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(CI-Perinoms) Study: An Answer to
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The Chemotherapy-Induced Peripheral Neuropathy Outcome Measures Standardization (CI-Perinoms) Study: An Answer to the Unsettled Question of Drug-Related Neuropathy Assessment in Cancer Patients

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Abstract: Chemotherapy-induced peripheral neuropathy is a potentially severe and dose-limiting side effect of anticancer treatment. Despite its clinical relevance several crucial aspects of chemotherapy-induced peripheral neuropathy remain unsolved. Among them, the proper assessment of the occurrence and severity of this side effect is one of the most important.

Chemotherapy-induced peripheral neuropathy severity is generally assessed using common toxicity criteria scales, but most of them mix objective and subjective impairment and disability aspects. In addition, marked inter-observer dis-

agreement exists using these scales, leading to misinterpretation of the results.

Various other scale types exist (eg, composite scales based on clinical and instrumental examinations; patient-reported outcome measures based on self-administered questionnaires), but these outcome measures have never been subjected to formal clinimetric evaluation.

The Chemotherapy-Induced Peripheral Neuropathy Outcome Measures Standardization (CI-Perinoms) study is a collaborative effort of 20 European and US oncology and neurology centres specifically designed to compare the validity and

reliability of different methods proposed for the assessment of chemotherapy-induced peripheral neuropathy in a formal way. The final aim of CI-Perinoms is to propose a standardized well-evaluated set of measures for optimal assessment of chemotherapy-induced peripheral neuropathy in future clinical studies. **Eur Assoc of NeuroOncol Mag 2012; 2 (1): 37–40.**

Key words: chemotherapy, neuropathy, assessment, Rasch analysis, toxicity

■ Introduction

Chemotherapy-induced peripheral neurotoxicity (CIPN) is a frequent and sometimes severe side effect of several very effective anti-cancer drugs [1, 2]. In fact, sensory impairment is potentially dose-limiting in patients treated with platinum drugs (cisplatin, oxaliplatin, less frequently carboplatin), thalidomide, or bortezomib, while sensorimotor CIPN is typical when anti-tubulin drugs (taxanes, epothilones, and vinca alkaloids) are administered [3]. Moreover, when several neurotoxic anti-neoplastic drugs are used together in chemotherapy regimens, the incidence and severity of CIPN changes due to the appearance of combined neurotoxicity.

■ Incidence

The incidence of CIPN has never been clearly established, largely due to methodological issues in its assessment [4–7]. Outcome measures differ from one study to the other, and interobserver disagreement has been described in the use of various well-known neurotoxicity rating scales [7], making it difficult to interpret literature data properly in terms of incidence and severity of CIPN. Moreover, several neurotoxic antineoplastic drugs are used together in chemotherapy sche-

dules for the treatment of selected kinds of solid or haematological cancers, with a subsequent possible increase in the incidence and severity of CIPN and/or the appearance of combined neurotoxicity.

■ Toxicity

Although some aspects of CIPN are similar among the various drugs, every class of drugs has its characteristic toxicity profile [3]. Typically, platinum compounds produce a pattern of sensory loss consistent with primary ganglionopathy and proprioceptive loss may result in ataxia leading to severe functional impairment [8, 9]. Besides its toxicity to the dorsal root ganglia and peripheral nerves, cisplatin is also toxic to the cochlea hairy cells leading to deafness [10]. Almost pure sensory impairment in pain, thermal and touch perception are the most common clinical features experienced by multiple myeloma patients treated with bortezomib and/or thalidomide [11, 12]. All the various classes of anti-tubulins induce distal sensorimotor neuropathy, but reduced pain/thermal perception and touch hypoaesthesia with non-painful paraesthesias are always more severe than motor impairment [13, 14].

Patients often report neuropathic pain after the administration of platinum drugs, paclitaxel, or vincristine [15], but it is particularly severe in the case of bortezomib administration in the treatment of multiple myeloma [12, 16–18].

Autonomic impairment is infrequent and may result in a wide spectrum of symptoms, including orthostatic hypotension, constipation, sexual dysfunction, and micturition disorders. This can be clinically relevant particularly in vincristine-treated subjects [19].

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■ CI-Perinoms

Since one of the main issues in the proper assessment of CIPN is represented by the absence of scientifically sound instruments (as depicted by Cavaletti et al [20]), we recently completed the Chemotherapy-Induced Peripheral Neuropathy Outcome Measures Standardization (CI-Perinoms) study, based on the collaboration among 20 US and European oncology and neurology centres (see list of centres and principal investigators at the end of this article) [21].

The 2 fundamental and original objectives of the CI-Perinoms study are (1) the analysis of the current status of CIPN assessment and (2) the implementation of a rigorous clinimetric approach [22], aiming to present a set of scientifically sound (valid and reliable) scales for the assessment of CIPN in future clinical studies.

It is now recognized that any useful scale to assess a medical disorder should be simple, valid, reliable, responsive, and it should provide results that can be easily interpreted. Although these concepts might appear quite obvious, some of them deserve to be considered in detail. This is the case for validity and reliability, 2 fundamental methodological aspects whose importance is frequently underestimated. None of the most widely used scales to assess CIPN properly fulfill these requirements [23].

Validity

Various types of validity are described.

- Face validity refers to the apparent sensibility of the measure and its components. It indicates whether the scale appears to be assessing the desired qualities and represents the subjective judgement based on a review of the measure itself by one or more experts.
- Content validity consists of a judgement by experts evaluating whether an outcome measure captures all the relevant or important contents or domains of an illness.
- Construct validity is demonstrated by examining the relations between a newly created test and other tests to show that the new test measures the same “construct”. Evidence for construct validity is gathered by undertaking a series of studies to determine
 - convergent validity (the extent to which a measure correlates with other measures of related entities),
 - discriminant validity (the extent to which a measure does not correlate with measures of different entities), and
 - divergent validity (the extent to which a measure correlates with measures of opposite entities).
- Criterion-related validity is demonstrated by examining the accuracy of a test compared with a “gold standard”.

Reliability

Regarding reliability, a reliable measure is one that produces results that are accurate, consistent, stable over time, and reproducible. There are 3 different types of reliability.

- Internal consistency is the extent to which items comprising a scale measure the same concept.
- Observer reliability is the agreement between observers or within an individual observer.

- Inter-observer reliability is the agreement between observations made by ≥ 2 raters on the same patient or group of patients while
- intra-observer reliability is the agreement between observations made by the same rater on 2 different occasions on the same patient or group of patients)
- Test-retest reliability is the agreement between observations made for the same patient on 2 different occasions.

The main aim of CI-Perinoms is to propose a standardized well-evaluated set of measures for optimal assessment of CIPN in future clinical studies starting from a series of instruments which have been used in daily practice and clinical trials in CIPN patients (Table 1).

In CI-Perinoms, the clinimetric assessment of CIPN was performed at 2 different levels of investigation: (1) the core study required the evaluation of patients to be done with common devices. As such, an evaluation can be performed at any medical site. (2) The extended study included the use of additional methods of assessment, including specific devices (ie, graduated tuning fork, 10 g monofilament) and nerve conduction studies in order to ascertain whether this approach could give a more careful and clinically relevant estimate of CIPN. Patients were also asked to complete a questionnaire to obtain a set of questions useful to develop a CIPN-specific Overall Disability scale specific to CIPN and based on the Rasch analysis (RODS-CIPN) [34, 35].

To assess inter- and intra-observer agreement 2 investigators in each participating centre applied the selected impairment and activity limitation scales. Subjects were examined twice within a period of 3 weeks (visits 1 and 2) and the patient-reported outcome measures presented in Table 1 were completed at both visits by each patient to allow a test-retest evaluation. A focused electrophysiological study was performed only once at visit 1.

Since the National Cancer Institute Common Toxicity Criteria version 3 (NCI-CTC v.3) for neuropathy is still the most

Table 1. Selected outcome measures

Impairment measures	Activity and participation measures	Quality of life measures
NCS	C-ODSS	QLQ-CIPN20
TNSc	TNSc	QLQ-C30
10 g monofilament		QoL-PS
mISS		
Rydel-Seiffer tuning fork		
NCI-CTC v.3 sensory and motor		
VAS		
PI-NRS		

NCS: nerve conduction studies; TNSc: Total Neuropathy Score, clinical version [24–27]; mISS: modified INCAT sensory sum score [28]; C-ODSS: calibrated-overall disability sum score [29]; PI-NRS: 11-point-pain intensity numerical rating scale [30]; QLQ-CIPN20: EORTC 20 items CIPN specific quality-of-life questionnaire [31]; QLQ-C30: EORTC 30 item questionnaire for quality of life in cancer patients [32]; QoL-PS: quality of life personal score; VAS: visual analogue pain scale [33].

widely used method for assessing sensory neuropathy in most studies of CIPN, this instrument was considered the clinical standard for the study, to be compared with the selected methods for its effectiveness and appropriateness.

At the end of the enrolment period 281 patients were available for the analysis which is still ongoing.

We are convinced that CI-Perinoms, the first study ever performed to approach the CIPN assessment issue with a

clinimetric method, will eventually provide the basis for an answer to a still unmet clinical need in the treatment of cancer patients. The final aim is to provide a standardized set of outcome measures for future clinical studies in CIPN.

■ Conflict of Interest

GC has no conflict of interest to declare.

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