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Review

Chemotherapy-Induced Peripheral Neurotoxicity assessment: A critical revision of the currently available tools

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ABSTRACT

Chemotherapy-Induced Peripheral Neurotoxicity (CIPN) is a frequent, potentially severe and dose-limiting side-effect of cancer treatment. Despite its clinical relevance that limits the use of several antineoplastic agents and even the future development of new anticancer drugs, several crucial aspects of CIPN remain unsolved, one of which is how to assess its occurrence and severity in the most effective and reliable way.

CIPN severity is generally assessed using Common Toxicity Criteria (CTC) scales, although it is well known that significant inter-observer disagreement exists using these scales. Moreover, most CTC scores mix impairment, disability and quality of life measures, which could lead to misinterpretation of the results and unpredictable under- or overestimation of the effect. This uncertainty may lead to different interpretations of the results of the same clinical trials by clinicians and also by regulatory agencies. The use of other types of scale based on clinical and instrumental examinations, or the use of self-administered questionnaires for patients, has not yet really improved the accuracy of CIPN assessment, although some of these tools are promising and deserve to be further validated. As a result, there is a general recognition that CIPN has still not been properly assessed and that improvements should be made.

In this review, the available data regarding the different tools used to assess CIPN will be revised and their features will be critically examined, with a special focus on their reliability and reproducibility across examiners and, when available, through direct comparison.

1. Introduction

In routine practice, Chemotherapy-Induced Peripheral Neurotoxicity (CIPN) is evaluated using clinical and paraclinical parameters. The role of instrumental examinations in CIPN patients is questionable in clinical practice and it is our opinion that they are really useful only in unusual cases or, sometimes, in the follow-up of selected patients with a particularly severe CIPN. The reasons for this limited usefulness of the electroneurography (ENG) of peripheral nerves are several, mostly related to the localisation of the primary site of toxic action of the drugs that prevents reliable investigation (e.g.

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the primary dorsal root ganglia damage with platinum compounds, with delayed involvement of the peripheral nerves explored by ENG) or to the type of nerve fibres' involvement (e.g. small myelinated and unmyelinated fibres damage during bortezomib treatment, while ENG can only detect large myelinated fibres' impairment). Electromyography (EMG) is painful, disturbing for the patients and it gives only a non-quantitative assessment of motor units' activity damage in the rare cases where motor impairment is severe and, therefore, already easily evaluable clinically. Semi-quantitative assessment of sensory threshold or of muscle strength has also occasionally been proposed, but standardisation of the instruments and of the methods to be used has never been achieved. Therefore, CIPN assessment should be based on effective and reliable clinical methods. Usually, objective assessment of neuropathic signs is performed with bedside clinical examinations (e.g. search for sensory and motor abnormalities, deep tendon reflex changes, orthostatic hypotension and constipation). Recently, increased attention has been focused on the patients' perception of CIPN severity and effects, and several patient-reported questionnaires have been developed to overcome the obvious limitation of the patient interview that is part of the routine medical examination.

The following sections will summarise, in a non-systematic revision, the background and the main characteristics of the scales most widely used until now to grade CIPN, with particular reference to their ability to detect and report the proposed aspects of CIPN and the exclusion of pain-specific scales because they have already been extensively reviewed in the recent literature, and none of them has been designed or validated to assess the occurrence of neuropathic pain in CIPN.[1]

2. Common Toxicity Criteria (CTC) scales

The following are the available CTC scales developed by established organisations and commonly used in clinical practice to report CIPN (Table 1).

2.1. World Health Organization (WHO) scale

In 1979, on the initiative of the WHO, recommendations were developed for standardised approaches to the recording of patients' baseline data, tumour characteristics, laboratory and radiological data, tumour response and treatment-related toxicity.[2]

The peripheral neuropathy section includes the occurrence of paraesthesias or changes in deep tendon reflexes and the extent of motor loss as parameters. These recommendations, already endorsed by a number of organisations, were proposed for international acceptance, but their use in the assessment of CIPN never gained widespread use.

2.2. Eastern Cooperative Oncology Group (ECOG) scale

In 1974 the ECOG developed a set of standardised toxicity criteria which has been used with minor modifications in all ECOG studies and publications since that time. The last review of these criteria took place in 1982.[3]

The peripheral neuropathy section of the ECOG scale includes more parameters than the WHO scale, such as autonomic symptoms (i.e. constipation and bladder dysfunction) and introduced the important concept of 'disabling' sensory loss.

2.3. National Cancer Institute – Common Toxicity Criteria (NCI-CTC)

In 1983 the Cooperative Oncology groups in North America and Canada agreed to establish a set of definitions for the classification and grading of toxicity named Common Toxicity Criteria (CTC). In these scales neurosensory and neuromotor parameters were included, with particular relevance to the interference with function.

In 1998 the NCI revised and expanded the CTC (version 2.0), including more than 260 individual adverse events regarding 24 different organs or physiological systems.[4]

The NCI-CTC was further expanded in 2003 to include late events, surgical effects and paediatric criteria (version 3.0), and the general guidelines for the construction of CTC grading were revised. Only minimal changes were adopted for the assessment of CIPN, but in this version the cranial neuropathies of each individual nerve were separately scored.[5]

2.4. Ajani scale

In 1990 the criteria were developed by members of the Chemotherapy Working Group and of the Departments of Medical Specialties and Neuro-Oncology in the Houston Cancer Center.[6] The prototype of this scale was based on the WHO criteria and on unpublished in-house criteria generated by qualified medical subspecialists for several organ systems. These criteria emphasised that each grade should represent a specific morbidity range that provides parameters for future therapy (WHO criteria did not assign any clinical significance to each toxicity grade).

Efforts were made to increase objective information and to normalise each grade of toxicity in different organ systems to reflect toxicity levels of similar importance. The data were based on the detailed interviews not only with the patients but also with their relatives and on accurate documentation encouraging patients to record the daily events.

For CIPN assessment, sensory and motor symptoms were considered, evaluating also the presence of functional abnormalities with a focus on the ability to ambulate.

2.5. Comparison among different CTC scales

In 1993 Brundage et al.[7] tried to determine the reliability of NCI-CTC and WHO scales using a clinical simulation of 12 patients in the final week of therapy with cisplatin and radiation. Repeated cases were presented by different simulators and inter-rater agreement across seven manager raters was calculated using the Kappa statistic,[7] while intra-rater agreement was calculated using Kappa over-repeated cases. Modest levels of inter- and intra-rater reliability were demonstrated in this study, primarily due to the differences in the interpretation of collected data and in the application of toxicity criteria. Despite the fact that NCI-CTC detected more

Table 1 – Common Toxicity Criteria scales

Adverse event	Grade				
	0	1	2	3	4
World Health Organisation (WHO) Scale (1979)[a]					
Neuropathy – motor	Normal	Subjective weakness	Mild objective weakness	Marked weakness	Paralysis
Neuropathy – sensor	Normal	Decreased tendon reflexes or paraesthesias	Severe paraesthesias	Intolerable paraesthesias	-
Eastern Cooperative Oncology Group (ECOG) scale (1982)[b]					
Neuropathy – motor	Normal	Subjective weakness	Mild objective weakness	Severe weakness	Respiratory dysfunction secondary to weakness, paralysis confining patient to bed/wheelchair
Neuropathy – sensory	Normal	Decreased deep tendon reflexes or mild paraesthesias	Absent deep tendon reflexes, severe paraesthesias	Disabling sensory loss, severe neuropathic pain	
Neuropathy – autonomic	Normal	Mild constipation	Severe constipation	Bladder dysfunction, obstipation	Obstipation requiring surgery
National Cancer Institute – Common Toxicity Criteria 2.0 (NCI-CTC 2.0) (1998)[c]					
Neuropathy – motor	Normal	Subjective weakness but not objective findings	Mild objective weakness interfering with function but not interfering with ADL	Objective weakness interfering with ADL; bracing or assistance to walk (e.g. cane or walker) indicated	Paralysis
Neuropathy – sensory	Normal	Loss of tendon reflex or paraesthesias (including tingling) but not interfering with function	Objective sensory loss or paraesthesias (including tingling) interfering with function but not interfering with ADL	Sensory loss or paraesthesias interfering with ADL	Permanent sensory loss that interferes with function

Adverse event	Grade					
	0	1	2	3	4	5
National Cancer Institute – Common Toxicity Criteria 3.0 (NCI-CTC 3.0) (2003)[c]						
Neuropathy: cranial select for each cranial nerve listed below the most appropriate description • CN I: smell • CN II: vision • CN III: pupil, upper eyelid, extra ocular movements • CN IV: downward, inward movement of eye • CN V: motor-jaw muscles; sensory-facial • CN V: lateral deviation of eye • CN VII: motor-face, sensory-taste • CN VIII: hearing and balance • CN IX: motor-pharynx; sensory-ear, pharynx, tongue • CN X: motor-palate; pharynx, larynx • CN XI: motor sternocleidomastoid and trapezius • CN XII: motor-tongue	Asymptomatic, normal on exam/ testing	Asymptomatic, detected on exam/testing only	Symptomatic, not interfering with ADL	Symptomatic, interfering with ADL	Life-threatening; disabling	Death

(*continued on next page*)

Table 1 – (continued)

Adverse event	Grade					
	0	1	2	3	4	5
Neuropathy: motor	Normal	Asymptomatic, weakness on exam testing only	Symptomatic weakness interfering with functioning but not interfering with ADL	Weakness interfering with ADL; bracing or assistance to walk (e.g. cane or walker) indicated	Life threatening disabling (e.g. paralysis)	Death
Neuropathy: sensory	Normal	Asymptomatic loss of tendon reflex or paraesthesias (including tingling) but not interfering with function	Sensory alterations or paraesthesias interfering with function but not interfering with ADL	Sensory alterations or paraesthesias interfering with ADL	Disabling	Death

Adverse event	Grade				
	0	1	2	3	4
Ajani scale (1990)[d]					
Neuropathy – motor	Normal	Mild or transient muscle weakness	Persistent moderate weakness but ambulatory	Unable to ambulate	Complete paralysis
Neuropathy – sensory	Normal	Paraesthesias. Decreased deep tendon reflexes	Mild objective abnormality, absence of deep tendon reflexes, mild to moderate functional abnormality	Severe paraesthesias, moderate objective abnormalities, severe functional abnormalities	Complete sensory loss, loss of function

[a] Adapted from the original version. Follow this link to the organisation site: http://www.who.int/.
[b] Adapted from the original version. Follow this link to the organisation site: http://ecog.dfci.harvard.edu/.
[c] Adapted from the original version. Follow this link to the organisation site: http://www.cancer.gov/.
[d] Adapted from the original version. See Ajani et al.[5]

Table 2 – Functional Assessment of Cancer Therapy/Gynaecologic Oncology Group-Neurotoxicity (FACT/GOG-Ntx) and Functional Assessment of Cancer Therapy-Taxane (FACT-Tax) scales (2003).

	Not at all	A little bit	Somewhat	Quite a bit	Very much
1. Physical well-being (PWB)					
– I have a lack of energy	0	1	2	3	4
– I have nausea	0	1	2	3	4
– Because of my physical condition, I have trouble meeting the needs of my family	0	1	2	3	4
– I have pain	0	1	2	3	4
– I am bothered by side-effects of treatment	0	1	2	3	4
– I feel ill	0	1	2	3	4
– I am forced to spend time in bed	0	1	2	3	4
2. Social Well-Being (SWB)					
– I feel close to my friends	0	1	2	3	4
– I get emotional support from my family	0	1	2	3	4
– I get support from my friends	0	1	2	3	4
– My family has accepted my illness	0	1	2	3	4
– I am satisfied with family communication about my illness	0	1	2	3	4
– I fell close to my partner (or the person who is my main support)	0	1	2	3	4
– I am satisfied with my sex life	0	1	2	3	4
3. Emotional Well-Being					
– I feel sad	0	1	2	3	4
– I am satisfied with how I am coping with my illness	0	1	2	3	4
– I am losing hope in the fight against my illness	0	1	2	3	4
– I fell nervous	0	1	2	3	4
– I worry about dying	0	1	2	3	4
– I worry that my condition will get worse	0	1	2	3	4
4. Functional Well-Being (FWB)					
– I am able to work (include work at home)	0	1	2	3	4
– My work (include work at home) is fulfilling	0	1	2	3	4
– I am able to enjoy life	0	1	2	3	4
– I have accepted my illness	0	1	2	3	4
– I am sleeping well	0	1	2	3	4
– I am enjoying the things I usually do for fun	0	1	2	3	4
– I am content with the quality of my life right now	0	1	2	3	4
5. Taxane subscale (Tax)					
5a. Neurotoxicity (Ntx) component					
– I have numbness or tingling in my hands	0	1	2	3	4
– I have numbness or tingling in my feet	0	1	2	3	4
– I feel discomfort in my hands	0	1	2	3	4
– I feel discomfort in my feet	0	1	2	3	4
– I have joint pain or muscle cramps	0	1	2	3	4
– I fell weak all over	0	1	2	3	4
– I have trouble hearing	0	1	2	3	4
– I get a ringing or a buzzing in my ears	0	1	2	3	4
– I have trouble buttoning buttons	0	1	2	3	4
– I have trouble feeling the shape of small objects when they are in my hand	0	1	2	3	4
– I have trouble walking	0	1	2	3	4
5b. Taxane component					
– I feel bloated	0	1	2	3	4
– My hands are swollen	0	1	2	3	4
– My legs or feet are swollen	0	1	2	3	4
– I have pain in my fingertips	0	1	2	3	4
– I am bothered by the way my hands or nails look	0	1	2	3	4

These scales consist of a 43-item self-reported questionnaire, divided into three groups: the first one is a 27-item general assessment of quality of life (FACT-G), the second one is a 11-item neurotoxicity subscale (Ntx subscale) and the last 5 items are included in the FACT-Tax scale. Adapted from the original version. Follow this link to the organisation site: http://www.gog.org/.

acute toxic effects than WHO criteria, no clear advantage was observed with either scale for those toxic effects common to both scales. Neither the NCI-CTC nor the WHO scale demonstrated a clear superiority in reliability.

Postma et al.[8] evaluated the agreement among observers in the interpretation of the WHO, ECOG, Ajani and NCI-CTC 2.0 scales in 37 patients. The highest percentage of grade 1, grade 2 and grade 3 CIPN was scored when employing, respectively, the WHO, Ajani and NCI-CTC 2.0 scales. Inter-observer agreement across all grades of severity ranged from 45.9% (NCI-CTC 2.0) to 56.7% (Ajani), 75.6% (ECOG) and 83.8% (WHO). Based on the intraclass correlation coefficient values[8] the agreement for the full score ranged from 'poor to fair' (Ajani) to 'substantial' (ECOG) and 'moderate' (NCI-CTC 2.0, WHO). Overall, in this study the use of the NCI-CTC 2.0 criteria appeared to result in a greater frequency of grade 3 peripheral neuropathy ratings compared with the other scales. The grade 3 definitions 'severe functional abnormalities' (Ajani), 'disabling sensory loss' (ECOG) and 'intolerable paraesthesias' (WHO) seemed to have a higher threshold than 'severe objective sensory loss or paraesthesias that interfere with the function' (NCI-CTC). The majority of patients with grade 1 neuropathy were scored using the WHO scale, possibly because of the 'relative paucity of sensory parameters in this scale', while grade 2 patients were more frequently scored using the Ajani scale.

Therefore, it can be concluded that CTC scales are quick to use and apparently easy to administer, but inter-observer disagreement is frequent[8] and they are most useful for carrying out a screening procedure and for choosing which patients need a neurological examination rather than for giving a true evaluation of the extent and severity of CIPN.

3. Functional assessment

3.1. *Functional Assessment of Cancer Therapy/ Gynaecologic Oncology Group (GOG)-neurotoxicity (FACT/ GOG-Ntx)*

In 1998 the GOG, collaborating with the Author of the Functional Assessment of Chronic Illness Therapy (FACIT) Measurement System, developed the FACT/GOG-Ntx subscale.[9] The FACT/GOG-Ntx is a 38-item self-reported questionnaire consisting of two components: a 27-item general measure of quality of life (FACT-G) and a 11-item neurotoxicity subscale (Ntx subscale) targeting symptoms and patients' concerns thought to be specifically associated with CIPN and also covering activity impairment (Table 2).

In the first study, this subscale was administered to 134 patients asking them to rate each item concerning signs and symptoms occurring during the previous 7 d.[9] CIPN was also independently assessed with the NCI-CTC 2.0 by a clinical investigator. The Ntx subscale showed good internal reliability (Cronbach's alpha average = 0.83). The construct validity was assessed by calculating the Spearman rank correlation coefficient between constituent items and subscale scores, and it appeared that the items on sensory neuropathy had an increased correlation with the subscale scores, reaching 0.6–0.8 by the end of treatment.

The study evidenced that the psychometric properties of the subscale were primarily attributable to the performance of the sensory neuropathy scores, suggesting that a reduced

Table 3 – Peripheral Neuropathy Scale (PNS) (2004). Part one: Functional Status Scale: Please, rate each item selecting the number which best applies to you: 1 = 'not at all', 2 = 'a little', 3 = 'quite a bit', 4 = 'very much'. Part two: Peripheral Neuropathy Scale: Please, rate each item selecting the number which best applies to you: 1 = 'not at all', 2 = 'a little', 3 = 'quite a bit', 4 = 'very much'.

Functional Status Scale				
(A) Physical function				
1. Do you need help with eating, dressing, washing, or using toilet?	1	2	3	4
2. Do you have to stay indoors most or all of the day?	1	2	3	4
3. Are you in bed or in chair most of the day?	1	2	3	4
4. Do you have trouble either in walking a short distance or climbing one flight of stairs?	1	2	3	4
5. Do you have trouble bending, lifting or stooping?	1	2	3	4
6. Do you have trouble either taking a walk or climbing a few flights of stairs?	1	2	3	4
(B) Role function				
1. Does your condition keep you from working at a job or doing household jobs?	1	2	3	4
2. Are you limited in any way doing your work or household jobs?	1	2	3	4
Peripheral Neuropathy Scale (PNS)				
1. Do you have difficulty in buttoning buttons?	1	2	3	4
2. Do you feel any stiffness or tightness in your hands?	1	2	3	4
3. Do you feel any stiffness or tightness in your feet?	1	2	3	4
4. Do you feel clumsy?	1	2	3	4
5. Do you fell any discomfort in your hands?	1	2	3	4
6. Do you fell any discomfort in your feet?	1	2	3	4
7. When holding an object in your hand(s), are you able to feel this shape?	1	2	3	4
8. Do you have tingling in your hands?	1	2	3	4
9. Do you have tingling in your feet?	1	2	3	4
10. Do you have numbness in your hands?	1	2	3	4
11. Do you have numbness in your feet?	1	2	3	4

Adapted from the original version. See Almadrones et al.[11]

Table 4 – Oxaliplatin-associated Neuropathy Questionnaire (2005).

– Do you have...			If you had symptoms during last cycle...									
			... how much of the symptoms did you have?[a]					... did the symptoms affect your daily activities?[b]				
1. UPPER EXTREMITY SYMPTOMS												
...tingling (pin and needles)?	No	Yes	1	2	3	4	5	1	2	3	4	5
... numbness?	No	Yes	1	2	3	4	5	1	2	3	4	5
... difficulty in telling the difference between rough and smooth surfaces?	No	Yes	1	2	3	4	5	1	2	3	4	5
... difficulty in feeling hot things?	No	Yes	1	2	3	4	5	1	2	3	4	5
... difficulty in feeling cold things?	No	Yes	1	2	3	4	5	1	2	3	4	5
... a greater than normal sense of touch (i.e. putting on gloves)?	No	Yes	1	2	3	4	5	1	2	3	4	5
... burning pain or discomfort without cold?	No	Yes	1	2	3	4	5	1	2	3	4	5
... burning pain or discomfort with cold?	No	Yes	1	2	3	4	5	1	2	3	4	5
... difficulty in identifying objects in your hand (i.e. coins)	No	Yes	1	2	3	4	5	1	2	3	4	5
... involuntary hand movements?	No	Yes	1	2	3	4	5	1	2	3	4	5
2. LOWER EXTREMITY SYMPTOMS												
...tingling (pin and needles)?	No	Yes	1	2	3	4	5	1	2	3	4	5
... numbness?	No	Yes	1	2	3	4	5	1	2	3	4	5
... difficulty in telling the difference between rough and smooth surfaces?	No	Yes	1	2	3	4	5	1	2	3	4	5
... difficulty in feeling hot things?	No	Yes	1	2	3	4	5	1	2	3	4	5
... difficulty in feeling cold things?	No	Yes	1	2	3	4	5	1	2	3	4	5
... a greater than normal sense of touch (i.e. discomfort with socks)?	No	Yes	1	2	3	4	5	1	2	3	4	5
... burning pain or discomfort without cold?	No	Yes	1	2	3	4	5	1	2	3	4	5
... burning pain or discomfort with cold?	No	Yes	1	2	3	4	5	1	2	3	4	5
... a feeling of heaviness in your legs?	No	Yes	1	2	3	4	5	1	2	3	4	5
3. ORAL/FACIAL SYMPTOMS												
... jaw pain?	No	Yes	1	2	3	4	5	1	2	3	4	5
... eyelids dropping?	No	Yes	1	2	3	4	5	1	2	3	4	5
... throat discomfort?	No	Yes	1	2	3	4	5	1	2	3	4	5
... ear pain?	No	Yes	1	2	3	4	5	1	2	3	4	5
... tingling in mouth?	No	Yes	1	2	3	4	5	1	2	3	4	5
... difficulty with speech?	No	Yes	1	2	3	4	5	1	2	3	4	5
... burning or discomfort in your eyes?	No	Yes	1	2	3	4	5	1	2	3	4	5
... loss of any vision?	No	Yes	1	2	3	4	5	1	2	3	4	5
... feeling shock/pain down back?	No	Yes	1	2	3	4	5	1	2	3	4	5
... problems with breathing?	No	Yes	1	2	3	4	5	1	2	3	4	5

Adapted from the original version. See Leonard et al.[12]

a In order to rate this item, a progressive scale is provided, in which: **1 stands for 'Hardly any', 5 stands for ' Very much'.**

b In order to rate this item, a progressive scale is provided, in which: **1 stands for 'Hardly at all bothered', 5 stands for 'Extremely bothered'.**

subscale consisting of four specific sensory items may be as effective as the complete scale when investigating predominantly sensory CIPN. This scale is not really a functional scale, since items also involve impairment and symptoms perceived by the patients.

In 2003 Calhoun et al.[10] performed a study in 2 groups composed of ovarian cancer patients with CIPN (43 patients) or of chemotherapy-naïve women (56 patients). The 11-item Ntx subscale significantly differentiated the two groups at baseline and in the follow-up, demonstrating effective assessment of the severity of CIPN on health-related quality of life (QoL). The scale also had a moderate but significant correlation with several objective measures of neuropathy, including sensory, motor and reflex changes.

3.2. *Functional Assessment of Cancer Therapy-Taxane (FACT-Taxane)*

In 2003 Cella et al.[11] tested in 143 patients the FACT-Taxane (Table 2), a self-reported instrument including the FACT-G items plus a 16-item taxane subscale, which combined the previously described 11-item Ntx subscale and 5 additional questions assessing symptoms related to arthralgia, myalgia and skin discoloration. Also the FACT-Taxane has the same limitation of the FACT/GOG-Ntx, with mixed functional, impairment and symptoms items. The scale demonstrated internal consistence reliability at each of the three assessment times (the Cronbach's alpha coefficient for the 16-item taxane subscale range was 0.84–0.88), known group validity and responsiveness to change over time (see Table 3).

3.3. *Peripheral neuropathy scale (PNS)*

In 2004 Almadrones et al.[12] adapted two existing scales to evaluate functional status and peripheral neuropathy in a population of ovarian cancer patients and generated the PNS. The original neurological 8-item scale was expanded to 11 items, separating hands and feet, and originally tested in 88 patients. Cronbach's coefficient alpha for internal consistency was 0.91 before and 0.89 after chemotherapy. The evaluation of the PNS items evidenced that items 9 and 15 had a particularly low item-total score correlation and required rewording. Criterion validity was also assessed by examining the convergence of the peripheral neuropathy scale score in the GOG toxicity criteria with the PNS, and by using a rank correlation test and demonstrating a significant association between PNS and GOG-CTC. Symptoms and impairment items are present in the scale, and functional limitation is more clearly collected by the first (i.e. non-neuropathy-specific) part than by the part of the scale specifically designed to assess CIPN.

3.4. *Oxaliplatin-associated neuropathy questionnaires*

In 2005 Leonard et al.[13] developed a drug-specific questionnaire (Table 4), designed to be filled out by a research nurse during a face-to-face interview with the patient, and it was administered to 86 patients. The patients were queried about the symptoms occurring in the upper and lower extremities and in the oro-facial zone and they were asked whether or not they had each specific symptom. In cases where there was a positive answer, they had to separately assess the

Table 5 – Oxaliplatin neurological toxicity specific grading (1992).

Grade	Symptoms
1	Paraesthesia of short duration (<7 d)
2	Paraesthesia lasting 8–14 d
3	Paraesthesia persisting in the intercycle period
4	Paraesthesia causing functional impairment

Adapted from the original version. See Levi et al.[13]

Table 6 – Scale for Chemotherapy-Induced Long Term Neurotoxicity (SCIN) (2006).

Subscales	Items	Answers			
		Not at all	A little	Quite a bit	Very much
1. Paraesthesias	1a. Have you suffered from pain and tingling in your feet/toes?	0	1	2	3
	1b. Have you suffered from pain and tingling in your hands/fingers?	0	1	2	3
2. Raynaud	2a. Have you suffered from numb or cold feet or toes?	0	1	2	3
	2b. Have you suffered from numb or cold hands or fingers?	0	1	2	3
3. Ototoxicity	3a. Have you suffered from ringing in your ears?	0	1	2	3
	3b. Have you suffered from reduced hearing?	0	1	2	3

Adapted from the original version. See Oldenburg et al.[14]

Table 7 – Patient Neurotoxicity Questionnaire (PNQ) (2006).

Oxaliplatin[a]	
Item 1 Please indicate by placing an X in the description that best applies to you	A. I have **no** numbness, pain, burning, tingling or change in my sense of touch in my hands/fingers, or feet/toes or mouth area B. I have **mild** numbness, pain, burning, tingling or change in my sense of touch in my hands/fingers, or feet/toes or mouth area. This does not interfere with my activities of daily living. C. I have **moderate** numbness, pain, burning, tingling or change in my sense of touch in my hands/fingers, or feet/toes or mouth area. This does not interfere with my activities of daily living. D*. I have **moderate to severe** numbness, pain, burning, tingling or change in my sense of touch in my hands/fingers, or feet/toes or mouth area. This interferes with my activities of daily living. E*. I have **severe** numbness, pain, burning, tingling or change in my sense of touch in my hands/fingers, or feet/toes or mouth area. It completely prevents me from doing most activities of daily living.
Item 2 Please indicate by placing an X in the description that best applies to you	A. I have **no** difficulty in swallowing, breathing, drinking or chewing food, or muscle spasms in my mouth/jaws, hands/fingers or feet/toes. B. I have a **mild difficulty** in swallowing, breathing, drinking or chewing food, or muscle spasms in my mouth/jaws, hands/fingers or feet/toes. This does not interfere with my activities of daily living. C. I have **moderate difficulty** in swallowing, breathing, drinking or chewing food, or muscle spasms in my mouth/jaws, hands/fingers or feet/toes. This does not interfere with my activities of daily living. D*. I have **moderate to severe difficulty** in swallowing, breathing, drinking or chewing food, or muscle spasms in my mouth/jaws, hands/fingers or feet/toes. This interferes with my activities of daily living. E*. I have **severe difficulty** in swallowing, breathing, drinking or chewing food, or muscle spasms in my mouth/jaws, hands/fingers or feet/toes. It completely prevents me from doing most activities of daily living.
*My ability to: If you have indicated a description that states 'moderate to severe' or 'severe' in one or both items above, please indicate by placing an X or writing in the space provided which activity or activities have been interfered with, as a result of therapy	Button clothes Use a knife Use a fork Use a spoon Swallowing Open doors Zippers Put in or remove contact lenses Dial or use telephone Operate a remote control Use other eating utensils Other eating utensils, etc Fasten buckles Sleep Climb stairs Type on keyboard Eating/chewing Write Walk Put on jewellery Knit Drinking liquids Sew Work Tie shoes Drive Shortness of breath Work or perform activities of importance to me, specify: ---------- ---------- ---------- ----------

(*continued on next page*)

Table 7 – (continued)

Taxanes, cisplatin and carboplatin[a]	
Item 1 Please indicate by placing an X in the description that best applies to you	A. I have **no** numbness, pain or tingling in my hands or feet. B. I have **mild** tingling, pain or numbness in my hands or feet. This does not interfere with my activities of daily living. C. I have **moderate** tingling, pain or numbness in my hands or feet. This does not interfere with my activities of daily living. D*. I have **moderate to severe** tingling, pain or numbness in my hands or feet. This interferes with my activities of daily living. E*. I have **severe** tingling, pain or numbness in my sense of touch in my hands or feet. It completely prevents me from doing most activities of daily living.
Item 2 Please indicate by placing an X in the description that best applies to you	A. I have **no weakness** in my arms and legs. B. I have a **mild weakness** in my arms or legs. This does not interfere with my activities of daily living. C. I have **moderate difficulty** in swallowing, breathing, drinking or chewing food, or muscle spasms in my mouth/jaws, hands/fingers or feet/toes. This does not interfere with my activities of daily living. D*. I have **moderate to severe weakness** in my arms or legs. This interferes with my activities of daily living. E*. I have **severe weakness** in my arms and legs. It completely prevents me from doing most activities of daily living.
*My ability to: If you have indicated a description that states 'moderate to severe' or 'severe' in one or both items above, please indicate by placing an X or writing in the space provided which activity or activities have been interfered with, as a result of therapy	Button clothes Use a kinfe Use a fork Use a spoon Put in or remove contact lenses Open doors Dial or use telephone Operate a remote control Use other eating utensils Other eating utensils, etc Fasten buckles Sleep Climb stairs Type on keyboard Write Walk Put on jewellery Knit Sew Work Tie shoes Drive Perform activities of importance to me, specify:- -

a Adapted from the original version. See Hauser et al.[15]

severity of the symptom and the effect on daily activities. The validity of the questionnaire was not formally assessed.

Another questionnaire was specifically developed and used to evaluate oxaliplatin-induced CIPN by Levi et al.[14] The interpretation of the results obtained with this scale is, however, complicated by the co-existence of items describing the duration of symptoms (without any descriptive discrimination between acute and chronic toxicities) and their impact on functional activities (Table 5).

3.5. *Scale for Chemotherapy-Induced Long Term Neurotoxicity (SCIN)*

The SCIN is a brief self-reported scale[15] based on three subscales (neuropathy, Raynaud's phenomenon and ototoxicity, with two items in each) proposed as a single scale reflecting 'overall-neurotoxicity' (Table 6). Single items were summed to give a score between 0 and 6, so that it is possible to divide the patients into low-score ($\leqslant 3$) and high-score groups ($\geqslant 4$).

Table 8 – European Organisation of Research and Treatment of Cancer (EORTC) QLQ-C30 and QLQ-CIPN20. Patients sometimes report that they have these following symptoms or problems. Please indicate the extension to which you have experienced them during the past week. Answer circling the number that best applies to you.

ANSWER ACCORDING TO YOUR GENERAL SITUATION	Not at all	A little	Quite a bit	Very much
1. Do you have any trouble doing strenuous activities such as carrying a heavy shopping bag or a suitcase?	1	2	3	4
2. Do you have any trouble taking a long walk?	1	2	3	4
3. Do you have any trouble taking a short walk outside of the house?	1	2	3	4
4. Do you need to stay in bed or a chair during the day?	1	2	3	4
5. Do you need help with eating, dressing, washing yourself or using the toilet?	1	2	3	4
DURING THE PAST WEEK	**Not at all**	**A little**	**Quite a bit**	**Very much**
6. Were you limited in doing either your work or other daily activities?	1	2	3	4
7. Were you limited in pursuing your hobbies or other leisure time activities?	1	2	3	4
8. Were you short of breath?	1	2	3	4
9. Have you had pain?	1	2	3	4
10. Did you need to rest?	1	2	3	4
11. Have you had trouble sleeping?	1	2	3	4
12. Have you felt weak?	1	2	3	4
13. Have you lacked appetite?	1	2	3	4
14. Have you felt nauseated?	1	2	3	4
15. Have you vomited?	1	2	3	4
16. Have you been constipated?	1	2	3	4
17. Have you had diarrhoea?	1	2	3	4
18. Were you tired?	1	2	3	4
19. Did pain interfere with your daily activities?	1	2	3	4
20. Have you had difficulty in concentrating on things such as reading a newspaper or watching television?	1	2	3	4
21. Did you feel tense?	1	2	3	4
22. Did you worry?	1	2	3	4
23. Did you feel irritable?	1	2	3	4
24. Did you feel depressed?	1	2	3	4
25. Have you had difficulty in remembering things?	1	2	3	4
26. Has your physical condition or medical treatment interfered with your family life?	1	2	3	4
27. Has your physical condition or medical treatment interfered with your social activities?	1	2	3	4
28. Has your physical condition or medical treatment caused you financial difficulties?	1	2	3	4

FOR THE FOLLOWING TWO QUESTIONS, PLEASE CIRCLE THE NUMBER BETWEEN 1 (= very poor) AND 7 (= excellent) THAT BEST APPLIES TO YOU

29. How would you rate your overall health during the past week?	1	2	3	4	5	6	7
30. How would you rate your overall quality of life during the past week?	1	2	3	4	5	6	7

DURING THE PAST WEEK	Not at all	A little	Quite a bit	Very much
31. Did you have tingling fingers or hands	1	2	3	4
32. Did you have tingling toes or feet?	1	2	3	4
33. Did you have numbness in your fingers or hands?	1	2	3	4
34. Did you have numbness in your toes or feet?	1	2	3	4
35. Did you have shooting or burning pain in your fingers or hands?	1	2	3	4
36. Did you have shooting or burning pain in your toes or feet?	1	2	3	4
37. Did you have cramp in your hands?	1	2	3	4
38. Did you have cramp in your feet?	1	2	3	4
39. Did you have problems standing or walking because of a difficulty in feeling the ground under your feet?	1	2	3	4
40. Did you have difficulty in distinguishing between hot and cold water?	1	2	3	4
41. Did you have a problem holding a pen, which made writing difficult?	1	2	3	4
42. Did you have difficulty in manipulating small objects with your fingers (for example, fastening small buttons)?	1	2	3	4

(*continued on next page*)

Table 8 – (continued)

DURING THE PAST WEEK	Not at all	A little	Quite a bit	Very much
43. Did you have difficulty in opening a jar or bottle because of weakness in your hand?	1	2	3	4
44. Did you have difficulty because your feet dropped downwards?	1	2	3	4
45. Did you have difficulty in climbing stairs or getting up out of a chair because of weakness in your legs?	1	2	3	4
46. Were you dizzy when standing up from a sitting or lying position?	1	2	3	4
47. Did you have blurred vision?	1	2	3	4
48. Did you have difficulty in hearing?	1	2	3	4
Please, answer the following question, only if you drive a car: 49. Did you have difficulty using pedals?	1	2	3	4
Please, answer the following question, only if you are a man: 50. Did you have difficulty in having or maintaining an erection?	1	2	3	4

Adapted from the original version. See Postma et al.[19] and http://www.eortc.be/.

The assessment of CIPN using this scale is limited to the occurrence of pain and tingling, and its usefulness is therefore questionable, at least as a single assessment method.

In 2005 Oldenburg et al.[15] used the SCIN as a part of a questionnaire survey (with 219 items) in 684 testicular cancer survivors. The SCIN showed good discriminant validity between the cisplatin-based chemotherapy group and the surgery or radiotherapy groups and a significant difference was observed in symptom severity between the high-dose and low-dose group scores. For convergent validity, only reduced hearing was tested. The significant association between the self-reported hearing loss and the audiometric measurements supports a high convergent validity for the SCIN hearing item.

In the same study, the SCIN was also compared with the 11-item FACT/GOG-Ntx, which includes four items nearly identical to the SCIN items. Both scales showed good psychometric qualities, although only for the FACT/GOG-Ntx was a test-retest reliability assessment performed.

3.6. *Patient Neurotoxicity Questionnaire (PNQ)*

In 2006 Hausheer et al.[16] developed the PNQ, a patient-based questionnaire for taxanes and cisplatin or carboplatin, and a modified version for oxaliplatin (Table 7). The PNQ comprises two items to identify the incidence and severity of sensory and motor disturbances. There is a specific demarcation between grades C and D, corresponding to the absence (grade $\leqslant$C) or presence (grade $\geqslant$D) of symptoms that interfere with activities of daily living.

The PNQ has been tested on a cohort of 300 patients by Shimozuma et al.[17]. In this study CIPN was assessed using two patient-based instruments (PNQ and FACT/GOG-Ntx) and one physician-based scale (NCI-CTC 2.0) and, according to the authors' evaluation, the PNQ had a greater sensitivity than the FACT/GOG-Ntx and NCI-CTC scales. Moreover, the PNQ evidenced a greater impact of CIPN on daily activities than that detected using the physician-based NCI-CTC. Both PNQ sensor and motor scores were significantly correlated with the FACT-GOG-Ntx ($r = 0.66$ and 0.51, respectively).

Evaluating the perspectives of 61 physicians regarding the utility and diagnostic value of PNQ[18] the scale was found to be a useful instrument with high acceptability for collecting information about CIPN. However, regarding making decisions about treatment modifications, this results were similar to those obtained with NCI-CTC 2.0.

Kuroi et al.[19] compared the PNQ and the NCI-CTC 2.0 in a prospective evaluation of CIPN in patients treated with weekly paclitaxel, suggesting a superior sensitivity for the former, especially for motor deficits, although further studies would be required to define which specific activities of daily living are affected or compromised. The importance of the PNQ is mostly linked to the presence for the first time of the formal assessment of the effect of CIPN on a pre-defined list of several activities of daily life.

4. Quality of life (QoL) assessment

The assessment of QoL in cancer patients is a relatively recent issue despite its clear clinical relevance given the increasing number of long-lasting cancer survivors achieved by improvement in cancer treatment. The use of general QoL scales in clinical trials and daily practice has the main aim of providing a more accurate evaluation of the well-being of the patients as well as of the benefits and side-effects that may result from medical intervention. However, only one of the available QoL scales has been specifically designed to evaluate the effect of CIPN.

4.1. *European Organisation of Research and Treatment of Cancer (EORTC) QLQ-CIPN20*

The EORTC QLQ-30 is a widely used cancer-specific questionnaire, designed to assess a core set of QoL issues and intended to be supplemented by additional condition- or treatment-specific modules.

In 2005 Postma et al.[20] developed a specific subscale, the QLQ-CIPN20 module (Table 8) to detect patients' experience of symptoms and functional limitations related to CIPN. A group of oncologists, haematologists, neuro-oncologists and an oncology research nurse, assisted by neurologists from other countries, produced a 33-item questionnaire, which was administered to 68 patients previously or currently treated with peripheral neurotoxic chemotherapeutic agents to

Table 9 – Total Neuropathy Score (TNS) and related reduced versions.

Parameter	SCORE				
	0	1	2	3	4
Sensory symptoms	None	Symptoms limited to finger or toes	Symptoms extends to ankle or wrist	Symptoms extends to knee or elbow	Symptoms above knees or elbows, or functionally disabling
Motor symptoms	None	Slight difficulty	Moderate difficulty	Require help/assistance	Paralysis
Autonomics symptoms	0	1	2	3	4 o 5
Pin sensibility	Normal	Reduced in finger/toes	Reduced up to wrist/ ankle	Reduced up to elbow/ knee	Reduced above elbow/knee
Vibration sensibility	Normal	Reduced in finger/toes	Reduced up to wrist/ ankle	Reduced up to elbow/ knee	Reduced above elbow/knee
Strength	Normal	Mild weakness	Moderate weakness	Severe weakness	Paralysis
Tendon reflex	Normal	Ankle reflex reduced	Ankle reflex absent	Ankle reflex absent, others reduced	All reflexes absent
Vibration sensation (QST vibration)	*Normal to 125% of ULN*	*126–150% of ULN*	*151–200% of ULN*	*201–300% of ULN*	*>300% of ULN*
Sural amplitude	Normal/reduced to <5% of LLN	76–95% of LLN	51–75% of LLN	26–50% of LLN	0–25% of LLN
Peroneal amplitude	Normal/reduced to <5% of LLN	76–95% of LLN	51–75% of LLN	26–50% of LLN	0–25% of LLN

QST = Quantitative Sensory Test; ULN = Upper Limit of Normal; LLN = Lower Limit of Normal

Note: In addition to the TNSc, parameters written in italics are used only in full-length TNS, underlined ones in TNSr.
Adapted from the original versions.[21–26]

rate the relevance of each issue. In a second phase 7 items were deleted, 4 were rephrased and condensed into 2 items, and 7 were condensed into 3 items to obtain the final 20-item questionnaire. The current version of the QLQ-CIPN20 has been validated and tested in several different languages. Based on pre-testing sample reliability Cronbach's alpha coefficient internal consistency was 0.82 for sensory subscale, 0.73 for motor subscale and 0.76 for autonomic subscale. It has been suggested that the QLQ-CIPN20 may be superior to the NCI-CTC 3.0 in detecting the effect of sensory impairment.[21]

5. Composite scales

Composite scales have recently been proposed to improve the accuracy, reliability and effectiveness of the assessment of CIPN and they have generally been developed by neurologists. However, despite the several theoretical advantages they may offer in the accurate neurological assessment of CIPN (e.g. discriminating among the different types of sensory impairment, giving a precise topographical localisation of the signs and symptoms, making it possible to perform the evaluation through a multimodal approach including patient-reported symptoms, providing physician objective assessment and instrumental evaluation), they are frequently perceived by oncologists as being too complicated and time-consuming. Moreover, when the use of instrumental evaluations is included, this raises the problem of their availability and standardisation and, in general, the need for easy access to a neurological department for the patients.

Despite these limitations, the Total Neuropathy Score is generating increased interest and deserves to be described as an example of these tools and of their potentiality in CIPN patients.

5.1. *Total Neuropathy Score (TNS)*

The complete version of the TNS combines information obtained from grading symptoms, signs, nerve conduction studies and quantitative assessment of the vibration perception threshold, providing an extended scoring range (Table 9). The TNS is the only composite scale that has been repeatedly tested in patients receiving neurotoxic chemotherapy. It assesses the presence, characteristics and location (i.e. distal versus proximal) of symptoms, as well as the presence, severity and location of several physical findings. However, this scale has not been specifically designed to assess the occurrence of neuropathic pain and the full assessment of its psychometric properties is still ongoing. TNS values range from 0 to 44 for the original 10-item version, from 0 to 36 for the more modern 9-item TNSr (without the quantitative sensory testing) and from 0 to 28 for the 7-item TNSc (based only on the clinical evaluation of symptoms and signs). Each neuropathy item is scored by a physician (not necessarily a neurologist) or a trained nurse on a 0 to 4 scale and the scores are summed to obtain the total score.

Several studies have evaluated the properties of the TNS, or its alternative versions, in patients with cancer. The TNS was used for the first time in prospective studies on CIPN by Chaudhry et al. in 1994[22] and it emerged that the scale could be used to monitor and assess its progression. The validity and reliability of this scale were then determined by Cornblath et al.[23] and high inter- and intra-rater reliability were evidenced.

In 2003 Cavaletti et al.[24] compared the TNS with the NCI-CTC 2.0, ECOG and Ajani scoring systems in 60 women with paclitaxel/cisplatin-induced CIPN confirming that the TNS could reliably be used for assessing the presence and severity of CIPN, and that its results were significantly correlated with those obtained with CTC scales routinely used by oncologists. Moreover, in this study the TNSr was found to be an easier tool to use in routine clinical activity and the results obtained with the TNSr were almost identical to those obtained using the complete TNS.

To evaluate the usefulness of the TNS in multicentre studies and the possibility of using the scale in various types of cancer patients, Cavaletti et al. performed a second study[25] on an unselected population of 428 cancer patients evaluated at 11 different centres with the TNSr or with the TNSc, comparing the results with the NCI-CTC 2.0 and ECOG scores. A highly significant correlation was demonstrated between the TNSr, NCI-CTC 2.0 and ECOG scores, although the TNSr evaluation allowed a more accurate assessment of the quality of CIPN than these CTC scales. Interestingly, the simpler and faster purely clinical TNSc allowed CIPN to be graded as accurately as with the TNSr, so it can be considered a valid alternative to the other TNS versions.

In a subsequent study,[26] both the TNS and the TNSc showed a higher sensitivity not only in the assessment of CIPN severity, but also in the detection and measurement of the changes occurring during chemotherapy in two series of cancer patients treated with platinum–taxane combinations They were evaluated at baseline and during chemotherapy with the TNS ($n = 122$) or the TNSc ($n = 51$) and with the NCI-CTC 2.0 scale, with the aim of comparing the responsiveness to changes in CIPN severity. The results of this study demonstrated that both the TNS and its reduced versions (TNSr and TNSc) are more responsive to CIPN changes when compared to the NCI-CTC 2.0 scale. This result has recently been confirmed by Chaudrhy et al.[27] in 27 newly diagnosed multiple myeloma patients treated with bortezomib and thalidomide. Slightly modified versions of the TNS have also been used to assess CIPN induced by several different antineoplastic drugs.[28,29]

6. Conclusion

From the available literature it appears that the existing scales currently being used are not satisfactory for evaluating CIPN. Moreover, evidence is emerging that health-care professionals tend to underestimate and underreport the severity and frequency of CIPN, especially the subjective symptoms such as fatigue and numbness, which impact on the patient's QoL. Therefore, better instruments to measure the severity of toxic neuropathy are needed for clinical management and for trials of preventive interventions, and these instruments need to fulfil strict biometric requirements, including simplicity, responsiveness, reproducibility and meaningfulness.[30,31]

Several initiatives have recently been launched to address all these unsolved issues regarding CIPN assessment.

The most important among them have been the first Clinical Trial Planning Meeting on CIPN organised by the NCI (March 23rd, 2009 – Rockville, MD) involving oncologists, neurologists and pain experts and the collaborative CI-Perinoms study on the comparison among outcome measures in CIPN currently ongoing in 10 European/North American countries involving 22 oncological and neurological departments.[32]

We are convinced that closer collaboration among the various health-care professionals with proper consideration for the 'patients' perspective' is the right way to achieve an adequate response to this as yet unsatisfied medical need. Until then it is our opinion to use the TNSc combined with a reliable QoL questionnaire (e.g. the EORTC QLQ-CIPN20), and a simple pain assessment (e.g. using a visuo-analogue scale) might allow the most effective description of the type and severity of CIPN.

Conflict of interest statement

None declared.

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