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ORIGINAL ARTICLE

Chemotherapy-induced peripheral neuropathy—patient-reported outcomes compared with NCI-CTCAE grade

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Abstract

Background Patient-reported outcomes (PRO) are becoming increasingly recognised as essential to comprehensively collect chemotherapy-induced peripheral neuropathy (CIPN) symptom information.

Materials and methods This study aimed to evaluate the utility and feasibility of CIPN PRO assessment tools in a real-world clinical setting through investigation of the correlation of PRO with NCI-CTCAE assessments particularly in relation to cumulative dose of chemotherapy. Patients receiving oxaliplatin or paclitaxel chemotherapy in Sydney, Australia, completed a questionnaire containing standardised CIPN PRO assessments (EORTC CIPN-20, PRO-CTCAE) via tablet device. PRO assessment scores were correlated with NCI-CTCAE grade determined by nursing assessment and analysed with respect to cumulative dose of chemotherapy.

Results There were 87 patients who completed a total of 145 questionnaires, 68 in patients receiving oxaliplatin and 77 in patients receiving paclitaxel. CIPN PRO scores were associated with NCI-CTCAE grade, for EORTC CIPN-20 ($r^2 = 0.19$, $p < 0.01$) and PRO-CTCAE ($r^2 = 0.41$, $p < 0.01$), although individual patient correlation was poor. PRO assessments, however, identified higher grade symptoms, in particular symptoms causing functional impairment, at lower doses of cumulative chemotherapy compared to NCI-CTCAE.

Conclusion This study demonstrated that CIPN PRO may provide complementary information to nursing assessed NCI-CTCAE grade, particularly in earlier stages of chemotherapy and can be considered an important component in the comprehensive assessment of neuropathy.

Keywords Chemotherapy-induced peripheral neuropathy · CIPN · Patient-reported outcomes · PRO

Introduction

The impact of cancer treatment side effects such as chemotherapy-induced peripheral neuropathy (CIPN) on cancer survivor quality of life is increasingly understood [1]. CIPN typically appears with greater cumulative treatment dose and can produce sensory loss, pain and balance deficits, leading to impairments in basic functioning and activities of daily living (ADLs) in severe cases [2, 3]. Furthermore, treatment efficacy may be compromised, due to treatment schedule alterations, dose reductions, treatment discontinuation or premature cessation and limitation of therapeutic options [4]. Despite this, there remains no gold standard assessment approach [5]. The National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE) Neuropathy subscale is the most commonly used assessment in clinical practice [6]. Oncology practitioners using the NCI-CTCAE, however, commonly underestimate the significance and severity of symptoms compared to patient reports [7], and interobserver reliability is variable [8]. The use of nursing assessments particularly in settings with physician time constraints may be a useful adjunct allowing for more frequent

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and/or comprehensive review, although similar issues may also arise. Despite their shortcomings, clinical grading scales such as the NCI-CTCAE are still the primary tool used to indicate dose reductions and delays and treatment cessation related to CIPN. It is also still the principal tool for clinical trial assessment of degree of neurotoxicity of novel agents and in studying the efficacy of neuroprotective agents.

Accordingly, in-depth patient-reported outcomes (PRO) are increasingly recognised as essential to comprehensively collect CIPN symptom information [9] and consequently intensify symptom management, improve symptom control and enhance patient well-being. A number of validated PROs for the collection of CIPN symptom information exist [10, 11], but there has been a gap in implementation of these tools into clinical settings outside of clinical trials. The recent development of the brief patient-reported outcomes version of the NCI-CTCAE (PRO-CTCAE) [11] may streamline the collection of PRO data and facilitate information transfer between clinical staff and patients. Providing further emphasis, a recent Delphi survey of available CIPN assessments rated brief PRO questionnaires as having the highest clinical utility of available assessment tools [5]. Relatedly, tablet-based methods of collection of PRO data have recently been demonstrated to be equivalent to paper-based surveys in chemotherapy patients [12, 13] and have demonstrated potential to improve care efficiency and quality [14] but their feasibility has yet to be demonstrated in patients with CIPN-related functional impairment. Furthermore, studies investigating the impact of cumulative chemotherapy dose on comparisons between clinical and PRO assessment tools in CIPN are lacking. The purpose of this study was to evaluate the utility and feasibility of CIPN PRO assessment tools in a clinical setting with respect to cumulative chemotherapy dose. The correlation of electronically administered PRO with NCI-CTCAE assessments in relation to cumulative dose of chemotherapy was investigated and the time course of CIPN assessment discrepancies between patients and clinical staff during early, mid and late chemotherapy treatment was examined.

Methods

Patient selection

From September 2015 to March 2018, patients treated at oncology centres in Sydney, Australia (South Eastern Sydney and Northern Sydney local health districts) were enrolled in observational studies of CIPN in chemotherapy treated patients. As part of a substudy, patients completed a questionnaire containing standardised CIPN PRO assessments via tablet device. Eligible patients were receiving oxaliplatin or paclitaxel chemotherapy and could be recruited at any time point during their treatment course including baseline (pre-cycle 1). Questionnaires were completed prior to receiving the next scheduled dose of chemotherapy. A subset of patients completed follow-up questionnaires after further cumulative chemotherapy of ≥ 2 additional treatment cycles on two or three occasions. Questionnaires were administered by study team members that included medical, nursing and clinical research staff and completed in waiting rooms, clinic rooms or the treatment unit. Approximately 5 to 10 min were required to complete all questions of the questionnaire. Patient demographics and treatment details were collected from the medical record. The study was approved by the South Eastern Sydney Local Health District (SESLHD) Human Research Ethics Committee (HREC) and patients provided informed signed consent.

Chemotherapy-induced peripheral neuropathy assessments

Patient-reported outcome measures

All patients completed the validated European Organisation for Research and Treatment of Cancer (EORTC) Chemotherapy-Induced Peripheral Neuropathy 20 (EORTC CIPN-20) [10]. The EORTC CIPN-20 consisted of 20 questions regarding sensory and autonomic symptoms and their impact on patient function, measured using a Likert scale from 1 (not at all) to 4 (very much). Total scores were linearly transformed to a 0 to 100 scale, with higher scores representing greater symptoms (Table 1). EORTC CIPN-20 scores were classified ('CIPN-20 symptom classification') into absent (total score = 0), mild CIPN symptoms (total score ≤ 20) or moderate CIPN symptoms (total score > 20). This classification was based on a previous study featuring a large cohort which demonstrated that EORTC CIPN-20 scores > 20 are associated with higher-grade clinical symptoms (NCI-CTCAE grade ≥ 2) [15].

The PRO-CTCAE [11] was also utilised, consisting of two questions relating to sensory neuropathy in the hands or feet in the previous 7 days (Table 1). The first question assessed the severity of numbness and tingling in the hands and feet from 0 (none) to 4 (very severe) and the second assessed interference of numbness and tingling with 'usual daily activities' from 0 (not at all) to 4 (very much). A sumscore for the PRO-CTCAE assessment was generated by combining both assessment items into a single grade: grade 0 = no reported numbness or tingling; grade 1 = severity of numbness and/or tingling ≥1 (mild), but no reported interference with daily activities; grade 2 = severity of numbness and/or tingling AND interference with daily activities ≥ 1 (mild/a little bit).

Feasibility of questionnaire delivery via tablet device was evaluated in a subset of patients with an ease of use question,

Table 1 Comparison of CIPN symptom classifications by assessment (NCI-CTCAE [6]; PRO-CTCAE [11]; CIPN-20 [10])

	No symptoms	Mild symptoms	Moderate symptoms
NCI-CTCAE version 4.03	Grade 0 (asymptomatic)	Grade 1 (asymptomatic; loss of deep tendon reflexes or paraesthesia)	Grade 2 (moderate symptoms, limiting instrumental activities of daily living)
PRO-CTCAE sumscore	Grade 0 (no reported symptoms)	Grade 1 (reported numbness and tingling but no effect on daily activities)	Grade 2 (reported numbness and tingling interfering with daily activities)
CIPN-20 sumscore	Score = 0 (no reported symptoms)	Score > 0 but < 20	Score > 20

NB: table includes only symptom grading relevant to analyses in this study. For full grading scales, please consult the respective references

on a scale of 1 (difficult) to 10 (easy). This question was added to the questionnaire towards the end of the recruitment period, and all patients accrued subsequently completed this question.

Nursing assessment of CIPN

As part of routine clinical practice, the NCI-CTCAE version 4 4-point clinical grading scale [6] was utilised for CIPN assessment by nursing staff immediately before each chemotherapy administration (Table 1). PRO surveys were completed within 1 week of nursing assessment of symptoms and prior to administration of the next chemotherapy cycle.

Data analysis

Patient characteristics were summarised using descriptive statistics. Patients were classified into dose groups based on cumulative chemotherapy doses. Early treatment dose group (roughly corresponding to cycles 1–3) received 0–240 mg/m^2 paclitaxel or 0–255 mg/m^2 oxaliplatin, mid treatment dose group (cycles 4–6) received 241–480 mg/m^2 paclitaxel or 256–510 mg/m^2 oxaliplatin, late treatment dose group (cycles 7+) received > 481 mg/m^2 paclitaxel or > 511 mg/m^2 oxaliplatin. Nursing assessments of CIPN were correlated with CIPN-20 scores and PRO-CTCAE sumscore using Spearman's correlation. Patient-reported CIPN-20 score and NCI-CTCAE grade was analysed using one-way ANOVA. Agreement between NCI-CTCAE and PRO-CTCAE was evaluated by Cohen's kappa coefficient, with the strength of agreement categorised as per Landis and Koch [16]. Statistical analysis was performed using SPSS (IBM, Armonk, NY, USA) and GraphPad Prism 7 (GraphPad Software, San Diego, CA, USA). $\alpha < 0.05$ was considered statistically significant.

Results

Patient characteristics and treatment details

A total of 145 questionnaires were collected from 87 patients enrolled in the study, with 44 patients completing questionnaires on two (30 patients; 12 with data from early and mid treatment dose groups, 6 with data from early and late treatment, 11 with data from mid and late treatment, 1 with data from late treatment only) or three (14 patients; 11 with data from early, mid and late treatment dose groups, 3 with data from early and late treatment) occasions. The median age was 56 years (range 26–80 years) and 63 (72%) patients were female (Table 2). The most common cancer type was breast in 43 (49%) patients and colorectal in 29 (33%) patients

Table 2 Patient characteristics

	n (%)
Patients	87
Age (median, range)	56 years (26–80)
Sex	
Female	63 (72)
Male	24 (28)
Cancer type	
Breast	43 (49)
Cervical	2 (2)
Colorectal	29 (33)
Gastric	2 (2)
Lung	2 (2)
Oesophageal	3 (3)
Ovarian	1 (1)
Pancreatic	5 (6)
Chemotherapy	
Oxaliplatin	37 (43)
Paclitaxel	50 (57)
Cumulative dose groups	Number of assessments (% of total for each chemotherapy type)
Early treatment dose group	
Oxaliplatin *(0–255 mg/m^2)*	28 (41)
Paclitaxel *(0–240 mg/m^2)*	26 (34)
Mid-treatment dose group	
Oxaliplatin *(256–510 mg/m^2)*	19 (28)
Paclitaxel *(241–480 mg/m^2)*	25 (32)
Late treatment dose group	
Oxaliplatin *(> 510 mg/m^2)*	21 (31)
Paclitaxel *(> 481 mg/m^2)*	26 (34)

(Table 2). In total, 47% (68) of questionnaires were undertaken by patients receiving oxaliplatin and 53% (77) by patients receiving paclitaxel. The median dose of chemotherapy received at time of assessment was 388 mg/m^2 and 400 mg/m^2 for oxaliplatin and paclitaxel, respectively. In patients that completed more than one questionnaire, median time between questionnaires was 1.9 months (range 0.8–6.3 months).

All CIPN-20 questionnaires were paired with a NCI-CTCAE grade documented in the medical record by nursing staff. PRO-CTCAE scores were completed in 86 questionnaires (59%), 42 in patients receiving oxaliplatin and 44 in patients receiving paclitaxel. PRO-CTCAE scores were distributed across dose groups ($N = 27$ early treatment group, $N = 27$ mid-treatment group and $N = 32$ late treatment group). In the subset of patients that completed an ease of use rating ($n = 33$, 38%), tablet-based delivery of questionnaires exhibited high feasibility, with a mean value of 9.73 (SD 0.63).

For NCI-CTCAE grade, 89 (61%) assessments indicated grade 0 symptoms, with 46 (32%) grade 1 and 10 (7%) with grade 2 assessments. The mean NCI-CTCAE grade was 0.46 (SD 0.62). Mean EORTC CIPN-20 score was 10.7 (SD 12.5, range 0–66.7), with 18 (12%) questionnaire responses indicating no CIPN symptoms, 106 (73%) indicating mild symptoms and 21 (15%) responses indicating moderate symptoms. Mean PRO-CTCAE sumscore was 0.90 (SD 0.82), with 36 (42%) responses indicating grade 0 CIPN, 26 (30%) grade 1 and 24 (28%) grade 2.

Correlation of NCI-CTCAE grade with CIPN PRO assessment

CIPN-20 score was significantly correlated with nurse administered NCI-CTCAE grade ($r^2 = 0.19$, $p < 0.01$). CIPN-20 scores were significantly increased between cohorts with NCI-CTCAE grade 0 versus grade 1 ($p < 0.01$) and grade 0 versus grade 2 ($p < 0.01$; Fig. 1). However, there was no significant difference in CIPN-20 scores comparing NCI-CTCAE grades 1 versus 2 ($p = 0.12$; Fig. 1). The majority of CIPN-20 responses indicated low-grade CIPN symptoms throughout treatment. During later treatment, responses from 100% of oxaliplatin-treated patients and 92% of paclitaxel-treated indicated some level of CIPN symptoms, compared to NCI-CTCAE grading identifying symptoms in only 62% and 62% of assessments, respectively.

PRO-CTCAE sumscore was also significantly correlated with NCI-CTCAE grade ($r^2 = 0.41$, $p < 0.01$). Concordance between NCI-CTCAE and PRO-CTCAE sumscore for the different dose groups displayed a range of correspondence between assessments (Table 3; Fig. 2). For oxaliplatin-treated patients, concordance varied between slight to substantial, depending on treatment stage. For paclitaxel-treated patients, concordance was moderate across early, mid and late treatment groups. A small proportion of responses from both oxaliplatin- and paclitaxel-treated patients (11–19%) reported CIPN symptoms affecting function in early or mid treatment, compared to no reporting of symptoms impacting function by NCI-CTCAE assessments (grade 2). Further, a higher percentage of PRO-CTCAE responses indicated symptoms affecting function in later treatment compared to nursing assessment (50% vs 22%). Accordingly, PRO assessment identified symptoms causing functional impairment, at lower doses of cumulative chemotherapy compared to NCI-CTCAE.

There was also significant correlation between CIPN-20 score and PRO-CTCAE sumscore ($r^2 = 0.41$, $p < 0.01$). CIPN-20 scores were significantly increased between cohorts with PRO-CTCAE sumscore grade 0 versus grade 1 ($p = 0.03$), grade 0 versus grade 2 ($p < 0.01$) and grade 1 versus grade 2 ($p < 0.01$; Fig. 1).

Discussion

In our study, overall CIPN PRO scores were associated with NCI-CTCAE grading; however, individual patient correlation

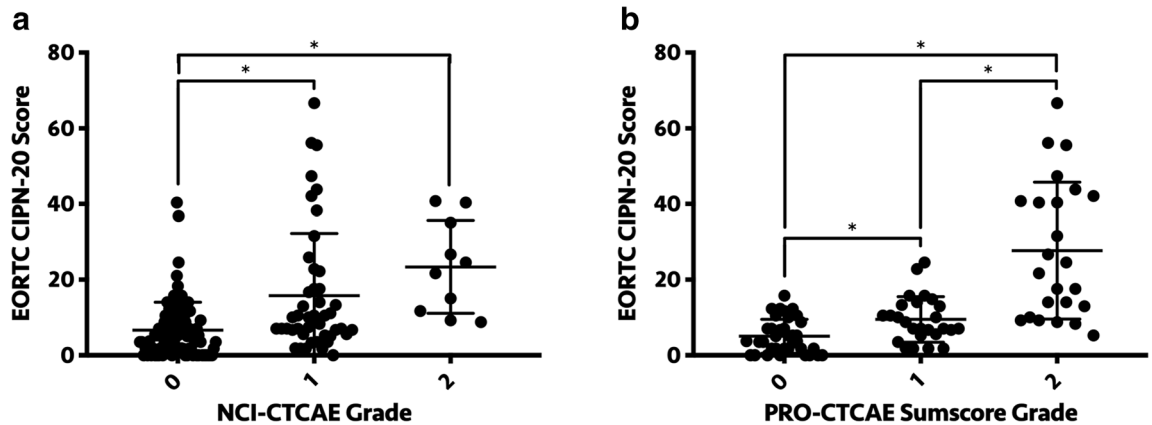

Fig. 1 Comparison of patient-reported CIPN and nurse-reported CIPN. Scatter plot of patient-reported EORTC CIPN-20 score compared with nurse-reported NCI-CTCAE grade (**a**) and PRO-CTCAE sumscore grade (**b**). *Significant difference between groups ($p < 0.05$)

Table 3 Agreement between NCI-CTCAE and PRO-CTCAE

	Kappa coefficient (95% CI) NCI-CTCAE and PRO-CTCAE
Early treatment dose group	
Oxaliplatin	0.61 (0.15–1.00)
Paclitaxel	0.53 (0.12–0.95)
Mid-treatment dose group	
Oxaliplatin	0.21 (− 0.22–0.65)
Paclitaxel	0.43 (0.10–0.76)
Late treatment dose group	
Oxaliplatin	0.13 (− 0.14–0.40)
Paclitaxel	0.56 (0.24–0.87)

was poor. This has been demonstrated in numerous previous studies comparing PRO with medical assessment of CIPN [9, 15, 17], at both single time points and over multiple visits during a treatment course. This may be due to several reasons, including clinical under-reporting, which is especially common for subjective toxicities [18]. Differences in the assessment methods are also crucial, with different CIPN grading systems demonstrating significant discrepancy [19]. Inter-observer and inter-patient variability is also likely to contribute substantially. Our cohort, comparing nursing assessment of CIPN with PRO, illustrates that these issues may extend to other healthcare providers, although a prior study reported higher agreement between patient and nurse versus medical assessments for a range of chemotherapy toxicities including CIPN [20]. Fundamentally, however, medical or nursing grading systems and PRO assessment tools both have a role in the assessment of CIPN. Clinician assessment has previously been shown to better predict unfavourable outcomes, whereas PRO better reflects daily health status [21].

Crucially, our study demonstrated that PRO was able to identify the presence of symptoms at lower cumulative doses of chemotherapy, and in particular symptoms causing functional impairment. PRO may provide complementary information on the impact of CIPN on a patient's quality of life, however, should not necessarily replace clinician or nursing assessment, but be considered one component in the comprehensive assessment of neuropathy. This multi-component assessment strategy for CIPN may be especially critical in managing CIPN during mid- and late oxaliplatin treatment, given especially low concordance between nursing and PRO assessment in these groups in the present study. The management may consist of treatment modification, direct intervention or early referral to rehabilitation or allied health services. Nursing assessment may also represent a useful adjunct or alternative to medical grading of toxicity, with prior studies demonstrating the validity of nurse toxicity reporting compared with physicians [20, 22].

The limitations of the NCI-CTCAE in evaluating CIPN are well documented [7, 15]. PRO assessment tools may provide greater clarity for subtle changes in symptoms. The EORTC CIPN-20 is the most comprehensive of the PRO assessment tools used in our study, and its reliability and validity have been demonstrated [23]. Additionally, the CIPN-20 has been identified to be more sensitive and responsive than clinician-based instruments, with a large range of CIPN-20 score evident within each NCI grade [15]. Similarly, in our study, the EORTC CIPN-20 was able to identify the presence of neuropathy symptoms, particularly for high-grade symptoms and at low cumulative doses of chemotherapy. This highlights the potential utility of the EORTC CIPN-20 to guide chemotherapy dosing management in the early stages of treatment. This is especially relevant, as there is increasing movement towards de-escalation or shortening of therapy to minimise long-term toxicity [24]. There was less clear delineation of EORTC CIPN-20 score between NCI-CTCAE grade 1 versus 2; however, this may be in part related to the small numbers of patients with NCI-CTCAE grade 2 neuropathy. The NCI PRO-CTCAE has also been validated [25], and in our cohort, it similarly identified patients with symptoms early in their

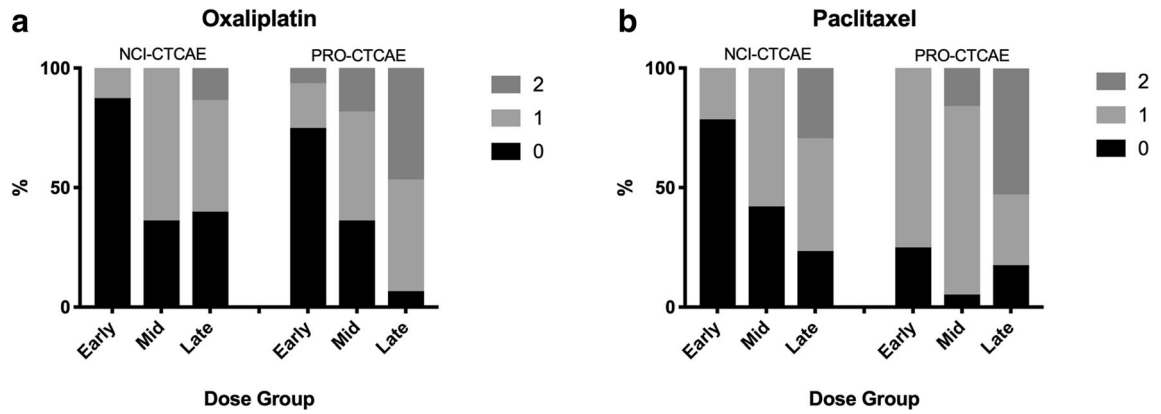

Fig. 2 Patient- and nurse-reported CIPN over the course of treatment. Chemotherapy-induced peripheral neuropathy assessments in patients who received oxaliplatin (**a**) or paclitaxel (**b**) according to dose groups (early treatment, mid treatment and late treatment), with NCI-CTCAE grade compared with PRO-CTCAE grade

treatment course. The NCI PRO-CTCAE also showed reasonable correlation with EORTC CIPN-20 score. Although no other direct comparisons of different PRO assessment tools have been performed, it may have a more appropriate place in real-world clinical practice, in which constraints on the feasibility of PRO tools are much greater.

Future studies to further define the utility of CIPN PROs in real-world clinical practice are crucial, including investigations focused on how clinical, PRO and formal neurological assessments of CIPN can best complement each other. It should be noted that our study is potentially limited by sampling biases, with data from 51% of patients included from multiple time points. Our study is also limited by inclusion of clinical grading from nurses only, and it should be considered that comparisons of PRO with oncology practitioner grading could vary, especially given prior study noting differences between nursing and clinician CIPN assessments [20]. Additionally, patients may have completed PROs up to a week before the nursing assessment, although both assessments were completed prior to the next chemotherapy cycle.

Finally, our study builds upon previous studies confirming the feasibility of tablet-based data collection for PROs [13, 26] by demonstrating its feasibility in patients across CIPN severities, including patients with reported difficulties with ADLs and fine motor skills.

Ultimately, CIPN remains a significant acute and late toxicity for many cancer patients and survivors. Critical evaluation of the most appropriate CIPN assessment tools to help guide management decisions and reduce long-term impact on quality of life is needed. This study demonstrated that tablet-based questionnaire of CIPN PRO has excellent feasibility. Although NCI-CTCAE correlation with PRO for individual patients was poor, PRO was able to identify the presence of more severe symptoms at low doses of cumulative chemotherapy. Understanding the complementary rather than conflicting role of clinician or nursing and patient assessment tools is crucial. Evaluation of CIPN PRO impact on clinical treatment decisions is warranted.

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Compliance with ethical standards

The study was approved by the South Eastern Sydney Local Health District (SESLHD) Human Research Ethics Committee (HREC) and patients provided informed signed consent.

Conflict of interest The authors declare that they have no conflict of interest.

Disclosures There are no relevant disclosures.

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