Chemotherapy-induced peripheral neuropathy and impact on quality of life 6 months after treatment with chemotherapy

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Background Chemotherapy-induced peripheral neuropathy (CIPN) is a major dose-limiting toxicity of cytostatics. With improved survival among cancer patients, CIPN may have a major impact on quality of life (QoL) of cancer survivors.

Objective To determine the occurrence of CIPN induced by oxaliplatin and taxanes and its impact on QoL median 6 months after chemotherapy.

Methods All patients who received their last treatment with oxaliplatin or taxanes in 2 consecutive years in the Máxima Medical Centre, the Netherlands, were eligible for the study. Neurotoxicity and its effect on QoL was assessed with the recently developed Chemotherapy Induced Neurotoxicity Questionnaire (CINQ) and the Functional Assessment of Cancer Therapy/Gynecologic Oncology Group-Neurotoxicity (FACT/GOG-Ntx) median 6 months after cessation of therapy.

Results Of the 58 eligible patients, 43 (74.1%) completed the questionnaire. After a median follow-up of 6.5 months after cessation of therapy, most of the patients experienced neurotoxicity in the upper and lower extremities (78.8% and 89.7%, respectively). Overall, the most-reported complaints included numbness and tingling in hands as well as feet, suffering from cold feet, and trouble distinguishing objects in the hands. Housekeeping difficulties were reported in 12.8% of patients, and 20.5% of patients became more dependent on others because of the neurotoxicity. Overall, QoL was negatively affected by the impact of CIPN in 48.6% of patients.

Limitations Due to the small sample size selection bias cannot be ruled out and no data about CIPN during treatment were available.

Conclusions After a median follow-up of 6.5 months after cessation of therapy with oxaliplatin or taxanes, CIPN is common and leads to impairment in patient QoL. More research is needed to assess the impact of neurotoxicity on QoL.

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In cancer treatment, cytostatics are often accompanied by side-effects that may have a major impact on the quality of life (QoL) of patients.[1] One of those side-effects is chemotherapy-induced peripheral neuropathy (CIPN), which is a major dose-limiting toxicity in the frequently used cytostatics, such as taxanes, to treat breast, ovarian, and prostate cancers, and the platinum derivative oxaliplatin, which are mainly used in colorectal cancer.[2-5] CIPN symptoms consist mainly of sensory impairment, but may also affect motor functions and the autonomic nervous system.[5-7] Patients with CIPN can experience symptoms in hands and feet, such as tingling, numbness, cramps, and aching or burning pain which can cause problems with regular daily activities such as buttoning clothes, holding a pen, opening a jar or bottle, or problems with standing, walking, or climbing stairs. The severity of these symptoms depends on the type of drug used, duration of administration, cumulative dose, and pre-existing peripheral neuropathy.[2-8] After 4-6 months, the neuropathy resolves in most patients, but it is most often irreversible in the patients (about 60%) who still have complaints after 6 months.[8,9] Despite multiple studies that have yielded promising results, there is still no consensus on how to prevent CIPN.[7] In addition, CIPN treatment also remains difficult and there is no well-accepted proven therapy.[10,11] Because the use of chemotherapy is increasing in the treatment of cancer, CIPN is

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becoming a major survivorship issue that may have a negative impact on QoL.

Although many questionnaires have been developed to assess neuropathy and QoL,[1,12-14] only a few studies have investigated the impact of CIPN on QoL as demonstrated by a recent systematic review.[15] Accordingly, only 8 studies have reported that most patients had symptoms of CIPN and worse QoL because of CIPN,[1,16-22] and 3 studies did not find a relation between CIPN and QoL.[12,23,24] In addition, other studies have demonstrated the impact of CIPN on daily functioning, but did not assess QoL directly.[25,26] The studies that directly assessed the influence of CIPN on QoL differed notably in applied study design, included patient population, and way of CIPN and QoL assessment, which makes comparison of these studies difficult.[1,12,16-18,20-22,24] In addition, CIPN and QoL assessments were completed over a range of follow-up periods, while patients with remaining complaints after 6 months are at risk of having irreversible CIPN. Therefore, recognition of CIPN and its influence on QoL is needed because of the importance of informing and guiding these patients. Consequently, more studies are required to investigate the direct impact of CIPN on QoL 6 months after therapy. Therefore, we aimed to study the occurrence of CIPN symptoms induced by oxaliplatin or taxanes and the impact of these symptoms on QoL median 6 months after cessation of treatment.

Methods

Patients

Patients who received their last course with oxaliplatin or taxanes (paclitaxel or docetaxel) during 2 consecutive years in Máxima Medical Centre in the Netherlands were eligible for this study. The indications for treatment with chemotherapy were neoadjuvant, adjuvant, or palliative. Patients received a questionnaire median 6 months after their last chemotherapy course, and nonrespondents received 1 reminder telephone call. All of the respondents gave written informed consent. A local Medical Ethics Committee approved this study.

Chemotherapy and cumulative dose

Patients treated with oxaliplatin received a dose of 150-300 mg/m^2 intravenously once in 3 weeks (cumulative doses ranging from 690-2,340 mg/m^2). Paclitaxel was given in a dose of 80 mg/m^2 weekly or 175 mg/m^2 once in 3 weeks (cumulative doses ranging from 560-1,960 mg/m^2). All patients who were treated with docetaxel received doses of 75 mg/m^2 (cumulative doses ranging from 720-1,120 mg/m^2). The median number of chemotherapy courses was 6 and the median duration of administration was 15 weeks. Dose reduction was applied in accordance to national guidelines.

Measures

Patients' sociodemographic and clinical characteristics, such as age, sex, type of malignancy and occurrence of metastatic disease, information on comorbid conditions and type and indication of chemotherapy, cumulative dose and duration of administration, were extracted from their medical files.

The recently developed Chemotherapy Induced Neurotoxicity Questionnaire (CINQ)[1] and the validated Functional Assessment of Cancer Therapy/Gynaecologic Oncology Group-Neurotoxicity (FACT/GOG-Ntx) questionnaires were used to evaluate the symptoms of CIPN and the impact of CIPN on patients' QoL.[27] The CINQ complements the FACT/GOG-Ntx because it asks patients about more and different symptoms and the relation of those symptoms to QoL. Patients were asked to answer the questions about symptoms they experienced in the previous 7 days.

The CINQ consists of common symptoms in the following the upper extremities, lower extremities, and head and neck regions; and it asks about other possible symptoms not already mentioned in the questionnaire. Symptom intensity is indicated on a Likert scale (0 = *not at all* to 5 = *very much*). A higher score indicates more severe CIPN. The maximum achievable score was 520. The last question of the CINQ assesses the impact of CIPN on QoL on a scale of 1 (*not at all*) to 5 (*very much*).

The FACT/GOG-Ntx has 2 parts: the FACT-GOG subscale comprised of 4 areas concerning QoL well-being – physical, social/familial, emotional, and functional; and the Ntx subscale containing 11 items that evaluate the amount of common neuropathy symptoms. Symptoms are indicated on a scale ranging from 0 (*not at all*) to 4 (*very much*). A higher score indicates more severe neuropathy. Maximum achievable score is 44.

Statistical analysis

Sociodemographic and clinical characteristics of the included patients were shown in absolute numbers and percentages. The occurrence of neuropathy symptoms experienced in the previous week were shown in percentages and reflect the answers *quite a bit*, *much*, and *very much* of the CINQ combined, and *somewhat*, *quite a bit*, and *very much* combined for the FACT/GOG-Ntx. Furthermore, mean total scores on the Ntx-subscale and CINQ, and QoL questions were shown.

The impact of CIPN on QoL was assessed by a comparison of mean total scores of the FACT/GOG-Ntx and CINQ between the combined answers *not at all*, *a little*, and *somewhat* vs *quite a bit* or *very much* on the FACT-G item *I am content with my QoL right now*; and with the CINQ item *How much do the complaints of hand, feet, and face reduce the QoL*. Analysis of covariance

(ANCOVA) were done with adjusted for indication of treatment and time of questionnaire. In addition, a comparison of mean FACT/GOG subscale scores were compared between low and high (eg, top 25% of patients) neuropathy symptom scores on FACT/GOG-Ntx with ANCOVA. Analyses were adjusted for indication of treatment, age, and time of questionnaire. The correlation between the CINQ and FACT/GOG-Ntx was computed with Pearson correlation. All *P* values < .05 were considered to be significant. All analyses were conducted using SPSS version 19.0.

Results

Demographics

In all, 68 patients were considered eligible for our study. Ten patients died between the time of inclusion and sending of the questionnaire. Of the remaining 58 patients, 15 did not return the questionnaire despite having received a reminder telephone call. Thus, 43 patients completed the questionnaire (response rate, 74.1%). The patients' sociodemographic and clinical characteristics are described in Table 1.

TABLE 1 Sociodemographic and clinical characteristics of included patients

Patients	n (%), unless otherwise indicated (N = 43)
Sex	
Male	17 (40)
Female	26 (61)
Mean age, y (SD)	60.7 (11)
Type malignancy	
Colon carcinoma	23 (54)
Rectal carcinoma	5 (12)
Mamma carcinoma	10 (23)
Prostate carcinoma	1 (2)
Ovarian carcinoma	3 (7)
Unknown	1 (2)
Chemotherapy	
Oxaliplatin	29 (67)
Paclitaxel	8 (19)
Docetaxel	6 (14)
Metastatic disease	
Yes	23 (54)
No	18 (42)
Indication	
Neoadjuvant	3 (7)
Adjuvant	18 (42)
Palliative	21 (49)
Unknown	1 (2)
Mean cumulative dose, mg/m^2 (SD)	
Oxaliplatin	1,379 (452)
Paclitaxel	1,120 (508)
Docetaxel	893 (205)
Median no. of chemotherapy courses (range)	6.0 (3-10)
Median duration of administration, weeks (range)	15.5 (3-27)
Median months follow-up (range)	6.5 (3-14)
Previous chemotherapy	6 (14)
Comorbidities	
Diabetes mellitus	4 (9)
Multiple sclerosis	0
Preexisting neuropathy	0
Hyperthyroidism	0
Cerebrovascular accident	2 (5)
Rheumatoid arthritis	0

[a]Percentages can exceed 100 because of rounding.

Neuropathy

After a median follow-up of 6.5 months after the cessation of therapy most of the patients had symptoms of CIPN in upper and lower extremities (78.8% and 89.7%, respectively). Overall, according to the FACT/GOG-Ntx-subscale, the symptoms that were reported by the patients during the previous week were mainly sensory and consisted of numbness or tingling (63.3% and 60.9%) and discomfort of hands and feet (48.8% and 56.1%; Table 2). Table 3 shows the most frequently reported neuropathy symptoms, divided into sensory, motor, or autonomic symptoms according to the CINQ. Answers of the CINQ corresponded well to answers of the Ntx, and the most frequently reported complaints according to the CINQ included numbness in the fingers or feet (48.7% and 51.2%), suffering from cold feet (51.2%), tingling fingers or feet (39.5% and 46.9%), trouble distinguishing objects in the hands (39.5%), and loss of strength in the legs (38.6%). Patients were limited in daily activities with major limitations being unbuttoning a blouse (39.5%), picking up things from the floor (27.0%), and opening a jar or bottle due to loss of strength in the hands (27.0%). In addition, 12.8% of patients reported housekeeping difficulties, and 20.5% of patients stated that they became more dependent on others because of the CIPN.

Mean total score on the Ntx-subscale was 13.4 (SD, 8.7; range, 0-32) and the mean total score for the CINQ was 82.6 (SD, 64.5; range,1-230). In addition, total scores on the Ntx-subscale were significantly correlated to the total scores of the CINQ (r = 0.8; *P* < .001).

Impact neuropathy on quality of life

On the FACT-G item *I am content with my QoL right now*, 48.8% of patients report to be *quite a bit* or *very much content* with their QoL. Patients who were less content with their QoL had worse total neuropathy scores than patients who were content with their QoL, as assessed with Ntx (15.7

TABLE 2 Patient responses to the most often reported neuropathy symptoms according to the FACT/GOG-Ntx (N = 41)

Sensory symptom or problem	Not at all	A little	n (%) Somewhat	Quite a bit	Very much
Numbness or tingling in hands?	10 (24.4)	8 (19.5)	6 (14.6)	14 (34.1)	6 (14.6)
Numbness or tingling in feet?	11 (26.8)	5 (12.2)	5 (12.2)	14 (34.1)	6 (14.6)
Feeling of discomfort in hands?	16 (39.0)	5 (12.2)	7 (17.1)	12 (29.3)	1 (2.4)
Feeling of discomfort in feet?	14 (34.1)	4 (9.8)	5 (12.2)	13 (31.7)	5 (12.2)
Trouble buttoning a blouse?	16 (39.0)	8 (19.5)	6 (14.6)	9 (22.0)	2 (4.9)
Trouble distinguishing objects in the hands	20 (48.8)	4 (9.8)	7(17.1)	8 (19.5)	2 (4.9)

FACT/GOG-Ntx, Functional Assessment of Cancer therapy/ Gynaecologic Oncology Group-Neurotoxicity

TABLE 3 Patient responses to the most frequently reported neuropathy symptoms[ab]

Symptom or problem	Not at all	Barely	n (%) A little	Quite a bit	Much	Very much
Corresponding score	*0*	*1*	*2*	*3*	*4*	*5*
			Sensory			
Tingling fingers or hands	14 (36.8)	2 (5.3)	7 (18.4)	9 (23.7)	6 (15.8)	0
Tingling toes or feet	15 (38.5)	1 (2.6)	4 (10.3)	8 (20.5)	9 (23.1)	2 (5.1)
Numbness fingers	14 (36.8)	1 (2.6)	9 (23.7)	5 (13.2)	9 (23.7)	0
Numbness toes or feet	16 (40.1)	0	3 (7.7)	7 (17.9)	11 (28.2)	2 (5.1)
Aching/burning pain in fingers/hands with coldness	21 (55.3)	3 (7.9)	1 (2.6)	7 (18.4)	3 (7.9)	3 (7.9)
Aching/burning pain in toes/feet	28 (71.8)	0	2(5.1)	4 (10.3)	5 (12.8)	0
Trouble distinguishing objects in hands	17 (44.7)	2 (5.3)	4 (10.5)	5 (13.2)	4 (10.5)	6 (15.8)
Suffering from cold feet	16 (41.0)	1 (2.6)	2 (5.1)	10 (25.6)	5 (12.8)	5 (12.8)
			Motor			
Trouble unbuttoning a blouse?	15 (40.5)	2 (5.4)	9 (24.3)	5 (13.5)	3 (8.1)	3 (8.1)
Trouble opening a jar or bottle due to loss of strength in hands?	14 (37.8)	3 (8.1)	10 (27.0)	4 (10.8)	4 (10.8)	2 (5.4)
Difficulty picking up little things?	15 (40.5)	4 (10.8)	8 (21.6)	4 (10.8)	3 (8.1)	3 (8.1)
Difficulty pushing tablets out of a strip?	23 (62.2)	1 (2.7)	3 (8.1)	3 (8.1)	5 (13.5)	2 (5.4)
Less strength in legs?	22 (56.4)	1 (2.6)	1 (2.6)	8 (20.5)	6 (15.4)	1 (2.6)
			Autonomic			
Trouble with bladder control?	24 (61.5)	2 (5.1)	4 (10.3)	6 (15.4)	2 (5.1)	1 (2.6)
Erectile difficulties (only for men, n = 15)	9 (60.0)	1 (6.7)	1 (6.7)	1 (6.7)	3 (20.0)	1 (6.7)
Dry vagina (only for women, n = 24)	12 (50)	1 (4.2)	3 (12.5)	4 (16.7)	1 (4.2)	3 (12.5)

[a]Based on questions of the Chemotherapy Induced Neurotoxicity Questionnaire. [b]N = 38 because not all patients completed the questionnaire.

vs 11.0, respectively; $P = .034$) and CINQ (93.8 vs 70.0; $P = .267$). The last question of the CINQ, *How much do the complaints of hand, feet, and face reduce the QoL?* showed that in 48.6% of patients (mean, 1.86; SD, 1.1), QoL was negatively influenced because of CIPN (answers *a little* to *very much* combined). A significant correlation (r = 0.37; $P = .02$) was found between scores on emotional well-being (FACT-G; range, 0-24; mean, 6.9; SD, 3.6) and neuropathy symptoms (Ntx-subscale; range, 0-32; mean, 13.4; SD, 8.7). Patients who reported many neuropathy symptoms on the FACT/GOG-Ntx (eg, top 25% of patients with highest scores) reported significantly worse emotional well-being (9.4 vs 5.8; $P = .002$) than the patients with less neuropathy symptoms (eg, lower 75%; Table 4). Other FACT-G subscales did not differ between the patients with lower and upper neuropathy scores.

TABLE 4 Comparison of FACT/GOG well-being subscales between patients with low or high neuropathy symptoms on the FACT/GOG-Ntx

	Mean score (SD)		
Well-being subscale	**Low[a]**	**High[b]**	***P* value**
Physical	23.0 (4.6)	21.6 (5.0)	.972
Social/familial	19.5(3.8)	20.6 (2.7)	.398
Emotional	6.2 (2.8)	8.9 (3.3)	.002
Functional	17.8 (6.5)	15.5 (5.5)	.636

FACT/GOG-Ntx, Functional Assessment of Cancer Therapy/Gynecologic Oncology Group-Neurotoxicity

[a]Low scores = 75% of patients with lowest scores on FACT/GOG-Ntx subscale. [b]High scores = upper 25% of patients with the highest scores on FACT/GOG-Ntx subscale indicating worse neuropathy symptoms.

Discussion

This study indicates the occurrence of CIPN and a decrease in QoL because of CIPN in 48.6% of patients after a median follow up of 6.5 months after cessation of chemotherapy. Most of the patients reported symptoms of CIPN in the upper and lower extremities (78.8% and 89.7%, respectively). Overall, most reported complaints included numbness and tingling in hands and feet, suffering from cold feet, and difficulty distinguishing objects in the hands. Patients were limited in their daily activities because of these symptoms, and a number of them stated that they became more dependent on others because of the neurotoxicity. Patients who reported many neuropathy symptoms reported significantly worse emotional well-being than did the patients with fewer neuropathy symptoms.

With the increase in the use of chemotherapy in treating cancer, CIPN is becoming a major survivorship issue that can have a negative impact on QoL. However, the few studies that have directly investigated the effects of this side-effect on QoL were highly diverse and used different assessment tools.[15] In addition, a comparison of studies that used the same assessment tools for CIPN and QoL still presents problems because they include different patient populations, have different follow-up times, and the results were presented in different ways. For instance, a study of 100 patients that used the FACT/GOG-Ntx questionnaire reported any degree of neurotoxicity in 80% of the breast cancer patients at a median follow-up of 12 months (range, 6-24 months) and a higher neurotoxicity score was likely to be associated with lower physical well-being on the FACT-G.[22] Another study also showed that neuropathy symptoms were significantly associated with worse QoL as demonstrated by significantly worse FACT-G subscale scores in 230 patients with non-small-cell lung cancer 6 and 12 weeks after cessation of chemotherapy.[16] Two studies, which included cancer patients with different types of malignancies and chemotherapy treatments, also showed worse QoL in patients with symptoms of CIPN after treatment,[1,21] whereas another study with 99 ovarian cancer patients did not find a relation between CIPN and global QoL.[12] We demonstrated the occurrence and severity of CIPN and the impact of CIPN on global QoL and emotional well-being median 6 months after cessation of chemotherapy. Our results confirm those of previous studies that also showed a mainly negative impact of CIPN symptoms on QoL. However, comparison with these studies is complicated for aforementioned reasons. Patients with remaining complaints after 6 months are at risk of having irreversible CIPN and recognition of symptoms and impact on QoL in these patients is therefore necessary.

This study has some limitations that should be mentioned. We used the relatively new developed and informative CINQ, which reports about many neuropathy symptoms, including the sensory, motor, and autonomic nervous system symptoms, and evaluates the influence of CIPN on QoL.[1] However, the CINQ requires further validation and therefore we used the validated FACT/GOG-Ntx for concomitant evaluation of CIPN and QoL, which showed the same common symptoms and interference of CIPN on QoL after median 6.5 months after cessation of therapy. We have combined the answers *somewhat*, *quite a bit*, and *very much* of the FACT/GOG-Ntx to demonstrate the occurrence of CIPN, as a patient who states to have *somewhat* complaints of CIPN has relevant symptoms. In addition, because of central tendency bias,[28] only a few patients will respond to the questions with *very much*. In our study with its relatively small sample size, selection bias cannot be ruled out because it is not known whether nonrespondents, for example, declined to fill out our questionnaire because they were prevented from doing so because of neuropathy symptoms in their hands or because of the lack of neuropathy and bias from unanswered questions (5%-10%) might have influenced the outcomes. Questionnaires were obtained after median 6.5 months only, so infor-

mation about symptoms during the chemotherapy lacks. Objective measures as neurological examination or nerve conduction studies were not carried out, as there is a lack of consensus on the value of these objective measures in daily practice[28-30] and they do not always correspond to subjective complaints and influence on QoL.

In summary, we believe that our results may contribute to the limited data available on the impact of CIPN on QoL after 6 months. The assessment of this impact not only with the FACT/GOG-Ntx, but also with the CINQ may be of additional value, although the CINQ needs further validation. In other studies however, investigators used different questionnaires that were completed during longer follow-up periods. Recognition of CIPN in patients after 6 months is needed because of the importance of these patients being informed and guided in regard to their condition. CIPN is becoming a major survivorship issue, especially because its prevention and treatment remains difficult. Therefore, more research concerning the prevention and treatment of CIPN is required. In addition, it is important that consensus will be reached in the assessment of CIPN and QoL in cancer patients and large studies are needed to assess the impact of CIPN on QoL, both during and after treatment.

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