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Published in:
Supportive Care in Cancer

DOI:
[10.1007/s00520-011-1336-0](https://doi.org/10.1007/s00520-011-1336-0)

Publication date:
2012

[Link to publication](#)

Citation for published version (APA):
Driessen, C. M. L., de Kleine-Bolt, K. M. E., Vingerhoets, A. J. J. M., Mols, F., & Vreugdenhil, G. (2012). Assessing the impact of chemotherapy-induced peripheral neurotoxicity on the quality of life of cancer patients. *Supportive Care in Cancer*, 20(4), 877-881. <https://doi.org/10.1007/s00520-011-1336-0>

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Assessing the impact of chemotherapy-induced peripheral neurotoxicity on the quality of life of cancer patients

The introduction of a new measure

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Received: 31 January 2011 / Accepted: 28 November 2011
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Abstract

Purpose To investigate the impact of chemotherapy-induced neurotoxicity on daily activities and quality of life (QoL) of cancer patients.

Methods QoL of all patients visiting the oncological outpatient ward of the Maxima Medical Centre in the Netherlands from October 2006 until March 2007 treated with taxanes, vinca-alkaloids and/or platinum compounds ($n=88$) was compared with the QoL of patients that did not receive these treatments yet ($n=43$). Patient-reported neuropathy symptoms were evaluated with the newly developed Chemotherapy Induced Neurotoxicity Questionnaire (CINQ) and the Functional Assessment of Cancer Therapy/Gynaecologic Oncology Group/Neurotoxicity (FACT/GOG-Ntx) questionnaire.

Results Patients treated with chemotherapy reported significantly more complaints of neuropathy ($p<0.001$) and more paresthesias and dysesthesias in the upper ($p<0.001$; $p<0.01$) and lower extremities ($p<0.001$) compared to those not treated with chemotherapy. They additionally experienced problems with fine motor function (e.g., getting (un)dressed, writing, and picking up small objects). Moreover, cold-induced paresthesias were frequently

reported. Overall, patients indicated that their neuropathy had a negative effect on QoL.

Conclusions The newly developed CINQ and the FACT/GOG-Ntx results suggest a considerable negative impact of patient-reported neuropathy symptoms on daily activities and QoL in cancer patients treated with chemotherapy. However, further validation of the CINQ is needed.

Keywords Cancer · Oncology · Neurotoxicity · Chemotherapy · Quality of life

Introduction

Chemotherapy, the major treatment modality in oncology, is often accompanied by side effects, including peripheral neuropathy. This may have a great impact on quality of life (QoL) [1–5]. Peripheral neurotoxicity is caused by chemotherapeutic agents, like vinca-alkaloids, platinum compounds, and taxanes [6]. The degree of neurotoxicity depends on the type and combination of drugs used, the duration of administration, and the cumulative dose applied [7, 8]. Depending on the drug, sensory, painful neuropathies (cisplatin, oxaliplatin and carboplatin) or combined sensorimotor neuropathies (vincristin and paclitaxel) may occur [2, 8, 9]. In some cases, these symptoms first emerge or worsen after cessation of chemotherapy, in particular in the case of treatment with cisplatin [8, 10].

Attempts to evaluate the treatment of peripheral neurotoxicity have yielded promising, but variable results [6, 9–14]. None of the known neuroprotective agents is currently recommended as a standard treatment [6, 11, 15]. Currently, peripheral neuropathy is treated symptomatically. Dose

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reduction or lowering dose intensities are typical ways to prevent peripheral neuropathy, but this may also affect the therapeutic potential.

Until now, there have been few systematic assessments of the impact of peripheral neuropathy problems, which may partly be explained by the lack of adequate measures. Special neurotoxicity supplements have been added to QOL measures, such as the FACT-taxane [1], the Functional Assessment of Cancer Therapy/Gynaecologic Oncology Group-Neurotoxicity (FACT/GOG-Ntx) [4], and the Chemotherapy Induced Peripheral neuropathy (CHIP) [5, 7]. However, these measures fail to evaluate the effects of neurotoxicity on daily functioning.

The aim of this study was to investigate the consequences of patient-reported chemotherapy-induced neuropathy on QoL with a newly developed Chemotherapy Induced Neurotoxicity Questionnaire (CINQ). The FACT/GOG-Ntx was used to validate the CINQ.

Patients and methods

Patients

All patients visiting the outpatient ward of the Department of Oncology at the Maxima Medical Centre in the Netherlands, between October 2006 and March 2007, who were treated with taxanes, vinca-alkaloids and/or platinum compounds or discontinued treatment less than a month ago were considered eligible. Patients with other comorbid conditions potentially causing CIN such as diabetes, thyroid disease or preexisting neuropathy were excluded. Patients gave informed consent before entering the study.

We compared patients prior to initiation of chemotherapy (CT-; $n=43$) with patients who had received at least three cycles with taxanes, vinca-alkaloids or platinum compounds (CT+; $n=88$). In this group, data were collected within 1 month after cessation of therapy. The median number of chemotherapy cycles per patient was 6, ranging from 3 to 14.

Measures

The newly developed CINQ was based on the questionnaire by Leonard et al. [16] and interviews with seven patients treated with vinca-alkaloids, platinum compounds or taxanes, specifically asking about neurotoxicity symptoms, and their impact on daily functioning. The preliminary CINQ was evaluated by experts and was subsequently adjusted.

The final version consists of experienced symptoms: (A) in arms, hands, fingers; (B) legs, feet, toes; (C) face and mouth, (D) other symptoms, and how this affects QoL. Each symptom question is followed by a question on the amount

of experienced bother and the influence on daily activities. For example, “Do you experience cramps in your hands (Yes/No)?” If yes; “How much did this bother you (range 0–5)?” and “Did this influence your daily activities (range 0–5)?” A high score indicates more severe patient-reported neurotoxicity symptoms.

To assess the validity of the Dutch CINQ, the Dutch version of the FACT/GOG questionnaire [2, 3] was used, which can be used for patients with any form of malignancy. This questionnaire contains 27 items, divided into four areas of QoL: (1) physical well-being, (2) social/family well-being, (3) emotional well-being and (4) functional well-being. The validated Ntx extension of the FACT/GOG questionnaire contains 11 questions which assess chemotherapy-induced peripheral neuropathy [17]. A lower score on the FACT/GOG indicates lower QoL. In addition, a lower score on the NTX component means that patients experience a greater impact of neuropathic symptoms in their life.

Statistical analyses

We compared socio-demographic and clinical characteristics of the CT+ and CT- group, using *t*-tests for continuous variables and chi-square analyses for categorical variables (Table 1). The Mann-Whitney test was used to evaluate the differences in neuropathy between these groups (Table 2). The association between the measures was computed with the Pearson *r* correlation. Statistical test were two-sided and significant if $p<0.05$. All analyses were conducted using SPSS version 17.0.

Results

Demographics

Of the total group of 146 eligible patients, three did not meet our inclusion criteria (brain metastases, a transverse lesion, and no signed informed consent form). The socio-demographic and clinical characteristics of the remaining 143 patients (88 CT+; 43 CT-) are compared in Table 1. The groups did not differ significantly in terms of mean age, sex and indication of treatment.

Impact of neurotoxicity on quality of life

CT+ patients reported significantly more complaints of neuropathy compared to CT- patients (110 vs. 124; $p<0.001$) as measured by the FACT/GOG. They also scored significantly lower on the FACT/GOG-Ntx (33 vs. 41; $p<0.001$). Finally, the CT+ patients obtained significantly higher

Table 1 Socio-demographic and clinical characteristics of patients treated with chemotherapy (CT+) and a control group (CT-)

	N (%)		<i>p</i> Value
	Group CT- ^a (<i>n</i> =43)	Group CT+ ^b (<i>n</i> =88)	
Socio-demographics			
Age (mean (min/max) SD)	61 (36/79) 11.4	62 (36/81) 10.0	ns
Gender			ns
Male	19 (44)	39 (44)	
Female	24 (56)	49 (56)	
Indication			
Neo-adjuvant	1 (2)	4 (5)	
Adjuvant	17 (40)	36 (41)	
Curative	2 (5)	7 (8)	
Palliative	23 (53)	41 (47)	
Type of malignancy			
Breast	7 (16)	13 (15)	
Colon	16 (37)	29 (33)	
Sigmoid	3 (7)	9 (10)	
Rectal	9 (21)	7 (8)	
Gastric	0	6 (7)	
Non Hodgkin lymphoma	1 (2)	8(9)	
Prostate	0	7 (8)	
Ovarian	2 (5)	5 (6)	
Pseudo myxoma peritonei	1 (2)	0	
Lung	0 (0)	1 (1)	
Endometrial	0 (0)	2 (2)	
Larynx	1 (2)	0	
Multiple myeloma	1 (2)	0	
Hodgkin lymphoma	1 (2)	0	
Esophagus	0	1 (1)	
Pancreatic	1 (2)	0	
Chemotherapy^c			
Oxaliplatin	29 (67)	45 (51)	ns
Paclitaxel	9 (21)	15 (17)	
Docetaxel	0	12 (14)	
Carboplatin	0	1 (1)	
Cisplatin	2 (5)	8 (9)	
Vincristin	2 (5)	7 (8)	
Vinblastin	1 (2)	0	

ns Not significant

^aCT-: control group of patients before the start of their treatment with chemotherapy

^bCT+: patients with at least three cycles of chemotherapy

^cThe CT- patients' column represents planned chemotherapy regimens; the CT+ column represents patients that already underwent at least three cycles of chemotherapy

Table 2 Mean scores on specific CINAQ questions and results of Mann-Whitney test

	Mean score±SD (range)		
	Group CT- (<i>n</i> =43)	Group CT+ (<i>n</i> =88)	<i>p</i> Value
Paresthesia upper extremity	0.2±0.5 (0–2)	1.9±1.8 (0–5)	<0.001
Dysesthesia upper extremity	0.2±0.7 (0–3)	0.8±1.3 (0–5)	<0.01
Paresthesia lower extremity	0.3±0.8 (0–3)	1.5±1.7 (0–5)	<0.001
Dysesthesia lower extremity	0.2±0.8 (0–4)	1.1±1.6 (0–5)	<0.001
Paresthesia mouth	0.2±0.7 (0–4)	0.9±1.4 (0–5)	<0.01
Paresthesia face	0.1±0.6 (0–4)	0.6±1.2 (0–5)	<0.001

Paresthesia is a sensation of tingling, pricking, or numbness of a person's skin

Dysesthesia is an unpleasant, abnormal sense of touch

scores on the CINO (59 vs. 17; $p < 0.001$) suggesting more severe patient-reported neuropathy symptoms.

The CT+ group experienced significantly more paresthesias and dysesthesias in the upper ($p < 0.001$; $p < 0.01$) and lower extremities ($p < 0.001$) than CT- patients (Table 2). In addition, the CINO reveals that CT+ patients had significantly more difficulty with fine motor function. They experienced more problems with buttoning up a blouse ($p < 0.001$), writing ($p < 0.003$), and picking up small objects ($p < 0.01$). They further reported more cold-induced pain when outside ($p < 0.001$) and when taking something out of the refrigerator ($p < 0.001$), more problems with the consumption of cold foods ($p < 0.001$) and drinks ($p < 0.001$) and more problems with controlling their bladder function ($p < 0.05$).

The CINO further disclosed patients' problems with taking care of their environment due to neuropathies. Patients experienced limitations in their activities due to problems in hands, foot, or mouth ($p < 0.001$) and they mentioned difficulties with accepting the consequences of neurotoxicity ($p < 0.001$). Their neuropathies further limited them with gardening ($p < 0.05$) and sport activities ($p < 0.01$). Overall, patients indicated that neuropathy had a negative effect on QoL.

Criterion validity of the CINO

Analyses showed a strong significant negative correlation between the FACT/GOG and the CINO (-0.73 ; $p \leq 0.001$) which suggests that severe patient-reported neuropathy symptoms were associated with a lower QoL. The Ntx and the CINO scores were also strongly correlated negatively (-0.84 ; $p \leq 0.001$) which indicates that both questionnaires assess a similar construct. However, the current findings are preliminary and formal validation with clinical formal assessment of neuropathy is still needed.

Discussion

Our findings suggest that neurotoxicity has a considerable negative impact on daily activities and QoL in cancer patients treated with chemotherapy. In particular, paresthesias and dysesthesias in upper and lower extremities, problems with fine motor function, problems with controlling their bladder function, and cold-induced paresthesias were frequently reported. Most of these patients were treated with oxaliplatin, which is known for its cold-induced paresthesias [6, 8, 10, 15].

In previous studies, the influence of neurotoxicity on QoL has been evaluated with the FACT-Taxane [1], FACT/GOG-Ntx [2, 17] and the EORTC-QLQ-C30 [5, 7]. However, the specific effects of neurotoxicity on daily

activities and the inconveniences for the patient do not become evident with these measures. Therefore, the CINO was developed and used in this study. The CINO is unique in revealing the problems in daily living caused by neurotoxicity. The strong association between the CINO and FACT/GOG can be considered as preliminary support for its validity. With increasing neurotoxicity, a greater decrease in QoL can be expected.

The degree of neurotoxicity as assessed in the present study is hard to compare to other studies. There is currently no consensus about the gradation of neurotoxicity. The World Health Organization criteria [18], the Eastern Cooperative Oncology Group score [19], or the Ajani score [7] are sometimes used, while in other studies nerve conduction tests have been applied. In this study, no gradation has been made.

Although our results showed a strong negative association between FACT/GOG and CINO, and although the FACT/GOG-Ntx subscale and CINO scores were strongly associated, the CINO needs to be further evaluated, in particular its reliability and validity. Also, the lack of an objective method of neurological assessment as a reference is a limitation. In addition, the relatively small number of patients did not allow us to investigate the influence of differential exposure to the various chemotherapeutic agents on patient-reported neuropathy symptoms. Future studies should investigate this further. Finally, the small number of included patients limits the generalizability of the results.

Despite these limitations, the present study is the first to provide support for the notion that neurotoxicity has a great impact on daily functioning of cancer patients and that these effects may require considerable adjustments. It is important for health care professionals to ask patients about problems related to neurotoxicity since the impact on daily activities may be considerable. Currently, hardly any treatment or preventive interventions are available [6, 8, 9]. However, patients should be adequately informed about possible side effects of their treatment. The CINO might be a useful and promising measure to evaluate patients' suffering from neuropathy symptoms. However, validation against clinical formal assessment of neuropathy is still needed.

Acknowledgement The authors thank all patients for their participation in the study.

Conflict of interest None declared.

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