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ORIGINAL ARTICLE

Impact of oxaliplatin-induced neuropathy: a patient perspective

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Abstract
Introduction Dose-limiting neurotoxicity is a major side effect of oxaliplatin treatment, producing initial acute neurotoxicity and chronic neuropathy with increasing exposure. The improvement in survival for patients with early-stage colorectal cancer treated with oxaliplatin has highlighted the need for valid and reliable assessment of peripheral neuropathy.
Objectives The objective of this paper was to explore neuropathic symptoms in oxaliplatin-treated patients as assessed using different methods.
Methods Consecutive symptomatic patients reporting peripheral neuropathy after oxaliplatin chemotherapy for colorectal cancer were interviewed using a semi-structured clinical interview. Neurotoxicity was also assessed using the National Cancer Institute Common Toxicity Criteria scale (clinician-rated), patient 'self-report' questionnaires (PNQ), nerve conduction and clinical assessment.
Results Twenty patients were assessed, 12.6±2.8 months after treatment cessation (mean cumulative oxaliplatin dose, 789 mg/m^2). In 40% of patients, neurotoxicity necessitated early cessation of treatment. Only 10% of patients were designated by clinicians with severe neurotoxicity, whilst, in contrast, patient interviews and self-report questionnaires described significant physical limitations due to neuropathic symptoms in 60% of patients. The majority (85%) of patients had objective evidence of sensory neuropathy with nerve conduction studies. Reports from clinical interviews were strongly correlated with patient self-assessment (Pearson coefficient=0.790, $p<0.0005$).
Conclusion Given the discrepancies in symptom prevalence highlighted by these findings, the monitoring of oxaliplatin-induced neurotoxicity would benefit from more informative clinical assessment, with inclusion of patient-reported outcome measures. Such an approach would be beneficial in a clinical trial setting to monitor the efficacy of interventions and in prospective studies of survivorship to determine the true burden of peripheral neuropathy in oxaliplatin-treated patients.

Keywords Chemotherapy · Oxaliplatin · Neuropathy · Qualitative analysis

Abbreviations

NCI	National Cancer Institute Common Toxicity Criteria for Adverse Events
PNQ	Patient Neurotoxicity Questionnaire
PRO	Patient-reported outcome

Background

Neurotoxicity is a severe and treatment-limiting side effect of several chemotherapeutic agents currently used to treat

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cancer, including taxanes, platinum-based agents and vinca alkaloids [1–3]. With 5-year survival rates increasing in cancer patients worldwide [4], minimizing the risk of treatment-related toxicity is now a major issue, particularly in relation to long-term quality of life.

The platinum agent oxaliplatin [5], first successfully used for the management of advanced colorectal cancer (in combination with fluorouracil and leucovorin), is now the regimen of choice for adjuvant treatment of patients with resected colorectal cancer [1, 6]. However, the major side effect, dose-limiting neurotoxicity, profoundly impacts on the sustainability of planned treatment [7–9].

Oxaliplatin produces a unique spectrum of nerve-related symptoms. Acute symptoms occur in the majority of patients, characterized by cold-triggered distal paresthesia and muscle cramps [7, 10]. These symptoms typically resolve within a week of infusion and do not usually require dose reduction. However, with continued exposure, chronic sensory neuropathy develops, manifesting as sensory loss and functional impairment [7, 8]. This neurotoxicity is strongly dose-related, with severe neuropathy typically occurring in 20% of patients at a cumulative dose of 750 mg/m^2 [11–13].

At present, there is no known effective prophylactic or symptomatic treatment, and it is increasingly recognised that oxaliplatin produces long-lasting, significant neurotoxicity [14–16]. Such persistent effects may exhibit a negative influence on long-term function and quality of life, particularly in the adjuvant setting where patients frequently have excellent long-term prognoses. As colorectal cancer survivors now represent the third largest cohort of cancer survivors [17], the development of significant chronic neurotoxicity with consequent impact on function is of major concern.

Due to the limitations of current grading scales, and the absence of consensus on the gold standard for symptom assessment, the incidence of chemotherapy-induced peripheral neuropathy is potentially underreported [10, 18, 19]. Clinicians typically rate chemotherapy-induced side effects as less severe than patient assessment of symptoms [20]. In addition, there is considerable inter-observer discrepancy in symptom identification and classification [18], emphasising the need for standardising assessment of peripheral neuropathy [19, 21, 22]. Self-report questionnaires can be used to clarifying symptom reporting [23, 24]. However, questionnaires or checklists based on closed questions may fail to provide a comprehensive picture. To date, there remains limited information about the day-to-day experiences of patients with oxaliplatin-induced peripheral neuropathy. As such, the aims of the present study were to explore the patient experience of oxaliplatin-induced peripheral neuropathy and to compare patient-reported outcomes with the maximum severity grade designated by their treating oncologist using a currently accepted grading system.

Methods

Twenty patients were consecutively recruited from the Department of Medical Oncology, Prince of Wales Hospital, for inclusion in the study. Purposive sampling [25] was used to identify patients who reported persistent neuropathic symptoms following completion of oxaliplatin treatment, regardless of whether the treatment was terminated prematurely because of symptoms. Accordingly, the study was designed to examine a cohort of chronically symptomatic patients with persistent neuropathic symptoms after cessation of oxaliplatin treatment. Additional inclusion criteria for the study were: literacy in English and absence of premorbid medical or psychiatric conditions which would preclude an interview. Patients were excluded if they had preexisting neuropathy prior to oxaliplatin therapy, if they had been treated with other neurotoxic drugs, or if they had a history of diabetes mellitus. Patients' demographic and clinical data, including cancer type, cumulative dose and dosing schedule, were obtained from their clinical records. Ethics approval for the study was obtained from the relevant institutional review board. Patients provided written informed consent in line with the declaration of Helsinki.

Assessments

Clinician assessment

The *National Cancer Institute Common Toxicity Criteria for Adverse Events Scale* (version 3), neuropathy sensory subscale (NCI) [26], was utilised by the treating clinicians to grade the severity of neuropathy. The following grading schematic applied: grade 1—loss of deep tendon reflexes or paresthesia not interfering with function; grade 2—sensory alteration or paresthesia interfering with function but not activities of daily living; grade 3—sensory alteration or paresthesia interfering with activities of daily living; and grade 4—disabling. NCI grades were recorded by treating clinicians across treatment and at all follow-up appointments. The maximum assigned grade during the course of treatment or the follow-up period was utilised for analysis to reflect the maximum level of neuropathy per patient as scored by the clinician.

Patient self-report questionnaire

The *Patient Neurotoxicity Questionnaire* (PNQ) [10, 18, 22, 23] provided subjective assessment of both sensory and motor symptoms. The PNQ was selected for use as a patient-reported outcome measure due to its inclusion of functional impact measures and assessment of the impact of neuropathy on patients' daily lives and as it has been found to be a valid and sensitive measure of the impact of

chemotherapy-induced neuropathy [23, 27–29]. The questionnaire was completed by the patient at the time of the semi-structured interview (see below). Patients select their symptom level corresponding to five grades from A to E, comprising two items. Item 1 addresses numbness, pain, burning, tingling or change in the sense of touch in hands/fingers, feet/toes or mouth area with grades comprising (A) none; (B) mild, but not interfering with activities of daily living; (C) moderate, but not interfering with activities of daily living; (D) moderate to severe, and interfering with activities of daily living; and (E) severe—completely preventing most activities of daily living. Item 2 addresses difficulty in swallowing, breathing, drinking or chewing food, or muscle spasms in mouth/jaws, hands/fingers or feet/toes with the same grading schema. There is also provision for the respondent to indicate which of the symptoms, if present, cause interference with activities of daily living and which particular activities are affected.

Semi-structured interview

The interview was conducted by interviewer (BB) experienced in clinical and symptomatic assessment of patients [30] (e.g. cancer-related fatigue, depression) and qualitative analyses. At the time of the interview, the interviewer was blind to the oncologists' clinical grading of peripheral neuropathy and results of nerve conduction studies. Subjects were interviewed using a series of open-ended questions and encouraged to freely describe their experiences in their own words. The questions canvassed the history of symptom onset together with more specific descriptions of the symptoms themselves together with any functional limitations consequent on the symptoms. Patients also described the worst symptoms they had experienced at any time following commencement of oxaliplatin treatment. Written records of subjects' verbatim responses were recorded for qualitative analysis.

Nerve conduction studies

Conventional nerve conduction studies were undertaken in upper and lower limb sensory and motor nerves, including tibial, sural and superficial radial nerves [31], using a Medelec Synergy system (Oxford Instruments, Oxfordshire, UK). Measurements of maximum amplitude and conduction velocity were undertaken.

Data analysis

Qualitative analyses of the interview data was aided by importation into *NVivo* [32], a software program which facilitates analyses by the organisation and management of the coding process. Data analysis was a multistage process (see similar methods described in [30, 33]) The content of the interviews was initially scrutinised for terms describing the experience of symptoms (numbness, clumsiness, loss of feeling) and the functional effects or consequences of these symptoms, together with any adaptations necessitated by the symptoms. Emerging themes were identified and categorised by discussion between the authors.

SPSS version 19 (Chicago, USA) was used for quantitative statistical analysis. Information from clinician assessment, clinical interview and self-report questionnaire were coded and assigned numerical grades for comparison. Following qualitative data analyses of the interview, the presence or absence of symptoms was assigned a dichotomous score (0—absent, 1—present) and the number of symptoms present summed to give a total severity score. Responses on the PNQ questionnaire were assigned a numerical value corresponding to symptom severity. Correlations were performed using Pearson's product–moment correlation coefficients between the summed interview score, PNQ grade and NCI grade, and between individual activities on the PNQ scale (Bonferroni-corrected for multiple comparisons).

Results

Twenty patients were interviewed (65% female, 79% married; mean age, 58 years, range, 33–73 years; Table 1). Recruitment was continued until data 'saturation' for qualitative analysis was obtained. No patient that was approached declined to be interviewed. The mean time since cessation of oxaliplatin was 12.6±2.8 months, following an average number of 9.5 treatment cycles. For 40% of patients, oxaliplatin dose was reduced or oxaliplatin treatment ceased prematurely due to the severity

Table 1 Demographic and clinical characteristics (n=20)

Age (mean±SEM)	58±3 years
Age range	32–73 years
Gender	13 female, 7 male
Type of cancer	80% colon
Stage (II, III, IV)	
Stage III B/IIIC	45%
Stage IV	55%
Cumulative oxaliplatin dose	789±39 mg/m^2
Number of treatment cycles	9.5±0.4 cycles
Time since treatment cessation	385±84 days
Early cessation due to neurotoxicity	40%
Maximum sensory NCI grade (1, 2, 3)	
NCI grade 1	40%
NCI grade 2	50%
NCI grade 3	10%

of neuropathic symptoms. The majority of patients had serum creatinine levels well within the normal range (median, 80 μmol/l; range, 40–102 μmol/l). Three of the 20 patients had a suboptimal creatinine clearance 59, 65 and 71 ml/min, respectively.

Descriptions of symptom experience from semi-structured interview

All patients (by study inclusion criteria) reported symptoms consistent with peripheral neuropathy. Whilst patients were interviewed whilst experiencing chronic symptoms, they included descriptions of their experiences related to the acute symptoms and did not necessarily discriminate between acute and chronic symptoms unless prompted to do so. The patients described the total experience of neuropathy and were not limited in their responses to the open-ended questions.

The main themes emerging from the interviews were the severity and persistence of oxaliplatin-induced neurotoxic symptoms and the unexpected nature of such symptoms. Patients did not expect the neuropathy to affect their lives to the extent that it did, and 35% of patients reported specific instances of lifestyle change or behavioural adaptation due to neuropathic symptoms. These included limitations or changes to exercise patterns, footwear or clothing choices, or detrimental changes in their confidence in walking on different terrains. The majority of patients reported having experienced cold-precipitated tingling and pain in both upper and lower limbs during their oxaliplatin treatment (Fig. 1). In addition, 30% of patients reported experiencing severe neuropathic symptoms in the orofacial area (jaw pain and throat discomfort).

Acute neurotoxicity

Patients described acute neuropathic symptoms temporally related to the time of infusion, "…(it)…*started at the end of each treatment and progressed over the next 3 to 4 days*".

Their experience of the unique exacerbation of acute symptoms by cold exposure was vividly described. For example, patients reported "…*even a drop of cold water would precipitate the symptoms*" and "*drinking a cold beer was like drinking a mouthful of nails—all sharp and prickly*" or "*like razor blades in the throat*" when having a glass of cold orange juice. Several patients also reported acute jaw pain, particularly when taking the first bite of food, commenting "*it feels like there's a party in my mouth and somebody invited the whole world to come*".

Symptoms were described both in 'classical' terms, e.g. "*pins and needles*"; "*tingling in my fingers and hands*" and, more graphically, "…*it's like being hit with an electric wire or something…*" or "…*it's like I have frozen hands and that they have only partially thawed…*", "*…there's a funny sensation walking on carpet—I don't feel it but know it's there*". The sensations of parasthesia were strikingly described as "*sand in my shoes*" or "*walking on crushed cellophane*" or "*feeling things through a film of glad wrap*" (i.e. fine plastic wrap/cling film).

Chronic neurotoxicity—effects and limitations of symptoms

Patients described chronic persistent symptoms including "…*numbness present all the time*" and "*no improvement over the past 12 months*". The effects and limitations imposed by the symptoms were often vividly described. One woman reported that she had lacerated her finger quite badly with a kitchen knife whilst cooking but had no sensation of pain at the time. Others reported functional difficulties with tasks requiring fine motor skills and manual dexterity. Problems were reported with a number of tasks including manipulation of jewellery, ability to do fine sewing work, holding chopsticks, handwriting, driving and playing golf.

For many patients, mobility or physical activity was predominantly affected because the symptoms were more prominent in the lower than the upper limbs. When asked about his symptoms, one patient said, "*It's not really tingling—more numbness, mainly in my toes—much worse than my hands. It's there all the time. It's not gotten better over the past 12 months*". Several patients experienced problems with balance due to lower limb numbness and reported feeling "*unsure and unsteady*" or "*difficulty in walking*", "*problems when driving…*", whilst others reported "*getting very clumsy…"* or "*nearly falling over*" on occasions. One man's attribution for this was because "*It feels like walking on a surface of cotton wool—like the heels and toes are not connecting…*".

These difficulties in walking and lower limb function often led to difficulty choosing appropriate footwear and prevented exercise. One patient described it as "…*heavy legs—like pulling a couple of logs around*."

Several patients commented on their actual experiences in comparison to their expectations. One woman remarked that the symptoms were "*much, much worse than she imagined they would be…*". This was similar to another patient who described how she was unaware of how bad the side effects would be and how long they would last. "*It's now just 12 months since I finished treatment and I still have problems with my feet*".

The prolongation of the symptoms was another commonly reported feature. "*It's now 2 years 8 months since my treatment was finished—the symptoms seem to have improved but they have plateaued for the past 18 months*". Another woman, who had finished her treatment 2 years

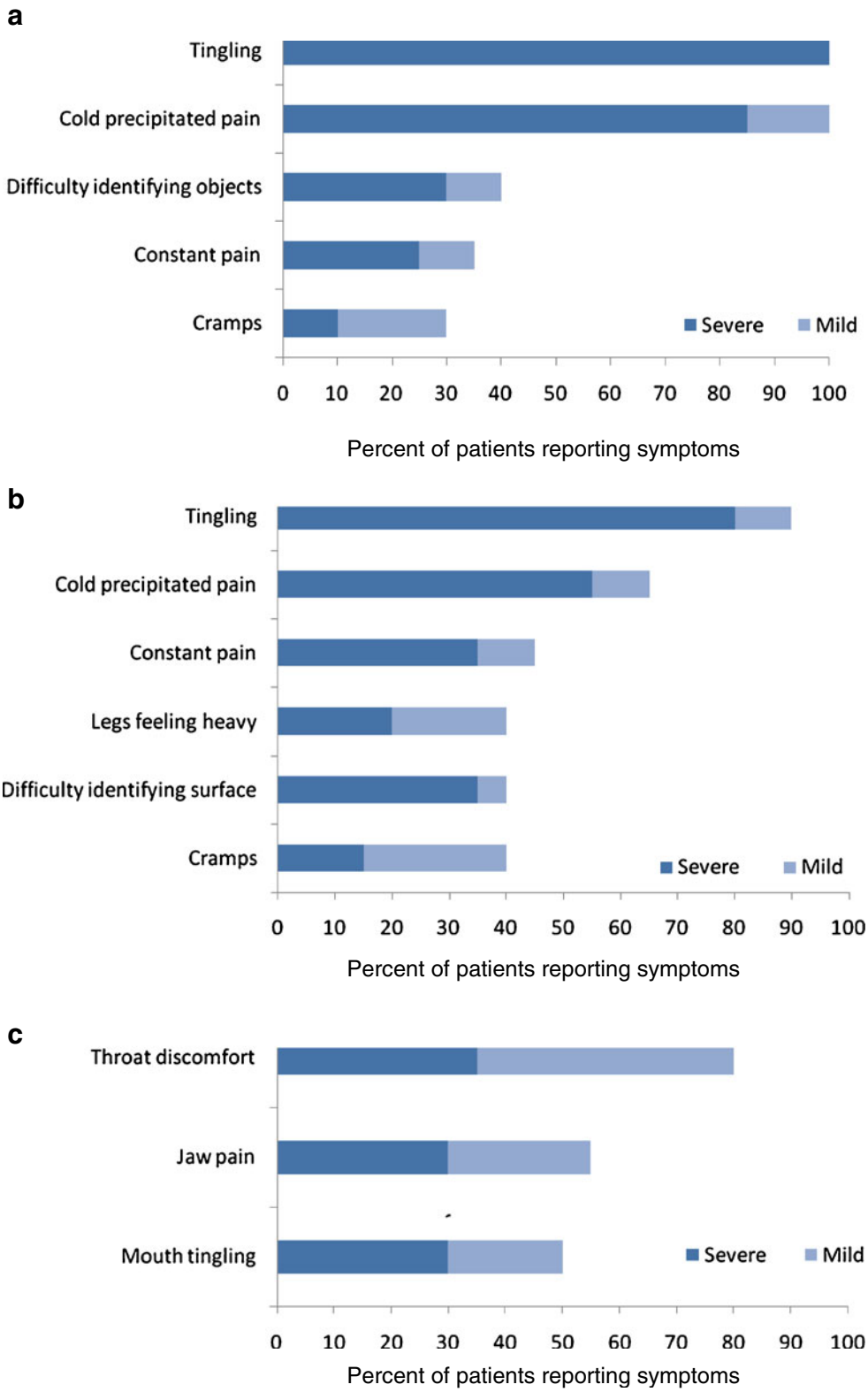

Fig. 1 Symptom frequency as described by patients during interview in upper limbs (**a**), lower limbs (**b**) and the orofacial region (**c**). Severity of symptoms (indicated as mild or severe) is differentiated on the graph

previously but still had symptoms in her legs, commented that she "*puts up with it*". Several patients reported the onset of severe symptoms or worsening of symptoms towards the end of treatment or even after cessation of treatment. "*…the balls of my feet are numb, this didn't start until after the treatment finished. My feet don't seem to have gotten any better*".

Quantitative symptom analysis

Patient Neurotoxicity Questionnaire

Complementary to the semi-structured interview, patients completed the PNQ questionnaire. In total, 30% of patients reported mild neurotoxicity (grade B), 40% reported moderate neurotoxicity (grade C), and 30% reported moderate to severe neurotoxicity (grade D). Overall, 60% of patients reported functional difficulties with activities of daily living due to neuropathic symptoms produced by their oxaliplatin chemotherapy (Table 2). The most frequently reported difficulties were with writing and walking, suggesting deficits in fine motor skills, proprioception and balance.

Symptom reports for activities requiring similar skills were highly intercorrelated, indicating that the PNQ demonstrated internal validity (Tables 3 and 4). For example, difficulties in items relating to eating (like handling cutlery) were positively associated, as were items related to dressing (like fastening zips or tying shoe laces).

Table 2 Self-reported responses (PNQ)—abilities and tasks affected by symptoms of peripheral neuropathy (n=20)

	% of subjects
Meals	
Eating/chewing	15
Drinking liquids	15
Using cutlery	15
Swallowing	25
Dressing	
Opening/closing zippers	15
Fastening buckles	20
Buttoning clothes	25
Tying shoes	10
Putting on jewellery	25
Mobility	
Opening doors	15
Climbing stairs	20
Walking	40
Driving	10
Occupation/hobbies	
Writing	40
Typing/keyboard	20
Knitting	5
Sewing	10
Other important tasks (not specified)	25
General health	
Sleep	35
Shortness of breath	10

PNQ Patient Neurotoxicity Questionnaire (Oxaliplatin)

Table 3 Correlations between self-reported difficulties with 'eating' items

	Knife	Spoon	Swallowing	Eating
Knife				
Spoon	0.793*			
Swallowing	0.404	0.577*		
Eating	−0.176	−0.140	0.404	
Drink Liquids	−0.176	−0.140	0.081	0.608*

*$p \leq 0.008$ (Bonferroni-corrected for multiple comparisons)

Clinician assessment

Each patient was graded by their treating clinician at standard review throughout the treatment phase and at post-treatment follow-up visits using the NCI-CTCAE scale [22, 26]. The maximum NCI grade assigned to patients was used for analysis. From the total cohort, 50% of patients received a maximum score of '2' throughout the whole treatment and post-treatment phase, reflecting moderate neurotoxicity, whilst 10% were graded '3', reflecting severe neurotoxicity. This may reflect discrepancies in clinician grading as, in contrast, 60% of patients reported difficulties with activities of daily living in the PNQ questionnaire.

Nerve conduction studies

To confirm that the interviewed patient cohort had objective and persistent evidence of neuropathy following oxaliplatin treatment, nerve conduction studies and sensory testing were undertaken. Using these approaches, 85% of patients had evidence of sensory neuropathy following oxaliplatin treatment, demonstrable via a reduction in sensory amplitudes or problems with sensation in distal limbs. Mean upper and lower limb sensory amplitudes were significantly reduced from baseline values (pre-sural, 13.2±1.6 μV; post-sural, 4.5±0.6 μV, p<0.005; pre-radial, 33.3±2.9 μV; post-

Table 4 Correlations between self-reported difficulties with 'dressing' items

	Button clothes	Zippers	Buckles	Put on jewellery
Button clothes				
Zippers	0.728*			
Buckles	0.866*	0.840*		
Put on jewellery	0.467	0.404	0.577	
Tie shoes	0.577	0.793*	0.667*	0.192

*p<0.001 (Bonferroni-corrected for multiple comparisons)

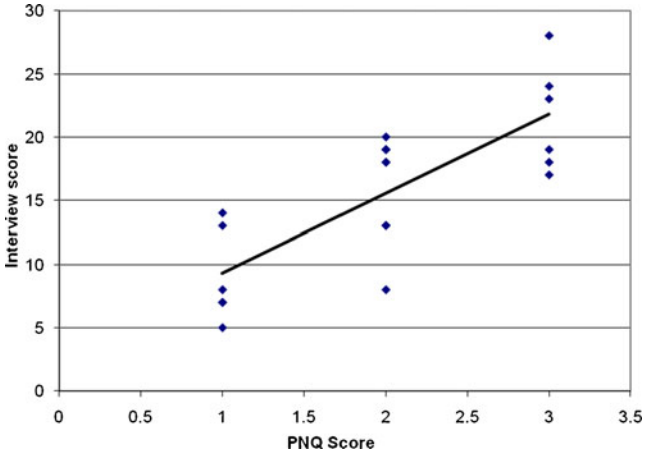

Fig. 2 The sum of symptoms in the upper and lower limbs derived from the interview was correlated with the PNQ grade, demonstrating a strong correlation between the two assessment methods (Pearson correlation coefficient=0.790, $p<0.0005$)

radial, 21.5±3.1 μV, $p<0.05$), whilst conduction velocity was preserved and not significantly altered (sural nerve conduction velocity: pre, 47.5±1.2 m/s; post, 44.9±1.6 m/s, NS; radial nerve conduction velocity: pre, 57.0±1.4 m/s; post, 56.5±2.3 m/s, NS). In contrast, motor amplitudes were within normal limits and did not demonstrate significant reductions (post-tibial, 8.6±1.1 mV). In total, these findings are consistent with the development of a sensory neuropathy of the axonal type.

Comparison of symptoms by different methods of assessment

To compare the assessment of neuropathic symptoms by the different methods, the patient symptom reports gleaned from interview data were summed to give a severity score. The summed interview score was more strongly correlated with PNQ grade (Pearson correlation coefficient=0.790, $p<0.0005$; Fig. 2) than with NCI grade, indicating that interviewer-elicited symptom reports were strongly linked to patient self-reported symptoms. The percentage of patients identified with severe neuropathy as derived from self-report was greater than the percentage identified by the clinician assessment (recorded as NCI grade; Fig. 3). This indicated that more patients rated their symptoms as more severe than their clinicians, further suggesting discrepancies between the assessment methods.

Discussion

The present study utilised and compared clinician assessment, self-report questionnaire, individual patient interview and objective assessment by nerve conduction studies to examine and further explore the processes and functional outcomes related to oxaliplatin-induced peripheral neuropathy. These assessment methods provided descriptions of both acute neurotoxicity following infusion and chronic cumulative sensory neuropathy persisting after treatment completion, demonstrating discrepancies in neuropathy grading, with the clinical interview identifying chronic symptoms that persisted for longer than current evaluation systems appear to suggest. These findings highlight the importance of the inclusion of patient-reported outcomes in determining the true burden of peripheral neuropathy in oxaliplatin-treated patients.

Few studies have examined the impact of chemotherapy-induced neurotoxicity on the functional status of patients. In particular, the patient perspective of the experience of oxaliplatin-induced peripheral neuropathy remains underexplored. Our patients reported that the severity and persistence of peripheral neuropathy following oxaliplatin treatment was unexpected, similar to findings in previous qualitative studies of patients receiving other chemotherapies [34, 35]. Whilst there is currently an increasing focus on patient-reported outcomes (PROs) in the assessment of chemotherapy side effects, thorough assessment of the patient experience has yet to be successfully implemented in mainstream clinical practice.

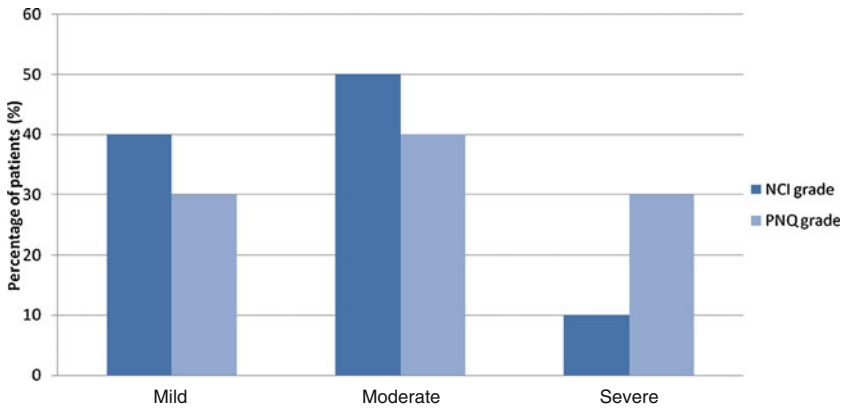

Fig. 3 Comparison of symptom severity by NCI criteria (clinician-assessed) and self-report questionnaire (PNQ questionnaire)

This study demonstrates discordance between PROs and clinician assessment using commonly accepted clinician grading scales, suggesting that these scales may lack sensitivity to identify patients with persistent neurotoxic symptoms. This confirmed findings of similar studies focusing on treatment side effects, including pain and fatigue, suggesting that clinicians underestimate the severity of patient symptoms [20] and that clinician-based assessments fail to recognise the true symptomatic burden of neurotoxicity and functional consequences such as falls and decline in mobility [36, 37]. Whilst discrete and coarse categorical grading of symptoms enables easy acquisition of information for toxicity reporting in a clinical trial, such processes do not provide the most appropriate method to accurately identify patient outcomes. As such, the functional and daily consequences of neurotoxicity for patients may be better assessed using questionnaire or interview-based approaches. In addition, accurate measurement of the onset and development of chemotherapy-induced neurotoxicity is also critical for use in clinical trials of potential neuroprotective agents.

Discrepancies between a clinical paradigm (the 'biomedical' model) in which the emphasis is on the aetiology, pathological processes and predominately clinical outcomes in comparison to the social science paradigm, the 'quality-of-life model' where the focus is on functioning and overall well-being, may account for the inconsistency between clinician and patient reports [38]. Assessment of the physiological effects (identified by neurophysiological testing) with the symptoms (e.g. parasthesia), effects on physical function and daily activities, and impact on subjective health and well-being (health-related quality of life) with more appropriate clinical assessment tools would provide a more cohesive picture of longer-term outcomes for patients treated with oxaliplatin chemotherapy. Assessment matrices have been developed to examine the treatment of depression and mood disorders [39] that address both symptoms and functional limitations. A similar approach, providing a more comprehensive assessment of the patient experience of neuropathy, would be a major advantage in clinical trials to monitor the outcome and efficacy of neuroprotective agents [3].

The present findings suggest the need to instigate longitudinal studies using a reproducible clinical interview to monitor PROs focused upon lifestyle adaptations forced upon patients to manage their symptoms. In addition, it will be important to further delineate the relationship between PROs and objective signs of nerve damage [40]. These findings are of particular relevance in light of the increasing use of oxaliplatin in the adjuvant setting in patients with early-stage colorectal cancer [6]. Specifically, the present study has demonstrated the persistence of subjective symptoms of peripheral neuropathy, consistent with previous studies that solely utilised objective measurement [14], although at variance with earlier published pharmacokinetics and safety profiles which suggested that symptoms typically resolved within 6–8 months [1, 11, 41]. Such information is vital for informed communication and decision making about the opportunity cost and trade-off of side effects compared with the benefits of more intensive versus less intensive adjuvant therapy [42] and for the assessment of neuroprotective benefit.

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Data responsibility The first author (Dr. Bennett), Susanna Park and senior author (Dr. Goldstein) had full access to all primary study data and take responsibility for the integrity of the data and accuracy of the data analyses. The authors agree to allow the journal to review their data if requested.

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This is an original work and all the authors meet criteria for authorship.