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The development of an EORTC quality of life questionnaire to assess chemotherapy-induced peripheral neuropathy: The QLQ-CIPN20

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Abstract

Chemotherapy-induced peripheral neuropathy (CIPN) is a common phenomenon, often resulting in serious limitations in daily functioning and comprosised quality of life. Currently available toxicity grading systems typically use a combination of clinical and paraclinical parameters and relies on the judgment of clinicians and/or nurses. However, because many of the symptoms of CIPN are subjective in nature, it is only logical that an assessment of CIPN be based, at least in part, on patient self-report data. We report on the development of a patient self-report questionnaire, the CIPN20, intended to supplement the core quality of life questionnaire of the European Organization for Research and Treatment of Cancer (EORTC). Following EORTC guidelines, relevant CIPN-related issues were identified from a literature survey and interviews with health professionals ($n = 15$) and patients ($n = 112$). The resulting 20-item questionnaire was pre-tested in three languages and four countries and is currently being examined in a large, international clinical trial. The EORTC CIPN20 should provide valuable information on CIPN-related symptoms and functional limitations of patients exposed to potentially neurotoxic chemotherapeutic and/or neuroprotective agents.

Keywords: Chemotherapy; Peripheral neuropathy; Quality of life questionnaire; EORTC; QLQ-CIPN20

1. Introduction

Peripheral neuropathy can be defined as a derangement in structure and function of peripheral motor, sensory and autonomic neurons causing peripheral neuropathic signs and symptoms. Chemotherapy-induced peripheral neuropathy (CIPN) is a major, potentially dose-limiting side effect of several chemotherapeutic agents including platinum analogs, vinca alkaloids and taxanes. The incidence of CIPN may be as high as 100% in treated patients, depending on dose and dose-intensity of the chemotherapy regime. The neurotoxic side effects may be very long lasting and its treatment

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is usually difficult. Neuroprotective agents are currently being investigated to prevent or ameliorate CIPN.

Chemotherapy-induced peripheral neuropathy may seriously compromise patients' quality of life (QL) [1,2]. Therefore, it is important to be able to assess CIPN in a valid and reliable manner, both in clinical trials of new chemotherapeutic agents and in clinical practice, where the treatment is known or suspected to induce CIPN [3]. The two most widely used cancer-specific QL questionnaires are the European Organization for Research and Treatment of Cancer (EORTC) QLQ-C30 and the Functional Assessment of Cancer Therapy (FACT-G) [4,5]. Both of these questionnaires are designed to assess a core set of QL issues and are intended to be supplemented by additional condition- or treatment-specific modules or subscales. Recently, a paclitaxel-induced peripheral neurotoxicity module was added to the FACT measurement system, comprising eleven neurotoxicity and five paclitaxel-related items [6,7]. The EORTC measurement system does not yet have a CIPN module, although several of the existing EORTC questionnaires include a few items pertaining to CIPN (e.g., pain, paresthesias). The primary objective of the current project was to develop a questionnaire module on CIPN to supplement the EORTC QLQ-C30.

2. Patients and methods

To ensure scientific rigor and quality, the EORTC Quality of Life Group has generated detailed guidelines for developing QL questionnaire modules [8]. The developmental process comprising four phases is shown in Table 1. This process was supervised by the EORTC QL Group. In this manuscript we describe the first three phases of the development of the CIPN module, the QLQ-CIPN20.

Table 1
Phases of development of the EORTC QLQ-CIPN20

Phase I – generation of quality of life issues
Literature search
Semi-structured interviews with health care professionals and patients
Selection of issues
This yields a list of potentially relevant QL items
Phase II – operationalisation
Construction of a provisional questionnaire
Items worded to be compatible with the QLQ-C30 format
Forward and backward translation
Phase III – pre-testing
Patients complete the questionnaire and undergo a "debriefing" interview
Data are analysed according to preset criteria (e.g. response prevalence and variance)
Formal report submitted to the EORTC QL group
Approval by the EORTC QL group
Phase IV – international field testing
Extensive evaluation of reliability, validity and responsiveness to change over time

3. Results

3.1. Phase I literature search

A Medline literature search was conducted, using the following keywords: chemotherapy and neuropathy, quality of life, health status or performance, questionnaire and peripheral neuropathy. In almost all of the oncology literature identified with this search, CIPN was assessed by means of standardised, physician-rated toxicity scales such as that of the World Health Organization and the Common Toxicity Criteria. Other studies employed single-institution classification systems that also relied on physicians' ratings [9–13].

In the neurology literature, several scales for assessing neuropathic signs and symptoms have been developed, including the Neuropathic Symptoms Score, the extensive Neuropathy Symptom Profile and the Neurological Disability Score [14–16]. These physician-based scales have been used primarily in clinical studies of diabetic neuropathy and most assessed the prevalence rather than the severity of symptoms. The Total Neuropathy Scale is a composite physician-based score using a combination of clinical features and neurophysiological parameters, formally validated for patients with diabetes mellitus but also used in small series of patients with cancer. Recently, a comparison was performed between the Total Neuropathy Scale and common oncological grading scales, which showed moderate correlations [17]. However, QL issues are not addressed in this approach. A patient-based diabetes symptom checklist is also available, but it contains only a limited number of neuropathy-related items [18].

3.2. Phase I selection of key issues

The literature review yielded 29 issues related to peripheral neuropathy. This list of issues was initially reviewed for completeness, relevance and importance by nine health care professional from the Netherlands and included: two medical oncologists, two hematologists, four neuro-oncologists and an oncology research nurse. Subsequently, two French neurologists, one Belgian neurologist, one British neurologist and two British medical oncologists were also asked to review this list of issues. All 15 of these individuals also provided suggestions for additional issues that had not been identified by the literature review. On the basis of this structured exercise, a provisional questionnaire consisting of 33 items was constructed in the Dutch language and translated into English and French following the

standardised translation procedures recommended by the EORTC QL Group [19].

This initial questionnaire was administered to 68 patients in the form of a semi-structured interview. Table 2 displays the socio-demographic and clinical characteristics of these patients. Patients were recruited from the Netherlands ($n = 38$), the United Kingdom ($n = 15$), France ($n = 10$) and Belgium ($n = 5$). They had a wide range of malignancies and all were previously or currently being treated with peripheral neurotoxic chemotherapeutic agents. All patients underwent a neurological examination to assess the presence of CIPN. The patients were asked to rate each issue with regard to its relevance and importance and to suggest any additional issues that should be included. Relevance was defined by the frequency and the perceived severity of the individual symptoms or problems. Evaluation of these candidate issues was based on both qualitative and quantitative data, including overlap of item content, prevalence, priority rating, mean scores and range of responses. Issues were retained in the list on the basis of preset criteria: a priority rating $\geqslant 25\%$ of the patients, a priority rating $\geqslant 33\%$ of the physicians, prevalence ratio $\geqslant 0.30$, a mean score $\geqslant 1.50$ and a range of response $\geqslant 2$. At least 3 of these 5 criteria had to be met for an individual item to be retained.

3.3. Phase II operationalisation

On the basis of patient and health care professional feedback, seven items were deleted (strange sensation in hands and feet, urinary and fecal incontinence, recognition of objects held in hand, brushing teeth and turning a key). Four items were rephrased and condensed into two items (burning and shooting pain). Due to content overlap, seven other items were rephrased and condensed into three items. Additional editing was carried out to match the layout of the questionnaire items and response categories to that of the core EORTC QLQ-C30. The resulting 20-item questionnaire, the CIPN20, was translated from Dutch into English and from English into French using the standard procedures recommended by the EORTC QL Group.

3.4. Phase III pre-testing the provisional CIPN20

A total of 44 patients from the Netherlands ($n = 15$), France ($n = 10$), the United Kingdom ($n = 14$) and Belgium ($n = 5$) participated in the pre-testing phase. The socio-demographic and clinical characteristics of these patients are reported in Table 2. All patients were asked to complete the provisional CIPN20 as well as a debriefing interview that inquired as to whether there were items in the questionnaire that were confusing, difficult to answer or upsetting. Preset criteria were used to determine if items from the provisional questionnaire should be retained or deleted. These criteria included: a mean score $\geqslant 1.50$, a response range $\geqslant 3$, a priority rating $\geqslant 33\%$ and prevalence $\geqslant 0.30$. At least three of these four criteria had to be met for an item to be retained in the questionnaire. Qualitative data from the debriefing interviews were also used to determine the final choice of items.

The items with the highest prevalence included: tingling and numbness, problems with standing or walking due to difficulty feeling the ground, difficulty with opening a jar or bottle and difficulty climbing stairs or getting up out of a chair due to weakness in the legs. No items were reported to be confusing, difficult to answer or upsetting. Only 2 items (cramps in the hands and blurred vision) did not entirely meet the preset criteria

Table 2
Characteristics of patients in phase I and III

	Phase I	Phase III
Number of patients	68	44
Gender		
Male	22	16
Female	46	28
Age (years)		
Mean	53	54
Median	54	55
Range	23–79	32–71
Malignancy		
Ovarian	37	17
Hodgkin's disease	2	2
Non-Hodgkin's lymphoma	9	1
Digestive tract	2	5
Breast		6
Leukemia	1	1
Lung	3	7
Testis	8	3
Bladder	1	1
Endometrium	2	
Brain	1	
Unknown primary adenocarcinoma	1	
Missing data	1	1
Chemotherapy		
Cisplatin/taxol	25	11
Taxotere	1	1
Vincristine	11	4
Vinblastine	1	
Cisplatin-based	19	8
Cisplatin/vincristine	4	1
Cisplatin only		6
Taxol/oxaliplatin		1
Oxaliplatin	2	1
Taxotere/cisplatin		1
Taxol	4	5
Taxol/vincristine/oxaliplatin		1
Other	1	3
Missing		1
Interval since therapy (months)[a]		
Mean	13	9
Median	4	3
Range	0–120	0–70

[a] Unknown for 3 patients.

Table 3
Contents of the EORTC QLQ-CIPN20

Sensory scale (*9 items*)
Tingling
Numbness
Pain
Instability when walking or standing
Distinguishing temperature
Hearing
Motor scale (*8 items*)
Cramps
Writing
Manipulating small objects
Weakness
Autonomic scale (*3 items*)
Vision
Dizziness after changing position
Erection disorder

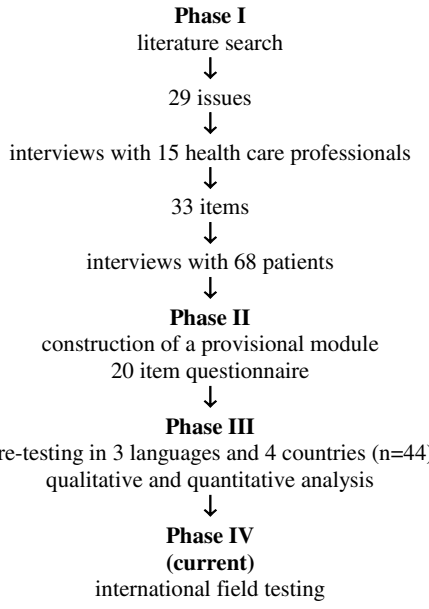

Fig. 1. CIPN20- phases and time frame of the developmental process.

(i.e., they met 2 rather than 3 criteria). However, they were retained at this stage due to the relatively small sample size. In the end, all 20 items were retained in the provisional module.

The current version of the CIPN20 includes three scales assessing sensory (9 items), motor (8 items) and autonomic (3 items) symptoms and functioning (Table 3). Based on the pre-testing sample, the internal consistency reliability (Cronbach's alpha coefficient) was 0.82, 0.73 and 0.76 for the sensory, motor and autonomic scales respectively. The CIPN20 is currently being field-tested in a large, randomised clinical trial including cancer patients treated with peripheral neurotoxic chemotherapy and a potential neuroprotective agent. Fig. 1 summarises the module developmental process.

4. Discussion

Chemotherapy-induced peripheral neuropathy is a common phenomenon, is frequently chronic in nature, is sometimes dose-limiting and often results in serious limitations in daily functioning and compromised quality of life. It is therefore important, both in clinical oncology research and practice, to be able to evaluate CIPN in a valid and reliable manner. Currently available toxicity grading systems typically use a combination of clinical and/or paraclinical parameters and rely on the judgment of clinicians and/or nurses. However, because many of the symptoms of CIPN are subjective in nature, it is only logical that the assessment of CIPN be based, at least in part, on patient self-report data. The QLQ-CIPN20 has been developed to elicit patients' experience of symptoms and functional limitations related to CIPN. Although the final version of the questionnaire awaits the results of the on-going international field study of its psychometric properties, we anticipate that the CIPN20, either in its current or in a slightly modified form, will be a useful instrument in clinical trials in which peripheral neurotoxic chemotherapy and/or potential neuroprotective agents are being investigated. In combination with the more classical, physician-based clinical rating scales, it should provide us with a more complete picture of the nature, frequency and severity of CIPN in a wide range of oncology patient populations.

Conflict of interest statement

None declared.

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