding may be influenced by the specific practice patterns in the oncology clinic where the study was

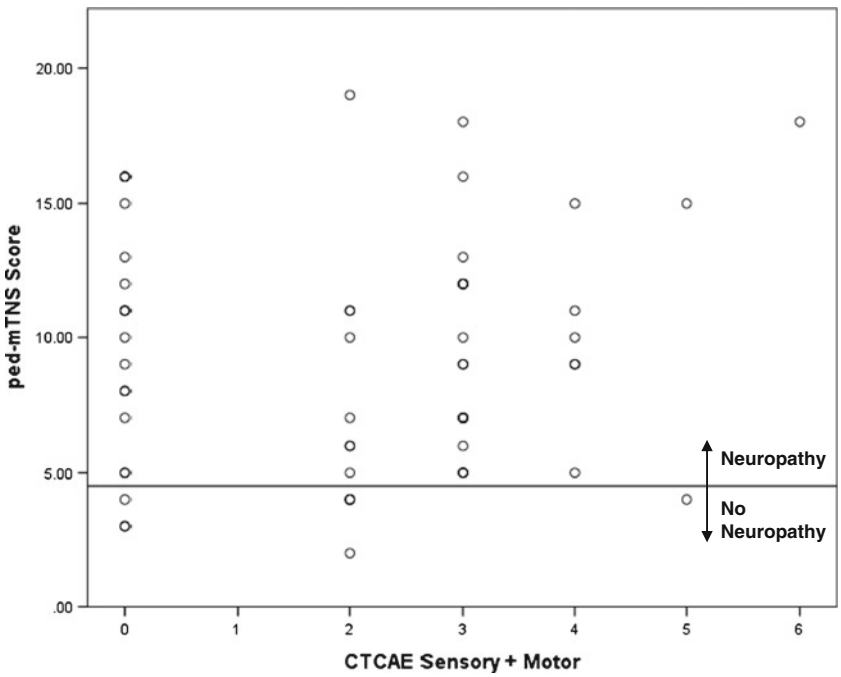

Fig. 2 Scatter plot of ped-mTNS and combined CTCAE sensory and motor scores ($N=60$) with reference line indicating neuropathy per ped-mTNS score (5 or greater) as per Gilchrist et al. [7]. *Darker circles* indicate multiple subjects with identical scores

Table 4 Spearman correlations for ped-mTNS and CTCAE scores

	CTCAE sensory+motor	CTCAE sensory	CTCAE motor
Ped-mTNS total	0.07	–	–
Individual items			
Sensory report	–	0.16	–
Light touch	–	0.04	–
Pin sensation	–	0.05	–
Vibration	–	0.01	–
Motor report	–	–	0.08
Strength	–	–	0.43*
Deep tendon reflexes	–	0.09	−0.09

– indicates not tested

*$p < 0.01$

completed. Specifically, Children's Hospitals and Clinics of Minnesota have physical therapists who are designated by the Rehabilitation Department to work in the Oncology Clinic. Protocols are in place to automatically refer patients with ALL for screening for rehabilitation needs. One of the routine procedures of this physical therapy practice is to refer patients for ankle foot orthotics when ankle dorsiflexion range of motion becomes excessively limited or foot drop interferes with gait. Thus, the bracing of a patient was often noted in the medical record and served as an indicator of motor neuropathy on the CTCAE. In clinics where rehabilitation is not integrated into oncology care or where orthotic intervention is not often utilized, the correlation between CTCAE motor scores and muscle testing may not be found.

This study builds upon others that have examined the use of the toxicity scales for use in measuring specific side effects such as CIPN [16–18] and extends these findings by applying it to the pediatric population. Cavaletti et al. [24] compared the Total Neuropathy Score (TNS) with the second version of the NCI-CTC in adults treated with platinum and/or taxanes and found that the TNS was more sensitive in detecting change in CIPN. Frigeni et al. [18] examined adult patients with grade 2 or 3 sensory and/or motor neurotoxicity using CTCAE v3.0. In their adult patients who received primarily platinum- or taxane-based chemotherapy, they found substantial disagreement between TNS and CTCAE scores in motor tests and more agreement between sensory scores. This is the opposite result of our finding that motor scores on ped-mTNS items and CTCAE v3 were in greater agreement than sensory scores. In part, this may be due to the variations in clinical practice leading to more obvious intervention for motor neuropathy in the pediatric patients studied or increased difficulty eliciting sensory symptoms during routine clinical care in children. Additionally, chemotherapy agents differ between these populations; most pediatric patients are treated with vincristine, while the adults receive platinum- or taxane-based treatment more frequently. Different neurotoxic agents likely result in different neuropathy patterns.

The findings of motor and sensory neuropathy in this population of patients are consistent with the scant data available on CIPN in pediatric cancer patients. Most data on CIPN is available for survivors of childhood ALL. Ramchandren et al. [15] reported on 37 survivors of childhood ALL who were on average 7.4 years post-treatment. They found that most survivors had evidence of mild neuropathy, with 94.6 % having a score of 2 or higher on a reduced version of the TNS. Similarily, 87 % of subjects in this study of children and adolescents on treatment for ALL or other non-CNS solid tumors had a score of 5 or higher on the ped-mTNS indicating at least mild neuropathy in most subjects while on treatment. The combined motor and sensory toxicity seen in our population is reflective of other studies of vincristine-related neuropathy in childhood survivors [15] and motor signs and symptoms appear to be more frequent in this population than in reports of adult cancer patients [23, 25].

The findings of this study need to be interpreted bearing in mind the limitations of the study design. All subjects were tested using the ped-mTNS by physical therapists experienced in the administration of the measure while the CTCAE was administered through review of the medical record by a trained abstractor. Although the CTCAE may be better at detecting mild neuropathy when administered prospectively by the oncology clinician, we decided to utilize the chart review method because it mirrors the current adverse event tracking for neuropathy in clinical trials at the participating institution. Indeed, the reporting of CIPN signs and symptoms on the CTCAE may have been improved if each clinician rated the subject on the CTCAE neuropathy scales at the time of the examination. We chose to not use this method because it does not reflect the current use of the adverse event criteria at the participating institution. If the participating institution were to have clinicians rate each patient on the CTCAE at each visit, each clinician would need to fill out over 330 scales, rating all 26 different systems [10]. Even if only the neurologic rating scales were used, the clinician would need to fill out 33 different scales [10, pp. 47–51].

The fact that CTCAE and ped-mTNS ratings were not significantly different between those subjects who were and were not enrolled on clinical trials suggests that oncology providers' knowledge that tracking of adverse events was occurring for their patients on trials did not influence their charting of neuropathy. Additionally, Fringi et al. [18] also found significant discord between common toxicity criteria ratings completed prospectively by the treating oncologist and TNS ratings administered by a neurologist; indicating that the differences found in ratings is not merely due to administration methods but is likely due to instrument properties. Secondly, while it cannot be assumed that other health care professionals would yield the same results when administering these scales, other versions of the TNS have been successfully used by both physician and nursing professionals, indicating the ability of these measure to be successfully implemented by multiple health professionals [15, 26, 27]. In the present study, the third version of the CTCAE was used, as it was the version in place at the time of the study inception. Use of version 4 of the CTCAE may change study outcomes. Lastly, all subjects were recruited from one institution, and the specific mix of patients and style of clinical practice at this institution may influence the results.

In conclusion, the prospective use of the ped-mTNS allowed for better detection and grading of the severity and type of neuropathy than medical record abstraction of the CTCAE v3.0 sensory and motor neuropathy ratings. Pediatric trials that have relied on CTCAE ratings to indicate prevalence of neuropathy may have underestimated the incidence of this side effect. For clinical and research investigations that specifically intend to assess neurotoxicity, we recommend that a specific measure of CIPN such as the ped-mTNS be used prospectively in conjunction with the CTCAE and other measures of function and quality of life.

Acknowledgements The authors thank A. Logelin for her expertise in clinical trials documentation and Dr. K. Ness and P. Mitby for their helpful reviews of the manuscript. This study was supported by Award Number G11HD039786 from the Eunice Kennedy Shriver National Institute of Child Health & Human Development.

Conflict of interest The authors have no financial relationship with the funding agency and have no conflicts of interest to disclose. The authors have full control of all primary data and agree to allow the journal to review their data if requested.

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