Patients' and physicians' interpretation of chemotherapy-induced peripheral neurotoxicity

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RESEARCH REPORT

Patients' and physicians' interpretation of chemotherapy-induced peripheral neurotoxicity

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To test if and how chemotherapy-induced peripheral neurotoxicity (CIPN) is perceived differently by patients and physicians, making assessment and interpretation challenging. We performed a secondary analysis of the CI-PeriNomS study which included 281 patients with stable

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CIPN. We tested: (a) the association between patients' perception of activity limitation in performing eight common tasks and neurological impairment and (b) how the responses to questions related to these daily activities are interpreted by the treating oncologist. To achieve this, we compared patients' perception of their activity limitation with neurological assessment and the oncologists' blind interpretation. Distribution of the scores attributed by oncologists to each daily life maximum limitation ("impossible") generated three groups: Group 1 included limitations oncologists attributed mainly to motor impairment; Group 2 ones mainly attributed to sensory impairment and Group 3 ones with uncertain motor and sensory impairment. Only a subset of questions showed a significant trend between severity in subjective limitation, reported by patients, and neurological impairment. In Group 1, neurological examination confirmed motor impairment in only 51%-65% of patients; 76%-78% of them also had vibration perception impairment. In Group 2, sensory impairment ranged from 84% to 100%; some degree of motor impairment occurred in 43%-56% of them. In Group 3 strength reduction was observed in 49%-50% and sensory perception was altered in up to 82%. Interpretation provided by the panel of experienced oncologists was inconsistent with the neurological impairment. These observations highlight the need of a core set of outcome measures for future CIPN trials.

KEYWORDS

assessment, chemotherapy, neurotoxicity, patient reported outcome measures, side effects

1 | INTRODUCTION

In chemotherapy-induced peripheral neurotoxicity (CIPN) stocking-and-glove numbness, paresthesias and sensory ataxia are predominant, but motor involvement can also occur after anti-tubulin drugs and "targeted" agents treatment.[1,2]

CIPN recognition and monitoring are crucial in clinical practice since improper assessment can delay treatment plan modification, at the moment the only effective way to limit CIPN severity, and cause more severe and long-term impairment. However, CIPN is perceived differently by patients and health care providers,[3] and sometimes under-reported by patients.[4]

CIPN assessment is a critical issue also in the design and interpretation of neuroprotection clinical trials.[5] The earliest clinical trials relied on the US National Cancer Institute-Common Toxicity Criteria for Adverse Events (NCI-CTC AE) scale to grade CIPN severity, but evidence suggests it is not the optimal endpoint.[6]

Therefore, different assessment tools have been developed, such as the Total Neuropathy Score (TNS), and self-administered questionnaires, particularly the European Organization for Research and Treatment in Cancer (EORTC) QLQ-CIPN20 and the Functional Assessment of Cancer Therapy/Gynaecologic Oncology Group-Neurotoxicity (FACT-GOG Ntx).[7,8]

According to Regulatory Agencies, these Patient Reported Outcome (PRO) measures may represent a robust primary endpoint (https://www.fda.gov/downloads/drugs/guidances/ ucm193282.pdf). However, concerns have been raised on their capacity to capture all CIPN clinical features.[9,10]

Moreover, simple questions related to daily living activities can effectively reflect personal impairment, but these limitations might be ascribed to different conditions besides CIPN: weakness due to severe anemia, cancer-related fatigue, chemotherapy-induced cognitive impairment ("chemofog"), cancer-related pain and psychosomatic disorders.[11]

To address these issues, we performed a secondary analysis of the CI-PeriNomS study dataset to test the association between patients' perception of activity limitation and actual neurological impairment and how patient responses are interpreted by the treating oncologist.

2 | PATIENTS AND METHODS

The CI-PeriNoms database, which included 281 patients with stable CIPN and no other cause of motor or sensory impairment, was used as the reference population for the survey. In that study, each patient was neurologically examined and at each visit the neurological status was evaluated according to the clinical version of the Total Neuropathy Score—clinical (TNSc) as previously described.[12] Two neurologists experienced in assessing CIPN (G.C., P.A.) selected, among the list of questions submitted to each patient participating to the CI-PeriNoms study, 8 tasks scored as "impossible to be performed" by at least 5% of the patients (Table 1). An electronic form that enabled assessment for each of the 8 tasks, to grade separately expected motor or sensory impairment from 0 (no impairment) to 10 (maximum severity), in a hypothetical patient unable to perform the task, was mailed to oncologists working at centers participating to the CI-PeriNoms study. A total of 44 oncologists completed the survey form and their responses were used for classifying the tasks as able or not to detect motor or sensory impairment.

In order to test the criterion validity of each self-report limitation, we have analyzed data according to the *presence* (frequency) of CIPN,

TABLE 1 Results of the oncologists scoring on selected questions according to motor or sensory impairment (*P*-values on the null hypothesis of median indecision score of 5)

	Motor			Sensory		
	Median	IQR	*P*-value	Median	IQR	*P*-value
Group 1—limitations attributed mainly to motor impairment						
Stand up from a squatting position	7.0	(3.0-8.0)	0.0096	2.0	(1.0-3.5)	<0.0001
Walking up two flights of stairs	7.0	(6.0-8.5)	<0.0001	3.0	(2.0-4.5)	<0.0001
Group 2—limitations attributed mainly to sensory impairment						
Handle small objects	2.0	(0.0-3.0)	<0.0001	8.0	(6.5-9.5)	<0.0001
Button a shirt/blouse	1.0	(0.0–3.0)	<0.0001	8.0	(7.0-10.0)	<0.0001
Zip your trousers	1.0	(0.5-4.0)	0.0003	8.0	(6.0-9.0)	<0.0001
Tie your laces	1.0	(0.0-4.0)	<0.0001	8.0	(6.0–9.0)	<0.0001
Group 3—limitations attributed both to motor and sensory impairment						
Stand on one leg	5.0	(2.0-8.0)	0.5114	4.0	(1.5-6.0)	0.1325
Walk on uneven ground	5.0	(2.0-7.0)	1.0000	6.0	(4.0-7.0)	0.2682

Abbreviation: IQR, interquartile range.

without taking into account its *severity*. Comparisons were performed between the oncologists' responses and the scores obtained in strength and vibration detection threshold using the TNSc criteria. Oncologists' interpretation of patients' answers was blind to the neurological assessment.

3 | STANDARD PROTOCOL APPROVALS, REGULATIONS AND PATIENT CONSENTS

The original CI-PeriNoms study protocol[12] was examined and approved by the IRB/EC of each participating center; written informed consent was obtained from all participants. The study was conducted in accordance with the guidelines of the declaration of Helsinki (amendment October 2000, Edinburgh), and applicable local regulatory requirements and laws.

4 | DATA AVAILABILITY STATEMENT

Any data not published within the article will be shared, in an anonymized form, by request from any qualified investigator.

4.1 | Statistical analysis

The oncologist's evaluation of the eight selected tasks was described by means of median and interquartile range (IQR). The median test was used against the null hypothesis (median = 5) of indecision between no impairment (0) and maximum severity (10). When the task obtained a median score of motor (sensory) impairment significantly different from the indecision score, it was classified as a task hypothetically able or not to recognize motor (sensory) impairment if higher or lower than 5, while in case of no significant difference from the indecision, it was classified as an uncertain task.

Patients were classified as pathological, or not, according to their strength and sensory loss evaluated by means of TNSc scoring (items strength and vibration sensibility), and they were considered as normal in case of score equal to 0, or pathological when the score was equal to or greater than 1.

Association between the response to the eight tasks and TNSc evaluations was represented as percentage of pathological patients by each task response and was tested by means of the Cochran-Armitage test for trend, to evaluate if the pathological patient's percentage was increasing by worsening answers. This association was evaluated overall on the entire sample and by received treatment (Platinum drugs and Taxanes). The multiplicity correction according to Hommel was applied. *P*-values were considered statistically significant if lower than 0.05. Analyses were carried out by means of the statistical software SAS v.9.4 (SAS Institute Inc, Cary, NC).

5 | RESULTS

The distribution of the scores attributed by oncologists to each daily life maximum limitation ("impossible") allowed for the categorization of the responses into 3 groups: Group 1 included the limitations that the oncologists attributed mainly to motor impairment (item median motor score = 7, item median sensory score 2-3), Group 2 consisted of limitations mainly attributed to sensory impairment (item median sensory score = 8, item median motor score = 1-2) and Group 3 included limitations with uncertain motor and sensory impairment (item median sensory score = 4-6, item median motor score = 5). Table 1 reports the detailed statistical analysis at the basis of the groups stratification which was used thereafter for all analyses.

5.1 | Correlation between activity limitation and neurological impairment

As expected based on the enrollment criteria of the original CI-PeriNoms study that was performed in patients with stable CIPN,[12] most of the subjects reported some degree of activity limitation. The presence of motor and sensory impairment in subjects who reported that each given task was "impossible", "difficult to be performed" or "easy to be performed" are reported in Table 2. Sensory impairment was generally more frequent than motor impairment in all groups and

TABLE 2 Percentage of patients with pathological scores at the TNSc, by different answers to questions in the three groups of limitations (*P*-values are adjusted for multiplicity correction according to Hommel)

				Percentage of patients with pathological scores, by answers			
Group	**Questions**	**Answers**	**N**	**Motor**	***P*-value**	**Sensory**	***P*-value**
Group 1—limitations attributed mainly to motor impairment	Stand up from a squatting position	impossible	37	51		78	
		difficult to be performed	126	25	0.2167	68	0.9265
		easy to be performed	105	29		76	
	Walking up two flights of stairs	impossible	17	65		76	
		difficult to be performed	113	31	0.0538	72	0.9265
		easy to be performed	142	25		75	
Group 2—limitations oncologists attributed mainly to sensory impairment	Handle small objects	impossible	19	47		84	
		difficult to be performed	131	34	0.0674	80	0.0148
		easy to be performed	123	23		63	
	Button a shirt/blouse	impossible	23	43		91	
		difficult to be performed	129	30	0.3179	81	0.0015
		easy to be performed	121	27		60	
	Zip your trousers	impossible	9	56		100	
		difficult to be performed	84	42	0.0127	84	0.0015
		easy to be performed	177	23		65	
	Tie your laces	impossible	25	48		92	
		difficult to be performed	110	36	0.0109	79	0.0015
		easy to be performed	127	20		62	
Group 3—limitations oncologists attributed both to motor and sensory impairment	Stand on one leg	impossible	51	49		82	
		difficult to be performed	111	24	0.1642	71	0.9265
		easy to be performed	103	29		72	
	Walk on uneven ground	impossible	22	50		82	
		difficult to be performed	143	73	0.3179	71	0.9265
		easy to be performed	105	70		72	

Abbreviation: total neuropathy score—clinical.

for all questions, with altered vibration detection threshold at the TNSc in 73% of patients (score 1 = 20%, score 2 = 27%, score 3 = 13%, score 4 = 13%), while strength was reduced in 30% of them (score 1 = 24%, score 2 = 5%, score 3 = 1%). In most cases (but not in all the set of questions) a significant trend between severity in subjective activity limitation reported by patients and neurological impairment at the TNSc was present (ie, highest percentage of TNSc pathological features in patients describing a given item as "impossible" to be performed vs "difficult to be performed" or "easy to be performed").

Regarding the subjective perception of drug-induced activity limitation, it is remarkable that in at least 65% of patients describing the activity as "easy to be performed", they had evidence of some degree of sensory impairment upon neurological examination, while neurological impairment at the TNSc was less evident for strength reduction (20-30%).

In this population, the percentage of subjects describing at least one of the selected eight daily life activities as "impossible" to be performed, who had at the neurological examination reduced strength, ranged from 43% to 65% according to the different items, while this occurred in 76%-100% of cases for abnormal vibration perception (Table 2). Despite the clear predominance of sensory impairment, a combined sensorimotor deficit was always present in each item, although this does not always imply that each patient had combined sensorimotor impairment.

The association between activity limitation and neurological impairment was highly variable among the different questions, and it was related in most cases to both the question and the type of chemotherapy treatment received (Tables 3 and 4). For instance, in Group 1 questions (attributed by oncologists to motor impairment), patients reporting the activity as "impossible" had motor impairment at the TNSc in 67% of subjects who received taxanes vs 35% of those who were treated with platinum drugs for the question "Stand up from a squatting position", but subjects were impaired in 71% of cases for both motor and sensory impairment considering the question "Walking up two flights of stairs". In Group 3 (where oncologists were unable to attribute the limitation to predominant sensory or motor impairment) at the question "Stand on one leg" were associated 73% of motor and sensory impairments after taxanes therapy, but 27% vs 86% for motor or sensory impairment after receiving platinum drugs. In the same group, "Walking on uneven ground" was more frequently associated with motor impairment after taxanes, but rather with sensory impairment after platinum-based chemotherapy.

TABLE 3 Percentage of patients with pathological scores at the TNSc, by different answers: only Platinum-drug (*P*-values are adjusted for multiplicity correction according to Hommel)

				Percentage of patients with pathological scores, by answers					
Group	Questions	Answers	N	Motor	*P*-value	Sensory	*P*-value	Both motor and sensory	*P*-value
Group 1—limitations attributed mainly to motor impairment	Stand up from a squatting position	impossible	17	35		76		29	
		difficult to be performed	62	21	0.9953	81	0.7604	18	1.000
		easy to be performed	71	24		77		24	
	Walking up two flights of stairs	impossible	7	71		86		57	
		difficult to be performed	62	24	0.2923	81	0.7604	23	0.7375
		easy to be performed	84	20		77		19	
Group 2—limitations oncologists attributed mainly to sensory impairment	Handle small objects	impossible	13	46		100		46	
		difficult to be performed	84	26	0.2146	86	0.0043	23	0.4454
		easy to be performed	55	16		64		16	
	Button a shirt/blouse	impossible	18	33		94		33	
		difficult to be performed	83	23	0.9853	84	0.0160	20	1.0000
		easy to be performed	52	23		65		21	
	Zip your trousers	impossible	6	33		100		33	
		difficult to be performed	52	35	0.3288	92	0.0103	35	0.1634
		easy to be performed	93	18		72		15	
	Tie your laces	impossible	15	47		100		47	
		difficult to be performed	69	26	0.1579	86	0.0074	25	0.1053
		easy to be performed	64	16		67		14	
Group 3—limitations oncologists attributed both to motor and sensory impairment	Stand on one leg	impossible	22	27		86		23	
		difficult to be performed	62	23	0.9953	81	0.5825	19	1.0000
		easy to be performed	64	25		73		25	
	Walk on uneven ground	impossible	9	33		89		22	
		difficult to be performed	77	19	0.9953	83	0.4413	17	1.0000
		easy to be performed	65	28		72		28	

Abbreviation: total neuropathy score—clinical.

It is also remarkable that the percentage of subjects with both sensory *and* motor impairment at the TNSc had for most items a nearly complete/complete overlap with motor impairment in platinum-treated patients, while this was less evident after taxane treatment.

5.2 | Oncologists interpretation of activity limitation

Because in daily practice it is crucial that patients report the occurrence of any side effect with as much precision as possible, to the treating physician in order to properly monitor and adjust the treatment, we tested the correlation between subjective perception of activity limitation and oncologists' interpretation of the neurological cause of the impairment. Next, we compared the interpretation with the actual neurological status assessed by an experienced neurologist.

In Group 1, including limitations in standing up from a squatting position and walking up two flights of stairs interpreted by oncologists as likely due to motor impairment, the formal neurological examination confirmed the presence of motor impairment (any grade, in most cases mild) in only 51-65% of patients belonging to the CI-PeriNoms cohort who defined that function as "impossible". Remarkably 76-78% of the patients also had vibration perception impairment (in 32-67% of them the impairment was grade 3 or 4 in the TNSc©, thus indicating moderate-to-severe impairment). Statistical analysis demonstrated a significant trend only between the difficulty in performing the task and motor impairment, while this trend was not present for sensory impairment (Table 2).

In Group 2, where the limitations referred in handling small objects (eg, coins), buttoning a shirt/blouse, zipping trousers and tie shoes laces were attributed by oncologists to sensory impairment, the percentage of patients in the CI-PeriNoms cohort with vibration detection impairment was extremely high (ranging from 84% to 100%), with severe sensory impairment occurring in 44%-70%, but also some degree of motor impairment occurred in 43%-56% of the patients. Analyzing this group of items, statistical analysis showed a significant trend between the difficulty in performing the task and not only sensory, but also motor impairment (with the only exception of buttoning a shirt/blouse) (Table 2).

In Group 3 (limitation in standing on one leg or walking on uneven ground) strength reduction was observed in 49% and 50%, respectively; and vibration detection threshold was altered up to 82% in

TABLE 4 Percentage of patients with pathological scores at the TNSc, by different answers: only Taxanes (*P*-values are adjusted for multiplicity correction according to Hommel)

				Percentage of patients with pathological scores, by answers					
Group	Questions	Answers	N	Motor	*P*-value	Sensory	*P*-value	Both motor and sensory	P-value
Group 1—limitations attributed mainly to motor impairment	Stand up from a squatting position	impossible	9	67		78		56	
		difficult to be performed	23	39	0.5419	48	1.0000	26	0.8627
		easy to be performed	15	47		73		40	
	Walking up two flights of stairs	impossible	7	71		71		57	
		difficult to be performed	18	44	0.5419	50	1.0000	33	0.8613
		easy to be performed	21	38		71		29	
Group 2—limitations oncologists attributed mainly to sensory impairment	Handle small objects	impossible	4	75		50		50	
		difficult to be performed	25	56	0.2563	64	1.0000	48	0.3653
		easy to be performed	19	26		63		16	
	Button a shirt/blouse	impossible	2	100		100		100	
		difficult to be performed	23	57	0.2051	70	1.0000	48	0.0327
		easy to be performed	22	27		50		14	
	Zip your trousers	impossible	2	100		100		100	
		difficult to be performed	15	60	0.2774	73	1.0000	60	0.0152
		easy to be performed	29	34		52		17	
	Tie your laces	impossible	5	60		80		60	
		difficult to be performed	18	67	0.3933	67	1.0000	61	0.0529
		easy to be performed	22	32		50		14	
Group 3—limitations oncologists attributed both to motor and sensory impairment	Stand on one leg	impossible	11	73		73		64	
		difficult to be performed	20	40	0.4358	55	1.0000	25	0.6267
		easy to be performed	17	35		65		29	
	Walk on uneven ground	impossible	6	83		50		50	
		difficult to be performed	27	37	0.5419	63	1.0000	30	0.8627
		easy to be performed	14	50		64		43	

Abbreviation: total neuropathy score—clinical.

both questions (37% and 36%, respectively with regard to grade 3-4 impairment) of the CI-PeriNoms patients unable perform the task. Statistical analysis in this group showed a significant trend between the difficulty in performing the task and motor impairment only for standing on one leg (Table 2).

6 | DISCUSSION

It is becoming more and more widely accepted that the assessment of CIPN must rely predominantly on subjective perceptions as reported by the affected subjects. The most widely used PROs are based on simple questions referring to common daily activities, and they are intended to be useful for all types of CIPN, although it is well known that different neurotoxic drugs have remarkably diverse neurotoxicity profiles.[1,2] However, one of the most widely used questionnaires, the QLQ-EORTC CIPN20, after validation analysis based on clinical trials data including more than 1000 patients, failed to show a stable subscale structure, while its use as a simple additive checklist resulted in acceptable validity.[13] Because this was the largest validation study of this type, it is possible that similar results might be obtained when testing other PRO questionnaires.

This secondary analysis was performed in order to test the criterion validity of each self-reported item selected by neurologists with long-lasting experience in the assessment of CIPN among a list of questions used to create a new, Rasch-built CIPN questionnaire[14] currently under validation. Since answers to simple questions, such as those used in this study and those forming the basis for PRO instruments, are likely to be influenced by several, convergent events/conditions, possible misinterpretations may occur when a patient reports daily life impairment to the treating oncologist. Therefore, a formal assessment of the relationship among patients' perception of CIPN severity, oncologists' interpretation of patients' report and actual neurological impairment might contribute to a more rationale selection of the optimal assessment to be used in clinical trials. However, this can also have important implications in daily clinical practice providing oncologists more precise understanding of the possible significance of patients' answers.

More reliable information on the real significance of patients' answers can be achieved only through a formal comparison of patients' self-assessment, oncologist's interpretation of their reports

and a neurological assessment. This complex analysis is not yet available, and it was the core objective of the current secondary analysis.

As a first observation, it should be noted that in our study population of patients with CIPN where we analyzed the *presence* (and not the *severity*) of neurological damage, there was a wide representation of both sensory and motor impairment, frequently occurring in the same patient, although from the original CI-PeriNoms study we know that in our study population motor impairment was less severe than sensory impairment, reflecting the typical CIPN patients.[13] However, the present analysis indicates that the reported absence of daily life activity limitation is already frequently associated with some degree of neurological impairment, particularly on the sensory side.

It is also remarkable that the interpretation of patients' report provided by the panel of oncologist with high level of attention to CIPN is poorly consistent with the actual neurological impairment, thus raising additional concerns, particularly for the possible implications in daily clinical practice and for decisions on treatment modification.

In order to test if any drug-related effect could be linked to patients' perception and oncologists' interpretation, we compared two subgroups with nearly exclusive sensory impairment due to platinum drugs administration vs sensorimotor damage due to taxanes. The drug-related differences evidenced in our analysis suggest that patients' answers to simple questions should be checked drug-by-drug in order to be more accurate, and this may suggest the need for "drug-specific" questionnaires, not yet available in validated forms. These drug-specific questionnaires, focused on more relevant effects of each drug class, might improve the capacity to detect significant effects of therapeutic intervention in CIPN avoiding the "dilution effect" of non-sensitive or non-relevant questions.

While our previously reported clinical study was performed in a highly selected, fully characterized population, with repeated check of each patients' self-assessment and neurological examination,[13] and oncologists' opinion were collected in a completely blinded fashion, the present results cannot be directly translated into CIPN assessment during treatment. In fact, our data come from a population of patients with *stable* CIPN, and thus our results may not totally apply to CIPN *development* during treatment. In this latter setting, we suspect that patients' answers might be even more prone to misinterpertation, since during chemotherapy, patients may be exposed to a wider range of confounding conditions unrelated to CIPN, but that limit daily activities and overlap CIPN effects (eg, infections, anemia, fatigue, depression and "chemofog").

In conclusion, we demonstrated that the interpretation of patients' report provided by the panel of oncologists is poorly consistent with the actual neurological impairment and that activity limitations capture more than simple impairments and reflect a broader impact than impairment measures. These observations form a critical basis for further research on the core set of outcome measures needed for future CIPN trials and at the same time raise concern on the current use of the available PROs alone as main endpoints in CIPN trials.

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